Sarcoidosis: A Primer

PATIENT EDUCATION GUIDE

AMERICAN COLLEGE OF CHEST PHYSICIANS

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Foreword

This document is the result of a project that was initiated by the Interstitial and Diffuse Lung Disease Network of the American College of Chest Physicians. The authors of the chapters you have before you all volunteered their time and effort to contribute to this document. They were invited to participate and share their experience and knowledge as recognized experts in the field of sarcoidosis.

Sarcoidosis is frequently a misunderstood disease. It was felt that by developing a comprehensive document, that is at the same time readable, which is reviewed and updated on a regular basis, we could provide a resource for patients, families, or anyone interested in learning more about this disease.

We hope that you find this information useful and that it gives answers to your questions and helps direct you to other resources if you want to learn more.

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Section I. Overview Topics

Introduction

Sarcoidosis is a disease characterized by lumps or nodules in the organs. This disease was first described more than 100 years ago. It is still poorly understood, however, both in terms of how it is diagnosed and how the disease occurs. This chapter describes sarcoidosis and what is known about how it develops.

What is sarcoidosis?

Sarcoidosis occurs all over the world. It affects all races, both sexes, and at all ages.[1] It is more common in certain ethnic groups such as African Americans in the United States. It is also more common in certain areas of the world, such as Northern Europe. Sarcoidosis primarily affects people between 20 and 40 years of age. It rarely develops before age 16. While it can affect the elderly, such occurrences are uncommon.

Sarcoidosis can involve any part of the body.[2] The parts of the body that have specific functions are called "organs." The lungs are the organs most commonly affected by sarcoidosis. The disease is also common in the skin and the eyes. The liver, spleen, and lymph glands are also frequently affected. While it is uncommon for the nervous system and heart to be directly affected by sarcoidosis, the indirect involvement of these organs may cause severe problems for patients suffering from the disease.

Sarcoidosis affects an organ by causing certain white blood cells to leave the bloodstream and cluster together with other white blood cells within the organ. These clusters of cells are called "granulomas,"[3] and can be seen with a microscope. (Figure 1) How and why these granulomas form in the organs of patients affected with sarcoidosis is unknown.

Many other diseases can lead to the formation of granulomas. This fact makes the study of sardoidosis even more confusing and challenging. Among the diseases with similar symptoms are infections such as tuberculosis, cancers such as lymphoma, and inflammation caused by exposure to certain metals such as beryllium .[1] Therefore, when a part of the body is biopsied (sampled) and granulomas are seen in the microscope, other diseases that can also cause granulomas must first be excluded before a diagnosis of sarcoidosis can be made.

What causes sarcoidosis?

While the cause of sarcoidosis is not known, medical professionals believe that sarcoidosis results from an interaction between the patient's immune system and an unknown exposure. Researchers have found evidence that sarcoidosis may have many causes; it may be triggered when a specific agent "fits" an individual patient's immune system and triggers the formation of granulomas. A useful analogy to describe this process is finding the right key that "fits" a specific lock. This may explain why several different exposures are associated with some, but not all, cases of sarcoidosis. These include bacterial exposures (including organisms that resemble tuberculosis), metals, combustible wood products, and mold.

It is important to note that although associations of these exposures have been associated with sarcoidosis, it is still not known whether or not they are true causes of the disease. Also, many cases of sarcoidosis are not associated with these exposures, or with any other known cause.

Summary

Sarcoidosis occurs throughout the world. Although the disease was first described more than 100 years ago, we still do not know what causes it, or how it specifically develops. It is believed that sarcoidosis involves the interaction of an exposure with the patient's individual immune system. The primary feature of sarcoidosis is the presence of granulomas within the affected tissues. However, the presence of granulomas alone is not enough for the diagnosis of sarcoidosis because granulomas can also be found with other diseases. For this reason, other causes of granulomas must be excluded before a sarcoidosis can be confidently diagnosed. HLA molecules (the Human Leukocyte Antigen) and T-lymphocytes probably have important roles as elements of the immune system in the development of sarcoidosis.

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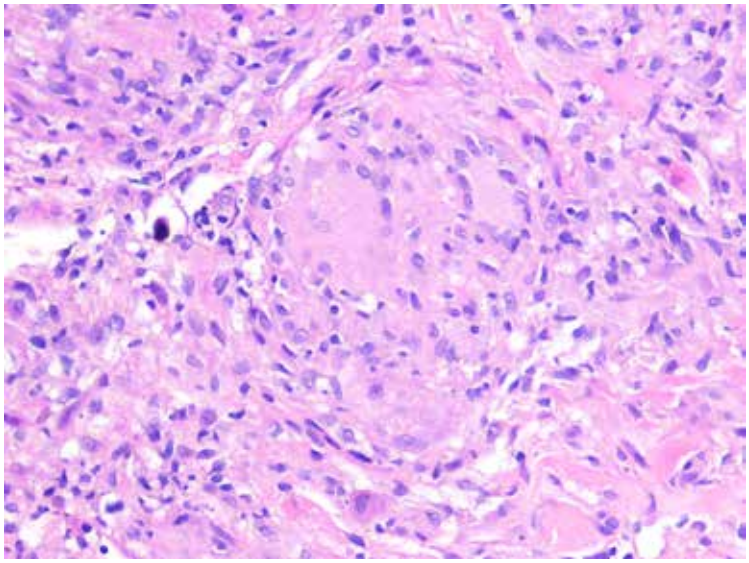

Figure 1. This picture shows a classic noncaseating granuloma composed of an aggregate of tightly clustered epithelioid cells admixed with multinucleated giant cells (Langhans' giant cells). (Pathologic review: Susan Wu, MD)

General Symptoms and Signs

A symptom is any change in body function associated with a disease that is noticed by a patient. Symptoms of sarcoidosis can be general (affecting the whole body) or specific to a particular organ. Symptoms of sarcoidosis are not unique, and can be associated with many other diseases. This lack of specific association between symptoms and sarcoidosis can lead to delays in making a diagnosis.[1] When no symptoms are present the patient is said to be asymptomatic. Sarcoidosis can still be present in an asymptomatic patient.

Along with symptoms, a patient may also display signs of a disease. A sign is an objective indication of a disease that can be detected by a physician during an examination. As with symptoms, signs of sarcoidosis may not always be specific for sarcoidosis and could indicate the presence of other diseases as well. For example, an irregular heartbeat associated with heart disease may not be noticed as a symptom by a patient. However, it may be detected by the physician as a sign. That irregular heartbeat, if present, might be caused by any one of several diseases.

Patients with sarcoidosis may have neither symptoms nor signs when their disease is diagnosed. Up to half of all individuals with sarcoidosis have no symptoms at the time of their diagnosis. When symptoms and signs are present, they may come on rapidly. In such cases, this rapid onset usually makes them easier to notice. Typically, however, symptoms and signs of sarcoidosis develop slowly. This can make it difficult to notice changes in the patient.

Factors Causing Symptoms and Signs of Sarcoidosis

Sarcoidosis has both an active and an inactive phase. In its active phase, granulomas form and grow in the tissue as part of the tissue inflammation that is occurring. Chemicals released by cells forming the granulomas can cause symptoms and signs of the disease. In this active phase, symptoms can develop from the inflammatory process as well as from the presence of granulomas. Scars may also form within the organ tissue where the granulomas are forming.

In the non-active phase of the disease, inflammation decreases and granulomas either shrink or stay the same size. Scars may remain unchanged within the tissues and may cause symptoms and signs even when sarcoidosis is in the inactive phase.[2]

Onset of Symptoms

Acute or subacute sarcoidosis develops abruptly over a period of a few weeks and occurs in 20% to 40% of all cases. These individuals usually have nonspecific symptoms such as fever, fatigue, malaise, anorexia, or weight loss. These symptoms are usually mild. However, they are severe in approximately 25% of reporting patients. Two specific syndromes have been identified in the acute group: The first is Lofgren's syndrome, which includes erythema nodosum and x-ray findings of bilateral hilar adenopathy. It is often accompanied by joint symptoms, including arthritis at the ankles, knees, wrists, or elbows. The second is called Heerfordt-Waldenström syndrome, a rare form of sarcoidosis that includes fever, parotid gland enlargement, anterior uveitis, and facial nerve palsy.

Sarcoidosis commonly develops over several months. It is most frequently associated with respiratory complaints without constitutional symptoms. In the United States, 40 to 70% of all patients with sarcoidosis belong to this category. About 10% of all sarcoidosis patients have symptoms related to organs other than the lung. These individuals – those who present with this more insidious form of sarcoidosis -- most commonly go on to develop chronic sarcoidosis which can lead to permanent damage to the lung and other organs.

Categories of General Symptoms and Signs

Fevers and Night Sweats: Fever and night sweats may occur in about one-third of sarcoidosis patients. Sarcoidosis is an important and frequently overlooked cause of fever of unknown origin and may be the first symptom to occur. Fever caused by sarcoidosis is usually low, but temperatures as high as 39 to 40 degrees Celsius (102.2 to 104.0 degrees Fahrenheit) may occur.[2]

Appetite and Weight Loss: Appetite and weight loss may occur in about one-third of patients with sarcoidosis. Appetite loss may be an early symptom. Weight loss is usually limited to 2 to 6 kilograms (4.4 to 13.2 pounds) and occurs during the beginning of the disease onset when someone is first developing symptoms.[2] These symptoms are more frequent in black patients.

Weakness, Fatigue (Malaise) and Overall Feelings of Ill Health: Weakness, fatigue (malaise) and an overall feeling of ill health may occur in about one-third of patients with sarcoidosis.[2] Fatigue, when present, can be quite disabling. Systemic inflammation may contribute to muscle weakness and exercise intolerance.

Depression and Quality of Life Assessment: In one study, 46% of those with sarcoidosis had Center for Epidemiologic Studies Depression Scale (CES-D) scores of 9 or greater, indicating depression. Decreased lung function and greater shortness of breath were associated with poorer quality of life. A full assessment of health-related quality of life measures is important when assessing the full impact of sarcoidosis.[3]

Other signs and symptoms may occur due to the involvement of particular organs. These issues are discussed more fully in subsequent chapters.

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General Screening Tests

Physicians perform screening tests to find the cause of a patient's symptoms or health problems. While completing a series of tests, a pattern of results may become evident to medical specialists that can help them diagnose sarcoidosis and rule out other possible causes or conditions. Testing done before a biopsy helps first determine whether a biopsy is even necessary. It also defines what part of the patient's body should be biopsied. If it is deemed appropriate, a biopsy can then be taken from an area that appears to be affected. This test will greatly assist physicians in their search for the presence of granulomas.

No single test can lead to a definitive diagnosis of sarcoidosis. Multiple tests and a combination of test results may give a physician enough information to make a confident diagnosis of sarcoidosis and rule out other diseases. Such testing also helps determine how many different organs may be involved, the amount of damage present and what treatment, if any, the patient may need.[1]

The following is a description of general screening studies for sarcoidosis, what they mean and why they are done.

History and Physical Exam

At the start of the diagnostic process, the patient's medical history is compiled to learn about his or her overall health status and well-being. The patient is asked a series of questions about any current and past health problems and any symptoms he or she may be experiencing. These include questions about whether the patient has any family history of sarcoidosis. The patient's work history is also considered. This is because some work environments may increase a person's risk of developing sarcoidosis. The patient is also asked to name all the medications he or she is currently taking. For this reason the patient should bring a list of all current medications, including any over-the-counter (OTC) products and herbal supplements. It is important for patients to answer all these questions accurately and with as much detail as possible.

During the physical examination, the physician will look for evidence of sarcoid. This exam will include checking for swellings or skin rashes, listening to the lungs and heart, and examining the abdomen. The physician may focus on any area of the body that is suspected or known to be affected.

Blood Tests

Blood is drawn from the body by inserting a needle into a vein, usually at the bend in the arm at the elbow. The blood sample is collected into small tubes which are then sent to the laboratory for study. Typical blood tests performed when testing for sarcoidosis include:

- Angiotensin Converting Enzyme (ACE) level - This test measures the level of an enzyme called angiotensin converting enzyme (ACE) in the blood. This enzyme may be elevated in patients with sarcoidosis. However, it is not specific for sarcoidosis and can be elevated by other conditions. For this reason, a positive ACE level test does not by itself confirm a diagnosis of sarcoidosis.

Low levels of ACE can be found in the epithelial cells lining blood vessel walls throughout the body. This enzyme has a critical role in regulating blood pressure and blood volume. It is found in higher concentrations in small blood vessels (capillaries) of the lung. The serum ACE level may be elevated in some patients with sarcoidosis. Researchers believe that this elevation is produced by the epitheilioid cells of the sarcoidosis granuloma. The specificity of ACE as a test for sarcoidosis is 50 to 60 %. This means that some patients with sarcoidosis may have normal levels of ACE yet still have sarcoidosis. At the same time, others with sarcoidosis may have elevated levels of ACE. To further confuse the matter for physicians, some individuals may have elevated levels of ACE serum, but not have sarcoidosis.

Research studies have been conducted on the gene that produces ACE in the hope of better understanding sarcoidosis. These studies have revealed notable unique characteristics in the gene (insertion/deletion polymorphism of a DNA fragment) that affects the serum level of ACE. Since these genetic differences can affect the level of ACE in the serum, scientists then questioned whether this gene difference could be related to the health issues experienced by sarcoidosis patients. The results of this research have not led to any definitive answers to this question. These studies discovered that the variation in the gene is not associated with which organ of the body is involved, the severity of the disease, or if fibrosis occurs in the patient's lungs. Also, no association was found between the level of ACE in the patient and the progression of the disease. Also, no abnormalities were detected on chest x-rays when the patient was re-examined 3 to 5 years after the ACE level was first drawn.[2] For this reason, the level of ACE cannot be used as a predictive marker for future occurrence of the disease.

Complete Blood Count (CBC) – The CBC measures the number and type of red and white blood cells in the blood. This can help doctors diagnose certain disease states and rule out other conditions.

Serum Chemistry – Measures levels of common electrolytes and checks the function of different organs.

Alkaline phosphatase – An enzyme from the liver which can be elevated when sarcoidosis affects the liver.

Other tests of the liver are SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase). These tests together are sometimes referred to as liver function tests for enzymes.

BUN (blood urea nitrogen) and Creatinine – These are blood tests which indicate the health of the kidneys, which can be affected by sarcoidosis.

Calcium – In some patients with sarcoidosis, the level of calcium in the blood can be high. This elevation is caused by increased absorption of calcium, an electrolyte, from food in the intestines or gut. The kidneys also affect the levels of calcium, as well as other electrolytes, in the blood.

Arterial Blood Gas

This test measures the level of oxygen and carbon dioxide in arterial blood. Blood is taken by inserting a needle into an artery, usually at the wrist. The levels of gas in the blood help determine how well the lungs are working to exchange these two gases. In patients whose lungs are damaged from sarcoidosis, the blood oxygen level may be low.

Pulse oximetry

This test helps determine how well the lungs are working by measuring the oxygen saturation of the blood. The patient's oxygen saturation is measured by placing a clip on the patient's finger tip or ear. This test does not provide as much information as an arterial blood gas test, but it is less invasive as does not require a needle puncture.

Urine Sample

A sample of the patient's urine may be sent to the lab for testing. The way the kidneys respond to the calcium in the body can be abnormal in sarcoidosis. Calcium levels can be high in the patient's urine. Sometimes it may be higher than the calcium level found in the blood. If this happens, more calcium than expected can be measured in the urine. Too much calcium in the urine can damage the kidneys and contribute to the development of kidney stones.

Radiographic Studies

Chest Radiograph or X-ray – This a picture of the chest that includes the lungs, heart, large blood vessels and ribs. The x-ray is a good initial test to see if sarcoidosis is present in the lungs or chest. Shadows in lung tissue may be seen on the x-ray if sarcoidosis is present. Swelling of lymph nodes in the middle of the chest can also be seen on this x-ray. If either of these conditions is present, this image can help physicians determine if further testing is necessary and if a biopsy should be done. Examples of chest radiographs showing the different stages of sarcoidosis can be seen in Chapter 12.[3]

Chest CT Scan – CT (Computerized Tomography) Scan – This is a special radiology study that can be performed on any part of the body, including the lung. CT scans provide images that show greater detail than routine x-rays. This study can also be done for the head, the abdomen, specific organs within the abdomen, the spine and bones. The name is based on the fact that pictures viewed by the doctor are computer-generated images. This technology allows physicians to see detailed images of the lungs and other structures in the middle of the chest near the heart, including any swollen lymph nodes.

High Resolution Chest CT Scan (HRCT) – This special study of the chest can provide more detail and detect smaller or less obvious changes in the patient that a routine X-ray. The HRCT scan creates computer-generated images of the structures within the chest. This study helps physicians determine if a biopsy is needed and what type of biopsy may be recommended. It may be done using contrast, a material that makes it easier to distinguish between different tissues or structures in the chest. Because the contrast may be toxic for the kidneys, patients may be instructed to drink large amounts of fluid and/or take the medication N-acetylcysteine before the study.

Note: It is important for any patients who are or might be pregnant to notify their health care provider and whoever is conducting this test of their condition before the test is performed.

Breathing Tests

Pulmonary Function Test – This series of tests measure how much air the lungs can hold (lung volume) and how well the air moves through the airways or breathing tubes (spirometry). It also evaluates how well the lungs work to bring oxygen into the body and remove carbon dioxide (diffusion capacity). These tests require patients to breathe through a mouthpiece. Different types of equipment may be used to perform these tests in either a Pulmonary Function Laboratory or a physician's office. One piece of equipment, called a 'body box' or plethysmograph, may look like a phone booth with a door and a seat inside. (Figure 1)

The results of these tests help form a pattern of information that can tell medical professionals if a patient's lung function has changed. These tests are performed multiple times. The first breathing test is performed when a diagnosis of sarcoidosis is first considered. It is then repeated periodically to determine if the patient's lungs are improving, remaining the same, or deteriorating.

Rest and Exercise Oxygen Test – This test can be performed in a variety of ways. Patients may use a treadmill, a stationary bike or stairs. They may also simply walk on level ground for six minutes. Oxygen saturation levels are measured using a finger or ear sensor. Alternately, the patient's actual oxygen levels may be measured using a blood sample. When a blood sample is taken, it is drawn from an artery (usually at the wrist) using a needle or a catheter. Oxygen saturation of the blood is measured both while the patient is at rest, and again both during and after exercise. This test provides information about how well the lungs are bringing oxygen into the body during exercise. These tests help medical professionals know how well the patient's lungs are functioning and indicate the extent of any damage to the lungs caused by sarcoidosis. This information can then help guide their treatment decisions.

Electrocardiogram or EKG

Sarcoidosis can also affect the heart. Granulomas may develop in heart tissue and interfere with the normal electrical conduction system of the heart. This can cause irregular heartbeats or other abnormalities that can interfere with the normal function of the heart. An EKG is an effective test for evaluating how well the electrical conduction system of the heart is working. This test is performed by applying sensors to the skin on the chest and the extremities. These sensors detect and record signals from the heart. This test tracks the activity of the heart only for a short period of time. For this reason, it might give normal readings even when sarcoidosis is present in a patient's heart. When a physician suspects that sarcoidosis is affecting the heart, other tests, discussed in Chapter 4, may also be performed.

Eye Exam

An eye examination is completed whenever a diagnosis of sarcoidosis has been established in another part of the body. This exam is done even when the patient shows no signs or symptoms of eye involvement. This is because sarcoidosis can affect a patient's eyes, the tissue around the eyes and vision. A sarcoid can be present in a patient's eye but offer no clear sign or symptom that a problem may be developing. To determine if a patient's eyes are involved, an ophthalmologist (an eye specialist), must examine the back of the eyes with a special instrument called a slit lamp. This device shines a high-intensity light beam into the eye to help the

ophthalmologist examine the internal eye structures and diagnose disease. The eye specialist also examines tissue around the eye which can swell because of sarcoidosis. This eye exam must be done when a patient is first diagnosed with sarcoidosis. Because sarcoid in the eye can develop after another organ of the body is involved, patients must have their eyes re-examined after one year. Eye involvement for patients with sarcoidosis is discussed further in Chapter 8.

Biopsies

A biopsy is a small sample of tissue, about the size of a pinhead, taken from an organ for examination. Most biopsies are taken from the skin or a lung. A biopsy sample is placed in a preservative fluid and sent to a pathology laboratory for examination. It may take several days to learn the results of a biopsy exam because the tissue must first be preserved and stained before a specialist can examine it under a microscope. The specialist will look for any abnormalities, including granulomas, and will send a report to the doctor describing any changes in the tissue found in the biopsy and what those changes may represent.[4]

Skin

When a doctor suspects that a patient's rash may be sarcoidosis, he or she will attempt to verify this suspicion by sending a small sample from the skin to a laboratory for study. A skin biopsy procedure can usually be done in a doctor's office. After numbing the patient's skin, the doctor will use special equipment to take a small piece of the skin from the site of the rash or the area where skin changes have occurred. This is often called a "punch biopsy".

Lungs

Bronchoscopy – This procedure allows a physician to examine a patient's airways, also called breathing tubes, and to take biopsies of lung tissue. It is performed using a special device called a bronchoscope. It consists of a flexible narrow tube that is small enough to pass through the nose. This tube contains multiple channels or pathways. These include a light source, like a tiny flashlight. This light makes it possible for medical specialists to see clearly inside the patient's airways. In addition, small instruments attached to wires can be passed within a channel of the bronchoscope into the lung. These instruments can be used to obtain tissue or fluid from the lung for examination in a laboratory. The bronchoscope may also have an eyepiece that allows the physician to see the inside of the airways, or a miniature camera that sends images to a monitor. (Figure 2) After numbing medicine is used in the patient's nose, throat and airways, the bronchoscope is passed through the windpipe (also known as the trachea) to the main airways of the lungs. Samples of tissue from the airway wall and the lung may then be taken. Special x-ray equipment may be used to help the doctor position the bronchoscope in specific areas of the lung to take samples. Two specific procedures that may be performed with a bronchoscope are:

- Transbronchial and/or endobronchial lung biopsy. This is a sampling of lung tissues in the distant airspaces or the airways themselves, and/or
- Transbronchial needle aspiration. This is a sampling of the lymph nodes surrounding the windpipe.

Patients are given oxygen during the bronchoscopy procedure, and are able to breathe around a narrow tube. Medication may be given to the patient that causes drowsiness but not sleep. Bronchoscopy is usually performed as an ambulatory or outpatient procedure. Patients are usually released the same day after first being checked to ensure that the effects of any medications have passed.

Bronchoalveolar Lavage - A bronchoalveolar lavage (BAL) is a diagnostic procedure that can be performed during a bronchoscopy. A small amount of sterile fluid is first washed through the bronchoscope into an area of the lung. It is then suctioned back out through the bronchoscope. This fluid can be examined in the laboratory for signs of infection or inflammation. The BAL procedure also collects cells from the lung which can be studied in special ways to identify both the types of cells found and their functions. Determining the types and number of cells present in the lungs can help physicians make a more accurate diagnosis of sarcoidosis.

Mediastinal lymph nodes in the chest

If a chest x-ray or chest CT scan reveals that the patient's lymph nodes (glands) in the chest are swollen, a biopsy of these lymph nodes may be performed to determine the cause of this swelling. Sarcoidosis is one of several reasons why lymph nodes may be swollen.

A variety of methods can be used to obtain tissue from swollen lymph nodes. These include:

Endoscopic ultrasound-guided fine-needle aspiration: This procedure obtains tissue from a swollen lymph node by using an endoscope in the esophagus (food tube) instead of the airway. The endoscope is a flexible tube with channels in it, similar to the bronchoscope. However, it is used for procedures in the gastrointestinal tract. The scope is passed through the mouth and into the esophagus (the food tube that connects the mouth to the stomach). A needle is passed through the wall of the esophagus into a swollen lymph node. Medical specialists use special radiograph equipment, an ultrasound, to guide the needle to the correct location.[5]

Mediastinoscopy: In some cases, surgery must be performed to reach the lymph node. Once the patient is placed under general anesthesia, the surgeon makes a small incision in the skin at the top of the breast bone. The surgeon uses special equipment to look for and remove the swollen lymph nodes that are behind the breast bone or around the airways and blood vessels of the lung. The surgeon removes only one or two lymph nodes as a part of this procedure. This can all be done through the small incision the surgeon makes. The lymph nodes, though swollen, are still relatively small – less than an inch in diameter. Once removed, the nodes are placed in a preservative fluid for special treatment and staining in the laboratory where they will be studied under a microscope to look for granulomas.

Ultrasound guided transbronchial needle aspiration: For this procedure, a needle is passed through a channel of a bronchoscope and guided through the airway wall into a lymph node located in the middle of the patient's chest. Medical specialists use special radiograph equipment, an ultrasound, to guide the needle to the correct spot. Material from inside an enlarged lymph node can then be drawn through the needle for examination. This procedure offers a way to diagnose sarcoidosis in the lymph nodes without doing the surgical intervention of a mediastinoscopy.[6]

Other organs may also be biopsied as part of a diagnosis procedure when sarcoidosis is suspected. This is done when the physician suspects that the organ may be involved and there is no evidence of either skin or lung involvement. Sometimes, a diagnosis cannot be made with

one type of biopsy and a different test may be recommended. At other times, a firm diagnosis of sarcoidosis cannot be made with a biopsy. In such situations, all available evidence will be collected together and examined as a whole to determine whether enough evidence exists to presume a diagnosis of sarcoidosis.

Kveim reaction - In the 1960s, the Kveim-Siltzbach test was thought to be the best method for diagnosing sarcoidosis of the skin. The test required the injection of a small amount of a prepared liquid into the skin that contained cells from sarcoid tissue. A biopsy of the area of the skin reaction (a nodular skin reaction) that occurred several weeks after the injection would then be studied under the microscope. A positive test would show granulomas of sarcoidosis.

This test was offered as an outpatient technique to establish a diagnosis of sarcoidosis. It required a month before results became available. No medications to treat sarcoidosis (such as prednisone) were used during this waiting period because they could alter the test result. Today, quicker techniques for establishing a diagnosis of sarcoidosis are available. This testing method is therefore no longer used. When therapy for a patient is indicated, it can now begin in a much timelier manner. When the Kveim-Siltzbach test was used, it provided positive results in about 80% of patients with sarcoidosis. Positive reactions in patients without sarcoidosis occurred in less than 1% of those tested.[7]

Resources:

(1) Flexible Bronchoscopy procedure – ACCP website, Patient Education Brochure: http://chestnet.org/downloads/patients/guides/Bronchoscopy.pdf;

(2) Mediastinoscopy: http://www.webmd.com/a-to-z-guides/mediastinoscopy-21507; http://www.health.harvard.edu/diagnostic-tests/mediastinoscopy.htm; http://www.nlm.nih.gov/medlineplus/ency/article/003864.htm#visualContent;

(3) PFTs: http://www.nlm.nih.gov/medlineplus/ency/article/003853.htm; http://www.nhlbi.nih.gov/health/dci/Diseases/lft/lft_whatare.html;

(4) Angiotensin Converting Enzyme: http://www.nlm.nih.gov/medlineplus/ency/article/003567.htm#visualContent

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   - A broad review article which covers many aspects of this disease from epidemiology to treatment, discusses initial diagnostic approach as well.
2. McGrath DS, Froley PJ, Izakovicova-Holla L, et al. ACE gene I/D polymorphism and sarcoidosis pulmonary disease severity. Am J Respir Crit Care Med 2001; 1642:197-201
   - A representative research article of studies done to demonstrate that while the gene for ACE differs, this difference is not associated with the disease manifestation of sarcoidosis and is not a predictive marker.

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   - A review article describing pulmonary and most common extrapulmonary involvement of sarcoidosis. A description of the diagnostic study findings of radiographs and pulmonary physiology studies is provided. The differential diagnosis and initial diagnostic evaluation is discussed as well as treatment.

4. Judson MA, Thompson BW, Rabin DL, et al. The diagnostic pathway to sarcoidosis. Chest 2003; 123(2):406-412

   - A retrospective study assessing the time of first physician visit until the diagnosis of sarcoidosis by biopsy. 189 patients were enrolled. This study demonstrated a delay in diagnosis, particularly in patients with pulmonary symptoms, because the patients' symptoms on presentation were nonspecific and common.

5. Annema JT, Veselic M, Rabe KF. Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Eur Respir J 2005; 25(3):405-409

   - Report of a prospective study utilizing endoscopic fine needle aspiration via the esophagus with ultrasound guidance. 51 consecutive patients with suspected sarcoidosis of stage I or II were included in this study. 71% had a previously non-diagnostic bronchoscopy. This method demonstrated non-caseating granulomas without necrosis in 82% of the patients studied. While some patients went on to require a mediastinoscopy, this study demonstrated that the majority of patients had a diagnosis established without the need for the general anesthesia procedure.

6. Garwood S, Judson MA, Silvestri G, et al. Endobronchial Ultrasound for the Diagnosis of Pulmonary Sarcoidosis. Chest 2007; 132(4): 1298-1304

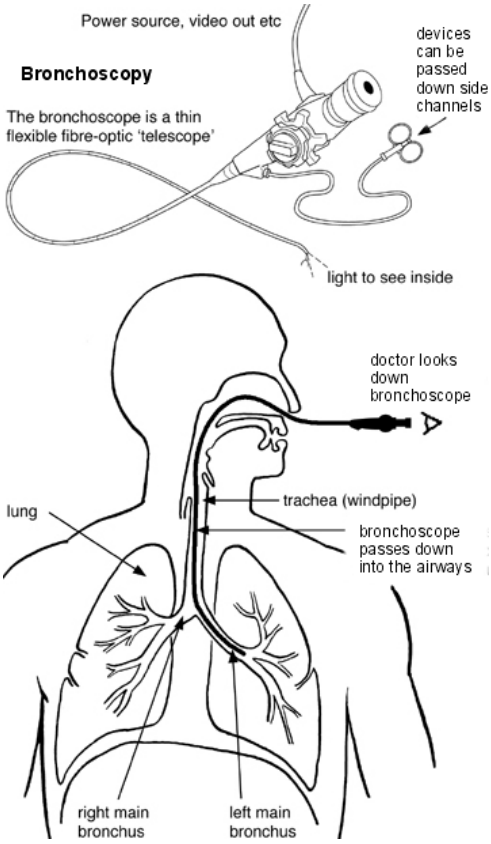
   - 50 consecutive patients with suspected pulmonary sarcoidosis were studied. An 85% sensitivity was found for the patients studied. This bronchoscopic procedure is minimally invasive, and when positive, prevents the need for mediastinoscopy.

7. Moller DR. Potential Etiologic Agents in Sarcoidosis. Proc Am Thorac Soc 2007; 4:465-468

   - A description of the Kveim-Siltzbach reaction as historically developed and clinically used and representation of ongoing studies from this reaction to learn causative or contributing factors in the development of sarcoidosis.

Figure 1: A "body box" or plethysmograph

Figure 2: A Bronchoscope



Introduction

Some tests are very sensitive in detecting changes from sarcoidosis. Others are more specific. Taken together, multiple test results may define a pattern of involvement recognized as consistent with sarcoidosis. The interpretation of some of these tests requires the expertise of physicians who have both a specific knowledge of sarcoidosis as well as experience in evaluating these tests.

This section discusses different tests that may be used to evaluate patients for the presence of sarcoidosis. Not all tests are required or indicated in any given patient. Specific tests are usually ordered to assess concerns about possible disease in specific organs (heart, brain, muscles, bones, etc). Individual tests are described, indications for when a test may be indicated are discussed, and the possible results of tests and their significance are reviewed.

Tests

Echocardiogram

A specific test or series of tests may be requested when a physician suspects that sarcoidosis may be affecting the heart muscle, the heart valves or the electrical circuit that creates impulses for the heart. Such tests may also be performed whenever a patient's electrocardiogram results are abnormal. One of these tests, the echocardiogram, uses sound waves to create a picture of the heart in motion. This picture is much more detailed than an x-ray image and requires no radiation exposure for the patient.

The echocardiogram is performed by a trained technician. The results are then interpreted by a heart doctor. To complete the test, the technician places a tool, known as a probe or transducer (Figure 1), on the ribs near the patient's breast bone. The probe is directed toward the heart. This instrument generates high-frequency sound waves. It also picks up the echoes of those sound waves and transmits them as electrical signals. The echocardiography machine converts those electrical signals into moving pictures of the heart. This test makes it possible for medical professionals to evaluate the valves and chambers of the heart without having to probe inside the body. This type of echocardiogram is known as a transthoracic echo, or TTE. No special preparation for the test is required and no significant risks are associated with this test.

TTE works well for most patients, and allows doctors to see the heart beating and visualize many structures of the heart as they function. Occasionally, the lungs, ribs, or other body tissue may prevent the sound waves and echoes from offering a clear picture of the heart in action. In such cases, a small amount of contrast medium, or agent, is injected into a vein through an intravenous tube. This material enhances visibility inside of the heart. In some circumstances, additional information is required and an echocardiogram can be performed with the probe that is passed through the patient's esophagus. This type of echocardiogram is known as a transesophageal echo or TEE. An echocardiogram can also be performed during a stress test using either exercise or medication to stimulate the heart to work harder. That test is called a stress echo.

These tests may reveal that a patient's heart muscle is weak and not pumping well, that the heart is enlarged or thickened, or that the valves between the chambers of the heart are abnormal. They may also suggest the presence of pulmonary hypertension -- increased pressure in the vessels of the lung. Because these results are not specific for sarcoidosis, the diagnosing physician must consider other possible diseases that may cause similar abnormalities. At the same time, the physician must also keep in mind that a normal echocardiogram does not exclude the possibility of sarcoidosis involvement in the patient's heart.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) uses a powerful magnetic field to create precise images of body organs. This is achieved by using naturally-occurring radio wave signals created by the cells of tissues. The MRI does not involve radiation, and typically requires between 30 to 45 minutes to complete. This test is often performed using gadolinium, a contrast agent, to improve the visibility of internal bodily structures. Gadolinium must be used with care because it can, in rare cases, cause a deterioration of kidney function.

The MRI is easy to perform and can be very informative for both the diagnosis and management of sarcoidosis. Some patients may have difficulty with this test if they are uncomfortable in enclosed spaces (claustrophobic). Medication to help reduce these symptoms may be prescribed. Alternately, an "open MRI" – a test that offers more space between the machine and the patient's body -- may be used if it is available. Because the MRI requires the use of a large and powerful magnet, patients with pacemakers or other metal implants such as cardiac defibrillators or joint replacements may not be able to undergo MRI. (Cardiac stents, surgical clips or wires, and non-metallic cardiac valves are safe.) It is important for all patients to notify their physician of any implants in their body whenever an MRI is being considered.

Heart MRI

MRI is used in a number of different ways for diagnosing and treating sarcoidosis.An MRI of the heart, also known as cardiac magnetic resonance (CMR), is a new technology that is used to detect cardiac sarcoidosis without requiring an invasive heart biopsy. The CMR test uses radio wave signals to create images of the heart muscle, heart valves, and other structures within and around the heart. This provides investigators with information about the appearance of the heart, blood flow through the heart, the condition of the heart tissue and the valves, and overall heart function. Gadolinium may be used with this test as a contrast material. If this agent is used, it is injected into a vein. It is then carried to the heart and the arteries that supply blood to the heart, then into the muscle tissue of the heart itself. If the arteries that feed the heart (also known as coronary arteries) are blocked, this dye will not be able to reach the muscle tissues. Therefore, if less dye is seen in a part of the heart than is expected, this may indicate the presence of narrowed coronary arteries. This is a condition that may lead to chest pain or angina. If the arteries are able to properly feed the heart muscle, it will normally absorb the dye by allowing it to pass freely into the spaces between normal muscle cells. The dye may also be soaked up more intensely in the presence of inflammation or edema (called hyperenhancement). Normally, the dye leaves the muscle cells on its own over time. If the muscle tissue is damaged, the dye will linger in the muscle and MRI images will indicate the existence of an abnormality.If sarcoidosis is present in the patient's heart, CMR imagery may show "hyperenhanced" areas, as well as bright bumps that may represent sarcoid granulomas.[1]

Head and Spine MRI

MRI may also be used to detect neurosarcoidosis. This is a form of sarcoidosis located in the head and spine. Before this MRI is performed, gadolinium dye is injected into a vein. This contrasting agent allows medical specialists to look for bright areas or accumulations of the dye in specific areas within the brain. Other areas examined include the spinal cord, the lining that covers these organs, and other structures in the brain such as the pituitary gland. The test can be repeated and may be used to track a patient's response to treatment.[2] MRI can also be used to detect granulomas from sarcoidosis in the muscles and bones.[3]

Nuclear Medicine Tests:

A variety of nuclear medicine tests may be considered when diagnosing sarcoidosis. All studies in nuclear medicine utilize small amounts of radioactive material. This material is attached to cells, proteins, or simple molecules (for example glucose, a sugar, in PET SCANs) and is then injected through the veins, swallowed, or inhaled depending on the specific study being performed. As the material circulates within the body, the radioactive material emits energy that forms an image when it is detected by a camera outside the body. These tests are simple and painless. The amount of radioactive energy used in these tests is minimal. This means that concerns about any harmful effects of radiation from nuclear medicine tests are unnecessary. The radioactive substances used in these tests are eliminated from the body through the kidneys, liver, and the intestines. As with other chest x-rays and CT scans, it is important for patients who are or might be pregnant to first notify their health care provider and whoever is performing the test.

Some nuclear scanning tests are performed to help measure the activity or degree of involvement of different organs by sarcoidosis or other diseases. The tests are also used to either help diagnose a disease or follow it for changes. In some tests, the blood flow to different tissues can be further assessed by asking the patient to exercise or by administering medicines that mimic exercise. This technique uses procedures similar to those used for a stress echo.

Thallium Stress Test is a nuclear scanning test also known as a myocardial perfusion imaging (MPI) test. It is used to evaluate how well the heart muscle is being supplied (perfused) with blood both at rest and also during activity, such as exercise. It identifies areas of the heart with reduced blood supply due to narrowing of one or more coronary arteries. A radioactive tracer is used to define the heart muscle. Different patterns of tracer distribution at rest and after exercise help distinguish heart involvement due to sarcoidosis from coronary artery disease that causes a lack of blood supply to the heart.When perfusion defects are detected on ^{201}thallium imaging for patients with known systemic sarcoidosis and normal coronary arteries, cardiac involvement of sarcoidosis is strongly suspected. A normal ^{201}thallium scan, however, does not exclude the possible presence of cardiac sarcoidosis. The combined use of ^{201}thallium and ^{67}gallium imaging of the heart increases the likelihood of recognizing cardiac sarcoidosis. . A ^{201}thallium scan can be a complementary tool in the assessment of cardiac sarcoidosis that supplements 24-hour electrocardiographic monitoring and echocardiography.[4] A thallium scan should not be used for screening patients with no cardiac symptoms.

PET Scan. Positron Emission Tomography (PET) scan is a new and frequently ordered nuclear diagnostic test that can be used to evaluate the entire body. A radioactive tracer is attached to a glucose (a sugar) solution and then injected in a vein. The tracer travels through

the body for 30-60 minutes and travels to very active areas (that is, to areas that have tissues with a high need for sugar). A camera outside the body captures an image of these high activity areas. The PET scan is sometimes combined with the common CAT scan to pinpoint particular areas of the lungs and other structures in the chest cavity that can be affected by sarcoidosis, including the heart. The PET scan is a very sensitive test for detecting areas of high activity. However, it is not specific for sarcoidosis, like many other tests. PET Scans can be useful tools in diagnosing sarcoidosis and locating other areas of the body that may be affected by the disease. If needed, they can also be used to evaluate a patient's responses to treatment.[5]

Before the PET scan is administered, a patient is given instructions about diet before the test and whether certain medications should be discontinued. Special planning may be needed to prepare diabetic patients for this test. The complete nuclear imaging test may last up to 4 hours.

Gallium Scan The gallium scan is one of the oldest and most frequently used nuclear tests in the diagnosis and treatment of sarcoidosis. Gallium builds up in metabolically active tissues such as the liver, spleen, lacrimal glands (the glands responsible for tears), salivary glands and the intestines. Patterns detected during a gallium scan may support a diagnosis of sarcoidosis and reflect the degree of activity for the disease. Normal lungs do not pick up gallium. If inflammation is present, gallium will be detected in the lymph nodes located in the middle of the chest or in the lungs.[4]

The tracer injection is performed on the first day and images (scanning) are taken 48 to 72 hours later. The entire body is scanned by a camera and sites of inflammation that are not otherwise apparent may be uncovered. This can be especially important when seeking a possible site for biopsy. A gallium scan that yields normal results does not necessarily exclude a diagnosis of sarcoidosis, nor does a positive result necessarily confirm a diagnosis of the disease. It is best used for patients who are experiencing diagnostic difficulties or when a diagnosis may be facilitated by identifying a biopsy site.

Other Tests

Heart

The most commonly performed heart test is the electrocardiogram. (See the discussion of this test in the previous chapter.) The EKG tracks the activity of the heart during a short time period and may yield normal results even when sarcoidosis is present in the heart.

Holter Monitoring: In some cases, a test that monitors and records heart rhythm over an extended period of time (24-48 hours) may be needed. Sensors are attached to the patient who then wears a recording device for a specified period of time. Symptoms are documented by the patient in a diary. Those symptoms are then correlated with the findings recorded by the monitor. If significant abnormalities in the patient's heart rhythm are detected, appropriate treatment can be initiated.

Electrophysiology (EP) Study: Some patients who have irregular heartbeats, or arrhythmias, require direct stimulation of the heart to determine the cause or site of origin of the arrhythmia, and to determine the best treatment for this condition. The EP test is performed by placing catheters into the heart through blood vessels in the groin. These catheters sense the electrical activity of the heart and detect any abnormalities. The heart's pulse rate may be

increased by a pacemaker to help uncover any abnormality in the rhythm. Treatment of such an abnormality may require medication, placement of a pacemaker or defibrillator, or the even the destruction of an abnormal pathway. For patients with sarcoidosis, this test can be very helpful in predicting possible risk for development of a potentially life-threatening irregular heart rhythm that will require urgent and specific treatment.[6]

Cardiac Catheterization: When evaluating sarcoidosis -- or managing certain associated problems such as pulmonary hypertension or coronary artery disease -- it may become necessary to perform a more accurate yet more invasive test called cardiac catheterization. This test of heart structures and function is used to study either the left or right side of the heart, or both sides simultaneously. The test is performed by first making a small puncture in a blood vessel in the groin, the inner bend of the elbow, the wrist, or the neck area. The physician then inserts a guiding instrument into the incision and threads it through the vessel into the area of the heart that requires evaluation. A contrast agent may also be administered during the procedure. Pressures within the heart are then measured. The patient may be asked to exercise during this test, or may be given medications that mimic the stress of exercise on the heart. This allows the physicians to obtain more helpful information or to answer specific diagnostic or treatment questions about the patient's condition. After the necessary test procedures are complete, the catheter is removed. If testing instrument was inserted into the patient's femoral artery, bed rest for several hours will probably be recommended to prevent bleeding.

Complications of this procedure are infrequent. However, when they occur, they may include arrhythmias (irregular heart rhythms), damage to the blood vessel, bleeding and, on rare occasions, death. The information gained from this test may be invaluable in determining the best and most appropriate treatment for a patient. A decision to perform a catheterization test is made only after considering all the possible risks to the patient when balanced against the benefits of the gaining the information that the test can provide.

Other: Other tests that are not specific for sarcoidosis but may be requested to evaluate problems that could complicate this disease include the following:

Bone densitometry or Dexa Scan: Bone density testing is an important technique for assessing the strength and mineral density of bones. Many factors, including aging, menopause and certain medications, particularly corticosteroids (prednisone), may cause bones to become thin and at risk for breaking (fracture). The bone densitometry test, known as a bone mineral density scan (BMD) or as the dual energy x-ray absorptiometry (DEXA) scan, is a quick diagnostic procedure that takes just a few minutes. This test does not require administering radioactive contrast material into the bloodstream and it can be done with devices that measure bone density in the hip and the spine. This test can be performed in a hospital, a doctor's office or in certain special facilities. Also, the DEXA scan requires a much smaller radiation exposure than a standard chest x-ray. No preparation is required for this test.

Sleep study: Complaints of snoring, restless sleep, early awakening, frequent nightmares, early morning headaches, increased sleepiness during the day or extreme fatigue may indicate disturbed sleeping patterns.A sleep study is a diagnostic test that monitors the body's activity during sleep. It involves spending the night in the sleep laboratory of a hospital or special facility. Equipment is used during this study to detect air flow, chest wall and abdominal movement, heart rhythm, and brain waves. In addition, the patient's oxygen and carbon dioxide levels in the blood along with the rate and rhythm of the patient's breathing are also tracked. Once the patient is asleep, activity is recorded and later analyzed to identify any sleep abnormalities. Sleep

specialists look for a variety of sleep disturbance patterns in these test results. Such abnormalities may include sleep apnea (interruption of breathing for 10 seconds or longer). Sleep apnea may be obstructive (blockage to airflow) or central (absence of brain signal to the respiratory system to breathe). Other problems may include insomnia (inability to fall or stay asleep); narcolepsy (inability to stay awake); or abnormal limb movement that may disturb sleep. For some sleep disturbances, it may be necessary for the patient to return to the sleep laboratory for additional testing. This testing will determine the treatment that would be most effective in reducing or eliminating the sleep disturbance. Sleep disturbances are very common and can be seen accompanying many illnesses. Sarcoidosis in and of itself does not predispose an individual to sleep problems. However, sleep problems may aggravate the symptoms of sarcoidosis, and addressing them can improve the general health and well being of the patient.

Resources:

For more specific information on the specific test and procedure:

Internet Site: Gallium http://www.webmd.com/a-to-z-guides/gallium-scan

Internet Site: PET http://www.radiologyinfo.org/en/info.cfm?pg=PET&bhcp=1#part_one

References:

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   - In this article, 106 patients with sarcoidosis underwent cardiac MRI and a battery of other cardiac tests to exclude diseases that may confound the pictures obtained by MRI. Utilizing various properties of MRI, with and without contrast, researchers were able to identify patterns seen in various stages of sarcoidosis and evaluate the effect of steroids in some patients who had repeated studies. Images of cardiac involvement are present with descriptive findings.
2. Spencer TS, Campellone JV, Maldonado I, Huang N, Usmani Q, Reginato AJ. Clinical and magnetic resonance imaging manifestations of neurosarcoidosis. Semin Arthritis Rheum 2005; 34(4):649-61
   - In this article, the authors describe clinical and MRI findings in 21 patients with neurosarcoidosis. Findings on magnetic resonance imaging (MRI) included mass lesions, diffuse intraparenchymal inflammatory lesions in the brain and spinal cord, leptomeningeal enhancement, hydrocephalus, and intracranial hemorrhage. They concluded that MRI findings and exclusion of other disorders can support the diagnosis of sarcoidosis when a biopsy is not possible. They provide images of the various manifestations of neurosarcoidosis on MRIs.
3. Moore SL, Teirstein AE. Musculoskeletal sarcoidosis: spectrum of appearances at MR imaging. Radiographic 2003; 23(6):1389-99
   - This article reviewed the many findings on MRI of the muscles and bones in patients with sarcoidosis and cautioned about the importance of these findings in order to avoid the mistake of calling them bony spread of cancer. Cases are presented that illustrate the findings.

4. Mañá J. Nuclear imaging. ^{67}Gallium, ^{201}thallium, 18F-labeled fluoro-2-deoxy-D-glucose positron emission tomography. Clin Chest Med1997;18(4):799-811

   - This article reviewed patterns seen in Gallium scans and Thallium scanning which are suggestive or typical of sarcoidosis. At the time of this review, minimal experience was available on PET scanning and sarcoidosis.

5. Teirstein AS, Machac J, Almeida O, Lu P, Padilla ML, Iannuzzi MC. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. Chest 2007; 132(6):1949-53. Epub 2007 Oct 9

   - In this study 137 patients with proven sarcoidosis underwent 188 PET scans. One hundred thirty-nine whole-body scans had positive findings. Eleven repeat scans exhibited decreased activity with corticosteroid therapy. In some patients the activity was detected in areas of the body where sarcoidosis was not suspected (occult disease). The authors concluded that PET scans are of value in identifying occult and reversible granulomas in patients with sarcoidosis.

6. Aizer A, Stern EH, Gomes JA, Teirstein AS, Eckart RE, Mehta D. Usefulness of programmed ventricular stimulation in predicting future arrhythmic events in patients with cardiac sarcoidosis. Am J Cardiol 2005; 96(2):276-82

   - This article reviews the utility of stimulating the ventricles to predict future arrhythmic events in patients with cardiac sarcoidosis and the benefit of placing cardioverter-defibrillators (ICDs) in patients with cardiac sarcoidosis. Thirty-two patients with cardiac sarcoidosis were studied and those in whom abnormal rhythms of the heart were detected, had placement of a defibrillator. The authors concluded that the testing appropriately identified patients at high risk of death and the appropriateness of defibrillators in preventing life-threatening rhythms.

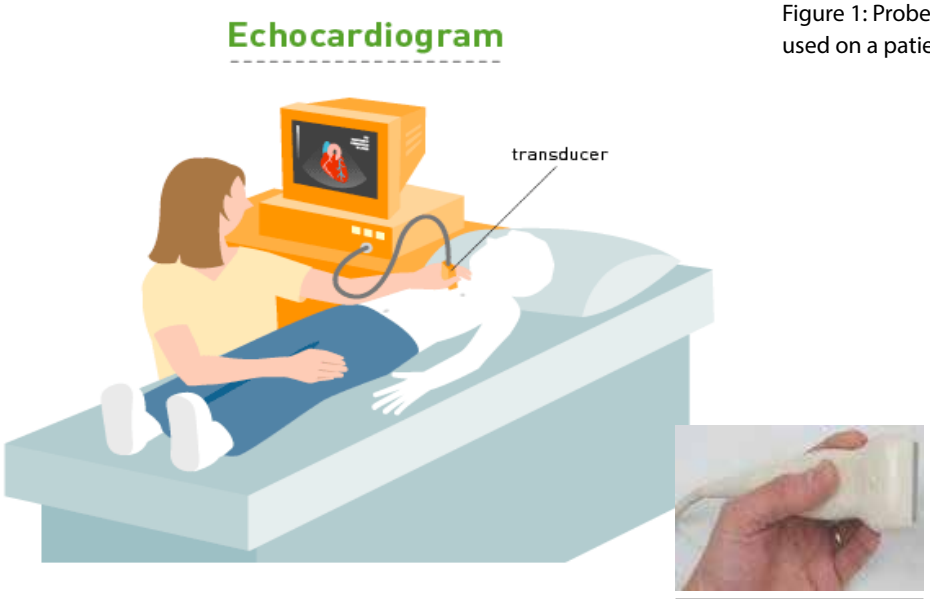

Figure 1: Probe: alone and being used on a patient

Once a diagnosis of sarcoidosis is made, the extent of disease involvement in the body must be determined. Physicians complete this process by collecting information on the organs involved and the severity of the involvement. Once this is known, a discussion can take place about whether treatment is necessary and what therapies should be used.

This chapter will discuss some of the more common medications used for treating sarcoidosis. There is no single, specific medication that can "cure" sarcoidosis. Medications and other therapies are used to control symptoms related to the disease and to prevent progressive loss of function in whatever organs are involved. Often, sarcoid may return after medications are stopped. A physician's decision about what medication or combination of medications to prescribe, the duration of treatment, and what tests will be needed as follow- up are specific to the individual. These decisions are also determined by the type and severity of sarcoid, the patient's other health conditions, his or her reaction to medications, and clinical response.[1,2]

Many patients with sarcoidosis show no symptoms, or their symptoms are mild and either stay the same or go away over time. Those patients do not require treatment with medications. Treatment may be deemed necessary by a physician when vital organs such as the heart, brain, or eye are involved, or there is evidence of disease of the lung or other organ that is worsening over time. When treatment with medication is necessary, prednisone, a corticosteroid, is the most common drug prescribed.[3]

Whenever possible, medication used to treat sarcoidosis is given locally. For example, drops may be prescribed for the eye or topical ointments for the skin.Injection of medications may also be given directly into skin lesions or the eye. When the patient receives medication either by swallowing or intravenously, this is known as systemic therapy. In such circumstances, the medication circulates through the entire body or system until it reaches its target.

For a variety of reasons, alternatives to prednisone may be recommended. Some of the more common reasons for seeking an alternative may include the patient's inability to take prednisone due to other health conditions; intolerable side effects; or progression of sarcoidosis despite an adequate trial of prednisone. Adding a drug to therapy with prednisone may be used in an effort to decrease the dosage of prednisone (this process is known as steroid sparing). Adding a medication may also be recommended when the disease is progressing despite the use of prednisone.[4]

The various types of medications used to treat sarcoidosis are chosen based on how they work against inflammation and/or how they suppress the immune system.[4] The exact mechanism for how some medications work to treat sarcoidosis is not completely understood. The following information describes some of the different categories of these medications. All of these categories, with the exception of non-steroid anti-inflammatory drugs, have some immunosuppressive effects.

Anti-inflammatory drugs

This category of medications includes both steroids and non-steroid anti-inflammatory medications. Non-steroidals can reduce the pain and inflammation of joint or muscle pain caused by sarcoid as well as other issues. Steroids may also be called corticosteroids, cortisone, prednisone, or methylprednisolone. This group of medications can be provided in several forms including injections, eye drops and skin creams. It can also be administered systemically by mouth or by injection into a blood vessel or muscle. Steroids decrease inflammation and the activity of the body's immune system by suppressing the movement of inflammatory cells. They also block the release of various chemicals from the inflammatory cells that would lead to additional inflammation and the formation of granulomas.

Inflammation is a process the body uses to protect itself against infections and foreign substances. When inflammation works against the body's own tissues and causes damage, as with sarcoidosis, steroids are sometimes used to reduce the body's production of inflammatory chemicals. Some possible side effects from steroids include the suppression of the body's ability to fight infection and foreign materials. This is called the immunosuppressive effect. To balance the benefits and the risks of using steroidal medication, physicians attempt to use the smallest amount of steroids needed to suppress unwanted inflammation. Many other side effects can occur from steroids as well. Some of these are listed in the table below. Not all patients treated with these medications develop side effects.

Antimetabolite drugs

Antimetabolite drugs interfere with the normal metabolism, or function, of an organism. Many different antimetabolite drugs, including antibiotics and anticancer drugs, are available. Methotrexate is an antimetabolite drug that is commonly used to treat sarcoidosis. This medication suppresses the function of certain cells involved in sarcoidosis and the formation of granuloma. It has immunosuppressive and anti-inflammatory properties which are thought to be caused by the blockage of lymphocyte multiplication. Methotrexate also inhibits neutrophil function by stimulating adenosine release from fibroblasts and endothelial cells (connective tissue cells). This drug collects inside the cell and interferes with both cell metabolism and its ability to reproduce and create more cells. Methotrexate also reduces the speed in which skin cells multiply. This medication is classified as a folate antagonist or antifolate, a group of drugs that impair the action of an essential B vitamin, folic acid, in cellular function.

Alkylating agents

Alkylating agents are a group of medications that can alter (alkylate) the function of different molecules that are important to certain processes within the body. One example is Chlorambucil. This drug is used to treat certain types of cancer by slowing or stopping the growth of cancer cells. It does this by binding to the cell's DNA so it cannot replicate or reproduce. This drug can also be used to treat sarcoidosis because it suppresses the immune system. It does this by attaching to the DNA of lymphocytes, an active cell in sarcoidosis.

Cytotoxic drugs

A cytotoxic drug is any drug that is toxic to cells. Cytotoxic drugs work by targeting and damaging cells that grow at a rapid rate and so have a greater impact on cells that are dividing, or replicating, quickly. One such medication used occasionally to treat sarcoidosis is cyclophosphamide. This drug slows or prevents the division of cells by changing their DNA, and is

toxic to cells as they try to grow. Cyclophosphamide can be beneficial by suppressing the cells involved in an immune or inflammatory response.

Immunosuppressive drugs

While medications listed in other categories work by suppressing the immune system, the medications in this group differ in the specific way they act. These drugs are often used together with corticosteroids or other medications. Many drugs in this category may also be used in patients who have received organ transplants. They can be helpful in preventing rejection of a transplanted organ by the immune system of the patient's body which might otherwise see the new organ as something foreign. Azathioprine is an immunosuppressive drug that is occasionally used in the treatment of sarcoidosis. This medication weakens the immune system by suppressing the formation of antibodies as well as cell activity of the immune system (lymphocytes). It does this by interfering with the synthesis of DNA and RNA as well as the process by which cells divide to create new cells. Another immunosuppressive drug, mycophenolate mofetil, inhibits inflammatory responses. It has an effect on lymphocytes, a cell involved in both the body's immune response and in sarcoidosis. This medication decreases the inflammatory response in the body by preventing cells from migrating out of the blood vessels.

Monoclonal Antibodies

Monoclonal antibodies are so named because they were developed from a group of cells cloned from a single cell. Infliximab is an artificial (that is, manufactured) antibody that functions by attaching to a chemical messenger in the body called tumor necrosis factor alpha, and then blocking it.[5] Tumor necrosis factor alpha (TNF-alpha) is a messenger chemical called a cytokine that plays a part in the body's immune response. Infliximab may also contribute to the destruction of activated T-lymphocytes, a cell type that plays a significant role in inflammation. This may help explain why infliximab has been found useful in treating certain diseases such as Crohn's disease and sarcoidosis when other TNF-alpha blocking drugs have not.

Antimalarial drugs

Chloroquine and hydroxychloroquine are medications used to treat malaria, a specific type of infectious disease. These medications also have properties that help fight inflammation in the body. It is thought that this category of drugs works to inhibit the early stages of granuloma development.

Immunomodulatory Drugs

Thalidomide is an example of a drug that belongs to the class of medications known as immunomodulatory drugs. This drug has anti-inflammatory properties. It was developed in the 1950s but then withdrawn when it was linked to serious birth defects. More recently it has been found to have immune-modifying capabilities. It reduces the activity of inflammatory cytokine tumor necrosis factor (TNF)-alpha by accelerating the degradation of its messenger RNA. Thalidomide inhibits activation of an intracellular enzyme by mediators of inflammation. It has been successfully used to treat dermatology disorders such as erythema nodosum leprosum. Thalidomide is seen as a promising agent for treating patients with sarcoidosis because it reduces granulomatous inflammation by suppressing the activation of a particular enzyme. It also interferes with the proliferation and differentiation of monocytes.

The following table summarizes the more common medications used to treat sarcoidosis[6]:

Medication Name	Category of Drug	Route	Used for	Frequency	Unwanted Effects
Prednisone Prednisolone	Corticosteroid Anti-inflammatory effects	Oral Inhaled Topical Eye drops Intravenous	Chronic, progressing lung Uveitis Neurologic (Brain & Nerves) Cardiac Kidney Hypercalcemia not responding to other treatment	Varies; usually daily	Diabetes, high blood pressure, stomach irritation (gastritis), water retention, weight gain, mood changes, cataracts, infections, acne, osteoporosis
Methotrexate	Anti-metabolite Immunosuppressive and anti-inflammatory effects	Oral Intravenous	Lung Skin Eye Neurologic(Brain & Nerves)	Once a week	Low blood cell count, liver toxicity, skin ulcers, mucous membrane (such as mouth) ulcers, kidney toxicity, loss of hair, skin sensitivity to sun, rash, cough, lung fibrosis, loss of appetite, nausea, vomiting
Chlorambucil	Alkylating agent Immunosuppressive effects	Oral	Progressive disease for steroid sparing effect	Daily	Low blood cell count, nausea, vomiting, liver toxicity, skin inflammation, infertility, cancer
Chloroquine	Antimalarial agent Anti-inflammatory effects	Oral	Lung Hypercalcuria (Kidneys & Calcium) Skin	Daily	Eye damage (retina), blindness, muscle damage
Hydroxychloroquine	Antimalarial agent Anti-inflammatory effects	Oral	Lung Hypercalciuria(Kidneys & Calcium) Skin	Daily	Low blood cell count, eye damage
Azathioprine	Immunosuppressive agent	Oral		Daily	Liver damage, low white blood cell count, nausea,
Cyclophosphamide	Cytotoxic agent	Oral Intravenous	Neurologic(Brain & Nerves)	Daily	Low white blood cell count, bladder cancer, nausea, infections, hemorrhagic cystitis
Infliximab	Blocks Tumor Necrosis Factor (TNF)-alpha	Intravenous	Neurologic(Brain & Nerves) Chronic lung disease Retinal disease Cardiac Skin	Once every few weeks on a set schedule	Infections, cancer, heart failure, neurologic injury(disturbance of the myelin sheath, multiple sclerosis, optic neuritis, Guillain-Barre syndrome), allergic reaction
Mycophenolate mofetil	Immunosuppressive agent Anti-inflammatory effects	Oral	Skin Renal	Daily	Low blood cell count, liver damage, nausea
Thalidomide	Immunomodulatory drug Anti-inflammatory agent	Oral	Skin	Daily	Low white blood cell count, drowsiness, seizures in those prone to have seizures, birth defects in children, blood clots, nerve damage, allergic reaction

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Sarcoidosis is recognized worldwide as a relatively common multisystem disease with no known cause. While knowledge of a specific cause for sarcoidosis remains elusive, a general understanding of the development of the disease, as well as the way in which the disease shows itself, has emerged. The origins of sarcoidosis are thought to be related to a complex interaction of an individual's 'internal' and 'external' environments. A patient's internal environment is affected by genetics. Genetics, the study of heredity, deals with similarities and differences of related organisms that result from the interaction of genes and the environment. An individual who is genetically predisposed to sarcoidosis may develop the disease if he or she is exposed to a specific stimulus in the environment. That exposure may also affect how the disease appears (that is, the signs and symptoms of the disease manifest themselves, as well as which organs in the person are affected). The specific genetics of an individual patient can also influence whether the disease will be a short-term illness that resolves itself or becomes a chronic and progressive disease.

While a genetic contribution to sarcoidosis is well accepted, the disease is considered 'complex,' with no known mechanism of genetic transmission. This process likely involves the interaction of multiple genes.[1] Genes, the basic physical unit of heredity, are made up of a sequence of nucleotides arranged on a segment of DNA. Genes provide the 'code' for production of materials that lead to the expression of hereditary characteristics.

Sources for a possible genetic contribution to sarcoidosis come from many different areas. These include family clusters (multiple family members with the disease) and different observed patterns in the development, presentation and prognosis of the disease in different ethnic groups. In addition, investigators have studied specific genes suspected of having a role in sarcoidosis (so-called "candidate genes"). They have also performed genome-wide scans to identify specific sites on a chromosome that may contribute to the formation of the disease.[2] While genetics certainly has a role in the development of sarcoidosis, it is important to emphasize that the risk of contracting this disease to family members of an individual diagnosed with sarcoidosis is relatively small.[3]

Genetic Markers and HLA Genes

Human leukocyte antigen (HLA) are proteins — or markers — found on most cells in the body. The immune system uses these markers to differentiate between cells that do and do not belong in the body. Genes are responsible for determining which HLA proteins an individual expresses. For example, if exposure to a specific agent is thought of as the "key" to starting the disease, then certain components of the immune system may be considered the "locks." A significant portion of the "lock" is believed to be HLA (Human leukocyte antigen) molecules. Individuals have different combinations of these HLA molecules based on their genetic makeup. HLA molecules are important factors in destroying substances such as bacteria, viruses, particulate matter and other substances that are foreign to the body.

This issue is further complicated by the fact that the exposure "key" must fit into a second lock (a receptor) which is attached to a white blood cell called a "T-lymphocyte." Researchers believe that if the exposure agent (the key) fits into the HLA molecule and the T-lymphocyte, various chemicals will be released that will cause white blood cells to leave the bloodstream and form granulomas.[4] Sarcoidosis is associated with certain HLA molecules and with certain T-lymphocyte receptors. However, these associations explain only a small percentage of sarcoidosis cases.

From Candidate Gene Studies to Genome Scanning

The study of a possible genetic explanation for the development and progression of sarcoidosis has been an active area of medical research in recent years. The HLA genes, along with certain non-HLA candidate genes, have been the most extensively studied. Occasionally, an association is found in one group of subjects that is not found in others. This is at least in part because different alleles (that is, the two versions of each gene -- one inherited from each parent) that code for a specific gene are more frequently present in certain populations. One technique used to help overcome this population association is to study the families (parents and siblings) of patients with sarcoidosis. Studying a family group offers a specific advantage in this research in that parent alleles can be studied to identify differences in the alleles inherited by both the affected family members as well as those not affected by sarcoidosis. More recently, genome-wide scans that use linkage signals have identified certain areas of interest on different chromosomes. However, additional studies will be needed to further define what role they may have in the genetics of sarcoidosis.

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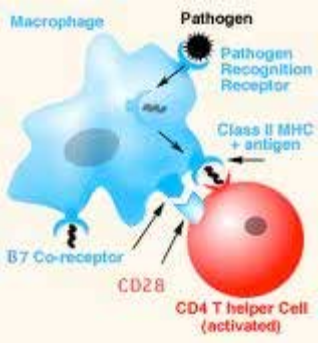

Figure 1: Diagram illustrating the lock and key arrangement between the cell receptors and antigens

Introduction

The brain and spinal cord (central nervous system, or CNS) and the other nerves of the body (peripheral nervous system, or PNS) may be affected in up to 10-15% of patients with sarcoidosis.[1] Symptoms may vary widely, depending on the nerves involved. CNS sarcoidosis is considered a potentially life-threatening form of the disease that should be treated aggressively with medications. PNS sarcoidosis is often not as severe as CNS sarcoidosis. However, it still usually requires therapy. CNS and/or PNS involvement with sarcoidosis rarely occurs without other organs being affected.[1]

Diagnosis of CNS sarcoidosis often relies on radiology imaging studies. These may include magnetic resonance imaging (MRI) or computed tomography (CT) scans of the brain or spinal cord. PNS involvement can be diagnosed by physical examination but it is usually confirmed with special nerve function tests. A tissue biopsy is rarely required to diagnose CNS or PNS sarcoidosis. Diagnostic tests for CNS or PNS sarcoidosis are discussed below.

Therapy for CNS sarcoidosis usually requires the use of corticosteroids together with other immunosuppressive medications.[2] In many cases, therapy must continue for the life of the patient.[1,2] For PNS sarcoidosis, lifelong therapy may not be necessary. However, prolonged treatment over many years may be required. Also, the management of patients with CNS or PNS sarcoidosis may require the assistance of a neurologist or neurosurgeon together with a specialist in sarcoidosis.

Symptoms

The symptoms of CNS sarcoidosis experienced by patients depend entirely on the location of the disease.[1] In some cases, symptoms of CNS sarcoidosis are similar to those of a brain tumor. A patient may experience seizures or a fluid buildup in the brain. In other cases, symptoms may result from hormonal imbalances caused by sarcoid involvement of the pituitary gland or the hypothalamus (structures in the brain that produce hormones and regulate many organ systems of the body). When nerves controlling the senses of sight, smell, or hearing are involved, patients may experience such symptoms as loss of vision, loss of the sense of smell or hearing difficulties. Involvement of the spinal cord may produce various signs or symptoms in patients depending on which areas of the spinal cord are affected. The signs and symptoms of PNS sarcoidosis vary widely. They may include single or multiple limb weakness, numbness or tingling along the distribution of a nerve, or a burning or painful sensation.

Diagnosis

A diagnosis of sarcoidosis involving the CNS or PNS often relies on a prior diagnosis of sarcoidosis, usually diagnosed elsewhere in the body, together with the appearance of symptoms compatible with neurologic sarcoidosis. The results of radiographic tests or functional studies that support the diagnosis would also be considered when making this assessment.[2] A lumbar puncture (spinal tap) may be performed to help confirm the diagnosis. This procedure is

usually performed in the outpatient clinic. To perform a lumbar puncture, a small area of skin over the spine (backbone) is cleaned and injected with a numbing medication. Once the area is made numb, a small needle is inserted into the fluid-filled space around the spinal cord and up to 10-15 milliliters of spinal fluid (equivalent to about one tablespoon) is removed and tested. In rare cases, a brain, spinal cord, or nerve biopsy may be performed by a neurosurgeon to establish a diagnosis with greater certainty.

An MRI of the affected region (brain, spine, etc) may also be performed both before and after the intravenous administration of a contrast dye called gadolinium. These imaging scans are very valuable as tools for evaluating areas of inflammation in the nervous system. They cannot, however, be performed on patients who have any metal implants in their bodies.

For patients who cannot undergo an MRI, a CT scan of the brain that uses an intravenous contrast dye may be performed. While this test is not as sensitive as an MRI, it may be able to identify certain abnormalities. These can include fluid buildup in the brain (hydrocephalus) or a mass caused by the sarcoidosis. Both MRI and CT scans can be used not only for diagnosing CNS involvement of sarcoidosis, but also for monitoring a patient's responses to medical therapy. Additional information about radiographic studies can be found in Chapter 3.

PNS involvement of sarcoidosis can be difficult to diagnose. Symptoms may be non-specific or they may be explainable for other reasons. For example, they may be caused by an injury or another disease, such as diabetes. Similarly, symptoms such as numbness, tingling, burning, or weakness in one location in a patient with sarcoidosis does not necessarily mean that sarcoidosis is the cause of the symptom. To help determine if peripheral nerves are involved with sarcoidosis, a nerve conduction study may be requested. This study measures the ability of nerves to transmit electrical impulses. Alternatively, a peripheral nerve biopsy may be performed. This procedure may reveal the classic sarcoidosis lesion, the non-caseating granuloma.

Treatment Options

Treatment of CNS sarcoidosis almost always requires medicinal therapy. This is provided in the form of pills or intravenous infusions, and often requires the use of two or more medications simultaneously.[3] Medications may include corticosteroids (prednisone), other immunosuppressants (methotrexate, azathioprine) and/or antimalarials (hydroxychloroquine). MRI or CT studies may be repeated to monitor the patient's progress and evaluate his or her response to therapy. If the disease goes into remission, medication may be reduced to minimize side effects. If the symptoms recur, however, therapy may be restarted. Treatment of PNS sarcoidosis also typically requires medications in tablet form, and may continue for an extended period. Evaluation of symptoms is routinely done to evaluate the patient's response to treatment. Repeated nerve conduction studies or other testing may also be necessary for a thorough evaluation of the patient's progress.[3]

Response to therapy for patients diagnosed with CNS and PNS sarcoidosis is very variable. That therapy usually must be continued for many years and perhaps for the patient's lifetime. Additional information about medications that may be used to treat neurosarcoidosis can be found in Chapter 5.

Resources

A good patient-centered overview of the diagnosis, treatment, and prognosis of sarcoidosis can be found at: http://www.thoracic.org/sections/education/patient-education/patient-information-series/index.cfm

A good website offering patient-centered support and information can be found at: http://www.stopsarcoidosis.org/

The National Heart, Lung, and Blood Institute of the National Institutes of Health website on sarcoidosis can be found at: http://www.nhlbi.nih.gov/health/dci/Diseases/sarc/sar_whatis.html

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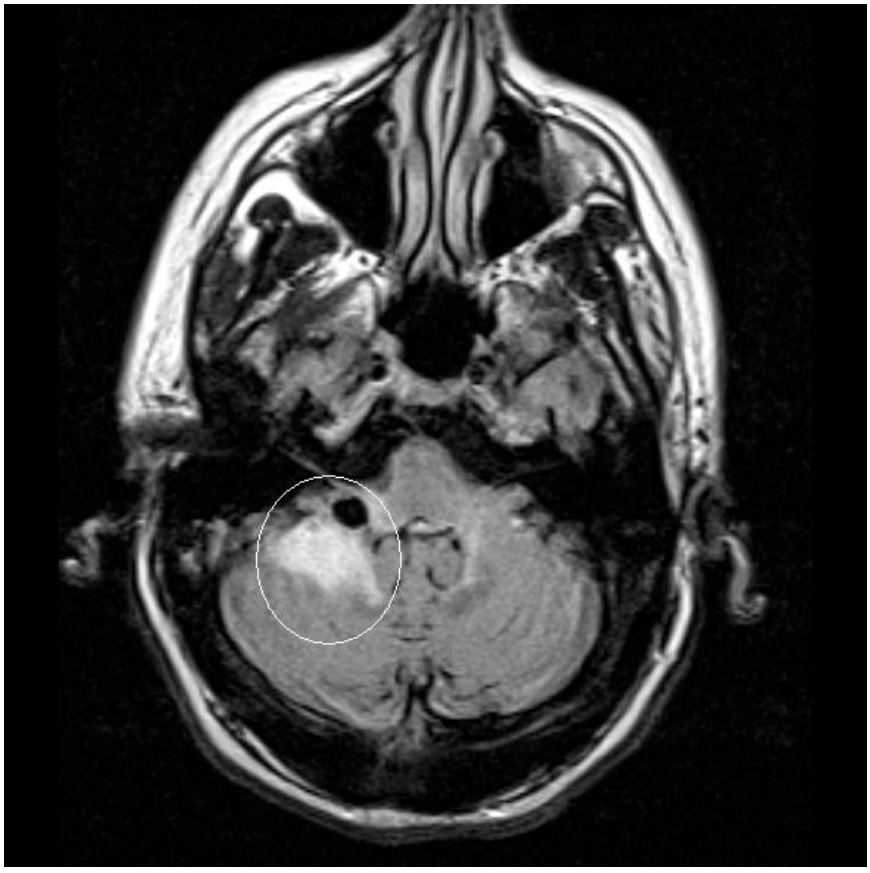

Figure 1: An MRI scan showing enhancement (lighting up when intravenous gadolinium contrast is administered) of a cerebellar brain sarcoidosis lesion (inside white circle). (from M. Judson)

Introduction

Sarcoidosis commonly affects the eyes. Approximately one patient of every five, or 20% of those diagnosed with sarcoidosis, has eye involvement. The likelihood of eye involvement varies significantly depending on the race and genetic background of the patients. For example, ocular sarcoidosis is more common in Japanese patients then in patients from Finland.

Sarcoidosis of the Eye

Uveitis.

The uvea is the middle layer of the eye. It is made up of three parts: the iris, the ciliary body and the choroid (Fig. 1). Inflammation can occur in any or all of these areas. When all parts of the uvea are involved, this condition is called uveitis. Inflammation of the iris alone is called iritis. Ciliary body inflammation is called cyclitis, while choroid inflammation is called choroiditis.[1,2]

Acute uveitis (inflammation of iris, ciliary body and choroid) presents suddenly with redness and watering of the eyes, cloudy vision, and photophobia (light sensitivity). Both eyes are affected. This condition typically affects patients between 20-35 years in age. An examination of these patients show redness around the cornea of the eye (ciliary congestion) and irregularly shaped pupils. Keratic precipitates (KPs), sometimes called 'mutton fat,' are nodular lesions made up of inflammatory cells in the anterior chamber of the eye – that is, the area between iris and cornea. Choroidal nodules are infrequent. The aqueous humor (watery fluid that fills the front of the eye between the lens and cornea) may become muddy. Nodules on the iris (the colored part of the eye) may also be present. Patients diagnosed with acute uveitis have a good prognosis and the condition often clears spontaneously. Acute uveitis usually responds well to corticosteroid eye drops and treatment rarely requires systemic steroids.

Chronic uveitis develops slowly. It may lead to adhesions between the iris and the lens, glaucoma, cataract formation or blindness. Ciliary congestion, or redness around the cornea, is absent. The patient usually complains of pain and blurred vision. This condition can be associated with other features of sarcoidosis including skin involvement, scarring of the lungs, and bone cysts. Chronic uveitis requires aggressive treatment, but the eye involvement may not respond to it. As noted earlier, this condition can progress to adhesions, glaucoma and cataracts.[3]

Intermediate uveitis is an inflammation of the vitreous and peripheral retina. An accumulation of inflammatory cells develops in the vitreous (space between lens and retina). Intermediate uveitis is not specific for sarcoidosis and may also occur in other conditions.

Posterior uveitis (choroidoretinitis) is much more common than is generally realized because it may be difficult to diagnose if anterior uveitis is also present. Evidence of posterior uveitis can be found in about two-thirds of patients diagnosed with ocular sarcoidosis. Examination of the fundi (the back part of the eye) may reveal choroiditis. White, waxy nodules may

be the only visible feature. Posterior uveitis requires treatment with systemic corticosteroids. Posterior uveitis can also be seen in patients with multiple sclerosis and is not specific for sarcoidosis.

Keratoconjuctivitis sicca (dry eyes) is a condition that involves the tear or lacrimal gland. More common in African-American patients, this condition almost always affects the tear glands of both eyes. Dryness due to tear deficiency is common even when no clinical evidence of lacrimal gland enlargement is evident.

Conjunctivitis. The conjunctiva is a thin membrane covering the outermost layer of the eye and the inner eyelids. Tiny nodules or conjunctival follicles may appear in groups in the conjunctival folds of the lower eyelids. These nodules can be biopsied to establish the diagnosis of conjunctivitis. Phlyctenular, or non-specific, conjunctivitis usually affects both eyes and may occur as a manifestation of acute or transient sarcoidosis with erythema nodosum (discussed in Chapter 16) and bilateral hilar adenopathy (discussed in Chapter 14).

Papilloedema (swelling of the optic nerve-head) occurs commonly in patients with brain tumors, uncontrolled hypertension and kidney failure. Papilloedema may also occur infrequently in patients with sarcoidosis, particularly in younger patients with facial palsy. These patients may also present with other symptoms, including complaints of chest wall pain that mimics pleurisy, pain of the abdominal wall that mimics appendicitis, spinal arthritis or shingles. For patients with papilloedema, the diagnosis of neurological sarcoidosis should be considered.[4]

Diagnosis

Many patients affected by ocular sarcoidosis experience no eye symptoms. For this reason, every patient diagnosed with sarcoidosis should have a complete eye examination, including a slit-lamp exam, at the time the diagnosis is made even when no direct signs or symptoms suggest that the eyes may be involved. In a patient with uveitis, lacrimal gland enlargement, papilloedema, or other unexplained eye lesions, sarcoidosis should be considered a possible diagnosis. A chest x-ray should also be obtained to look for any evidence of enlarged hilar nodes or lung tissue involvement.

Lacrimal gland and conjunctival biopsies are valuable resources for finding and identifying non-caseating granulomas. Either structure can be biopsied in a patient with no other histological evidence of sarcoidosis.[5,6]

Treatment of Ocular Sarcoidosis

Corticosteroids (prednisone, prednisolone) are the primary drugs used to suppress granulomatous inflammation of sarcoidosis. Anterior uveitis can be controlled with corticosteroid eye-drops, but chronic uveitis and posterior uveitis require systemic corticosteroids. Mydriatics (drugs that dilate the pupils) should be used to rest the eye and prevent adhesions of the iris to the lens. Systemic corticosteroids have many side-effects including weight gain, osteoporosis, cataracts, worsening of diabetes mellitus and depression. To avoid these possible side effects, ophthalmologists occasionally inject small amounts of corticosteroids directly into the lesion in the eye. This procedure is tolerated well. If a patient cannot tolerate prednisone, methotrexate, azathioprine or anti-tumor necrosis factor, blocking drugs might be useful.

Additional information about medications that may be used to treat ocular sarcoidosis can be found in Chapter 5.

Conclusion

Ocular sarcoidosis is an important complication of sarcoidosis. While the incidence of eye involvement varies, all patients with sarcoidosis should be given a complete eye examination to check for this condition. Untreated eye lesions may lead to glaucoma, cataract, or blindness.

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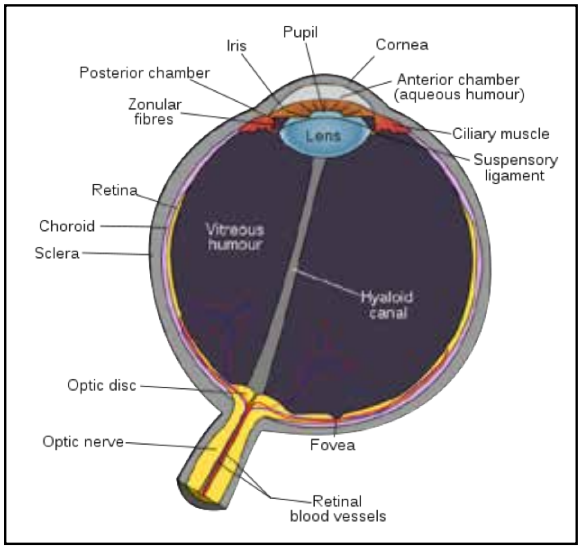

Figure 1: Anatomy of the Eye

Cardiac Sarcoidosis

Introduction

Sarcoidosis can affect both the heart and blood vessels. Cardiac sarcoidosis can occur in about one quarter of patients diagnosed with the disease, but only a small number of patients experience symptoms. However, as with sarcoidosis of the eye, heart involvement can cause significant problems for the patient even when no symptoms are present. For this reason, both medical professionals and patients must be alert and attentive to the possibility of this problem.

The heart is an organ made up of muscles that form the pumping chambers of the heart. Valves to these chambers open and close to allow blood to flow from one chamber to another. An electrical system conducts impulses to the heart muscles. These impulses cause the muscles to contract and effectively pump blood throughout the body. (Figure 1) Granulomas involving the heart can cause heart impulse disturbance or contraction problems for the heart muscle.

The frequency of cardiac sarcoidosis in the United States is not accurately known. However, it is estimated to affect about 25% of patients diagnosed with sarcoidosis. It is also associated with complaints in about 5 to10% of those patients, and has been the cause of death in about 13 to 25% of sarcoidosis patients who died.[1,2] In a group of newly-diagnosed sarcoidosis patients, 2.3 % were shown to have heart involvement.[3]

In Japan, cardiac involvement by sarcoidosis is much higher than the lung or other organ involvement. The mortality rate from heart involvement in this population is also greater. Impulse disturbances that may be caused by sarcoidosis include extra beats, irregular heartbeats, a fast or slow heart rate, and even dropped beats (heart blocks). If an irregular heart beat affects the pumping chamber (ventricle), the blood supply to the body may be stopped temporarily, causing patients to faint or even suffer sudden death. This abnormal rhythm is called ventricular tachycardia or fibrillation. Sarcoidosis that involves the heart muscle may lead to weak or sluggish contractions of the heart and the clinical condition of heart failure.

Sarcoidosis of the heart is difficult to diagnose. The specific treatment recommended by physicians depends largely on the underlying form of heart involvement they discover.

Symptoms and Signs

Patients with sarcoidosis of the heart may have few or no symptoms. When symptoms occur, they may include rapid heart rates, irregular heartbeats, fluttering of the heart, lightheadedness or feelings of near fainting, passing out or blacking out, shortness of breath, fatigue, the inability to lay flat due to shortness of breath, or swelling of the feet. Physical examination may reveal an irregular heart rate or rhythm. It may also uncover signs of heart failure such as an increased breathing rate, fluid buildup in the lung (known as rales) or in the feet or legs (known as edema). The first sign of cardiac sarcoidosis may be sudden death. The cause of death may be identified when an autopsy is performed.

Diagnosis

In the past, the only technique that could ensure a certain diagnosis of cardiac sarcoidosis was a biopsy. This is not commonly used to confirm the diagnosis as heart involvement may be patchy – that is, showing evidence of involvement in some areas of the heart but not in others. For this reason, a biopsy that shows evidence of granulomas confirms the presence of disease in the heart, a biopsy that does not show granulomas does not always mean that that sarcoidosis is not present. Other tests may reinforce a diagnosis of sarcoidosis of the heart without a biopsy. The tests that help physicians make a diagnosis of cardiac involvement -- or at least strongly suspect it -- are described below. They are also described in greater detail in Chapter 4.

The simplest and most routine test when cardiac sarcoidosis is suspected is an electrocardiogram, or EKG. This test records the heart rhythm and may show changes that suggest sarcoidosis of the heart. For this test, patients may be asked to wear a Holter monitor, a device that monitors and records heart rhythm for an extended period of time (usually 24 to 48 hours). Data gathered by the monitor is analyzed to determine if any serious heart rhythm abnormalities are present.

An echocardiogram is another diagnostic test that creates images of the heart using sound waves. The echocardiogram is a helpful tool for evaluating the function of a patient's heart. Images from this test may identify abnormal heart function, but they cannot reveal the cause of the problem. They also cannot determine the difference between sarcoidosis of the heart and other cardiac problems, which may also lead to heart failure.

Nuclear imaging studies that include thallium, gallium, and PET scans have also been used to diagnose sarcoidosis of the heart. These studies involve injecting an isotope into the patient's body, then taking pictures to see where the isotope has gone. Thallium and PET scans are more accurate studies for recognizing the inflamed tissue that is typical of sarcoidosis of the heart. Magnetic resonance imagery of the heart is also very helpful in identifying inflammation or scarring in the heart muscle in patients with cardiac sarcoidosis.

Physicians may sometimes discover their first clue to a diagnosis of sarcoidosis when a cardiac biopsy is performed for other reasons. For a few patients, a biopsy may be deemed necessary if other tests have not proven to be helpful. When a biopsy is needed, it is performed by placing a tube (catheter) into a blood vessel. The tube is then advanced into the heart. A small tool at the end of the tube is then used to take a small sample of heart tissue (the biopsy) for testing.

A combination of tests may be needed to establish a diagnosis of cardiac sarcoidosis. Once diagnosed, a specialized test called an electrophysiologic study (or EP study) may be considered. The purpose of this test is to try to determine, under controlled conditions, if the patient is at risk of developing dangerous irregular heartbeats that may increase the risk of sudden death. If the EP study demonstrates a risk, the patient may be equipped with a protective device known as a defibrillator.[4]

Treatment

The treatment for sarcoidosis of the heart is similar to the treatment for sarcoidosis in other parts of the body. In cases of active inflammation of the heart, steroid drugs such as prednisone may be used.[5] Other medications may be used together with, or instead of, steroids. These drugs include methotrexate, azathioprine, hydroxychloroquine, and cyclophosphamide.

If the major sign of cardiac sarcoidosis is heart blockage or irregular beats, other types of treatment are employed. For example, devices to protect the heart will be put in place if an irregular heart rhythm is found in patients with sarcoidosis. One such device is a pacemaker, a medical

device that regulates the heartbeat using electrical impulses. Pacemakers are placed by a surgeon or cardiologist. A pacemaker has small wires that are attached to the heart wall. Those wires are connected to a battery pack placed under the skin of the patient's chest. Pacemakers can deliver electrical impulses to the heart whenever the heart rate is low or natural electrical impulses are blocked. If a patient is at risk of a dangerous irregular heartbeat, a device may be used that shocks the heart and returns it to a normal rhythm. These devices are called defibrillators or AICD (automatic implantable cardioverter defibrillator). Some devices can provide both functions. Both the pacemaker and the defibrillator monitor the patient's heart rhythm continuously and activate automatically when needed. (Figure 2)

When sarcoidosis of the heart causes severe damage leading to heart failure, the heart may no longer be able to pump effectively. Several medications can be used to treat heart failure. These medications improve the function of the heart in the majority of the patients. In some patients, aneurysms (a bulge in an area where the muscle in the wall of the chamber of the heart is damaged) may develop, making treatment of heart failure and persistent rhythm disturbances very difficult. For some patients, surgery of the heart is the best method for removing the aneurysm successfully.[1]

When medications are not effective in treating heart failure, patients may need to be evaluated for heart transplantation. Heart transplantation has been performed successfully in a significant number of cardiac sarcoidosis patients who do not respond to other treatment. Results for these patients have been at least as good as, and sometimes slightly better than, results for patients undergoing transplants for other reasons. Interestingly, the diagnosis of sarcoidosis in some of these patients has been discovered only after the transplant procedure when the heart had been removed and studied. On rare occasions, sarcoidosis may recur in a newly transplanted heart. Fortunately, this condition does not cause significant signs or symptoms for the patient or affect the function of the transplanted organ. Follow-up treatment for the patient would then include watching for any changes in the condition of the heart.

Different treatments may be used either individually or in combination with others to treat sarcoidosis of the heart. The choice of treatments is determined individually, for each patient, through careful evaluation. In recent years, the selection of treatments and interventions has improved the outcome for patients suffering from cardiac sarcoidosis. It has also significantly improved the survival rate for patients diagnosed with this condition.[5]

Conclusion

Generally, patients diagnosed with sarcoidosis have a very good outcome. For many, the disease disappears with or without medication. However, this good outcome or prognosis changes once cardiac involvement develops. A study in England that followed a large group of patients with sarcoidosis of the heart showed that survival at five years after the detection of cardiac sarcoidosis was not as good as the survival rate for patients with sarcoidosis but no heart involvement.[6,7] To improve this outcome it is important for physicians to make an accurate diagnosis as early as possible. This result can be accomplished by protecting the heart against irregular heartbeats and sudden death, and by treating heart failure due to sarcoidosis more successfully. If sarcoidosis of the heart is suspected, it is critically important to perform diagnostic tests as early as possible and institute appropriate therapy promptly.

As with other types of heart disease, which together affect more than 80 million Americans, cardiac sarcoidosis patients face emotional hurdles that may cause added stress to their bodies and contribute to cardiac decline. This aspect of treatment must also be addressed. Support

groups and counseling may help patients and their families deal with their diagnosis and assist them in learning useful relaxation and coping skills.

Pulmonary hypertension

Introduction

The pressure needed to circulate blood through the pulmonary blood vessels is much lower than the pressure needed to circulate blood to all other organs of the body (systemic pressure). When pressure in the pulmonary blood vessels is elevated, this condition is called pulmonary hypertension. Pulmonary hypertension can have many different causes. When pulmonary hypertension occurs in association with another disease, this condition can lead to symptoms and complications that adversely affect the outcome of the disease.

In about 5 to 15% of sarcoidosis patients, pulmonary hypertension may be present. This condition can further aggravate the symptoms normally associated with lung sarcoidosis. The association of pulmonary hypertension with sarcoidosis can affect the outcome of patients with a 5 year survival estimated at 59%.[1] Pulmonary hypertension can develop in patients with sarcoidosis because of scarring of the lung, as a reaction to decreased oxygen level, or as a consequence of vessels compression by the lymph nodes. It may also develop because of blood clots or the direct involvement of granulomas in the vessels of the lung. These granulomas can lead to a narrowing of these vessels resulting in increased blood pressure.

Pulmonary hypertension occurs more frequently in advanced-stage sarcoidosis that includes the presence of fibrosis of the lungs. However, it can also be seen in early-stage sarcoidosis.[2] A recent study compared sarcoidosis patients with and without associated pulmonary hypertension and found notable differences between the two groups of patients in certain clinical, radiographic and functional abnormalities. Pulmonary hypertension has also been detected in patients with advanced disease awaiting lung transplantation. Moderate levels of pulmonary hypertension can reduce the survival rates in patients with sarcoidosis.[1,3] Granulomas can also be present in the blood vessels without leading to any evidence of pulmonary hypertension.

Symptoms

Mild levels of pulmonary hypertension can exist even when the patient shows no significant symptoms. When symptoms do occur, they may include shortness of breath with exercise, cough, chest pain, lightheadedness, and, in extreme cases, swelling of the lower extremities and fainting. If pulmonary hypertension is suspected, tests may be needed to confirm or exclude this diagnosis.

Diagnosis

The systemic pressure of the body can be measured using a blood pressure cuff placed on the arm. This is a routine test done to determine if a patient's blood pressure is normal, high or low. High blood pressure is called hypertension.

Measuring the pressure in the pulmonary blood vessels is more difficult. An echocardiogram may be used to look for evidence of pulmonary hypertension. The size of the pulmonary arteries on a chest radiograph or CAT scan of the chest may also suggest pulmonary hypertension. Confirmation of the presence or absence of pulmonary hypertension depends on cardiac catheterization, a procedure in which the pressures in the pulmonary vessels are directly measured. This procedure requires the introduction of a catheter (a thin tube like instrument) into

a blood vessel. The catheter is then advanced into the heart and pulmonary vessels. (Figure 3a and b) As the instrument advances, it measures blood pressures directly and accurately. If the pressures are greater than the normal number of 25 (measured in millimeters of mercury), a diagnosis of pulmonary hypertension is made. This cardiac catheterization procedure can also be used to determine if certain treatments would be beneficial or harmful to a patient with pulmonary hypertension. Cardiac catheterization is an important technique for confirming and studying the presence of pulmonary hypertension in patients. It can be equally important in evaluating the effect of medications in patients diagnosed with sarcoidosis and associated pulmonary hypertension.[4]

Treatment

Idiopathic pulmonary hypertension is a type of hypertension that is not associated with other conditions. Several medications are used to treat idiopathic pulmonary hypertension. However, there is no specific FDA approved therapy for pulmonary hypertension as a result of sarcoidosis, or in association with it. Steroids are sometimes used to treat pulmonary hypertension associated with sarcoidosis, especially for patients who do not have fibrosis of the lung.[1] Some treatments prescribed for idiopathic pulmonary hypertension have also been used and studied in patients with sarcoidosis. Results have been encouraging with certain medications such as bosentan, sildenafil and inhaled vasodilators. However, only small studies with a limited number of patients are available. Also, because no direct comparison has been made to other treatments in these studies, it is difficult to interpret their results with precision.

When treatment is implemented, the patients' response to therapy is tracked by repeating echocardiograms and evaluating their functional status and performance on the 6 minute walk test (MWT). This test has been validated in the management of patients diagnosed with idiopathic pulmonary hypertension. It is now also being used and studied to evaluate pulmonary hypertension when this condition is associated with other diseases or causes. The walk test requires the patient to walk on a level surface for 6 minutes. He or she then rests as needed and utilizes oxygen if required. The distance traveled, the degree of symptoms exhibited and the amount of oxygen needed is recorded during the test. Test elements can be repeated at periodic intervals to track the patient's improvement.

If the patient's degree of hypoxemia warrants it, he or she should use oxygen supplementation. Medications frequently used to treat the consequences of pulmonary hypertension include diuretics and anticoagulants. These may be used in patients who show evidence of right ventricular dysfunction resulting from pulmonary hypertension associated with sarcoidosis. Some patients with advanced sarcoidosis experience the complication of pulmonary hypertension that is not improved by medical therapy. For these patients, lung transplantation is one available treatment option. Sarcoidosis patients on waiting lists for a lung transplant who also have pulmonary hypertension have a greater risk of dying while waiting for a transplant than patients without pulmonary hypertension. For this reason, these patients require close monitoring during the transplantation period in order to successfully undergo this procedure.[3]

Pulmonary hypertension remains a significant complication of sarcoidosis. Because no clear-cut recommendation of a single best treatment strategy exists at this time, it is important for medical professionals to examine for pulmonary hypertension and encourage their patients to participate in trials to determine the best or most reasonable treatment in sarcoidosis patients.

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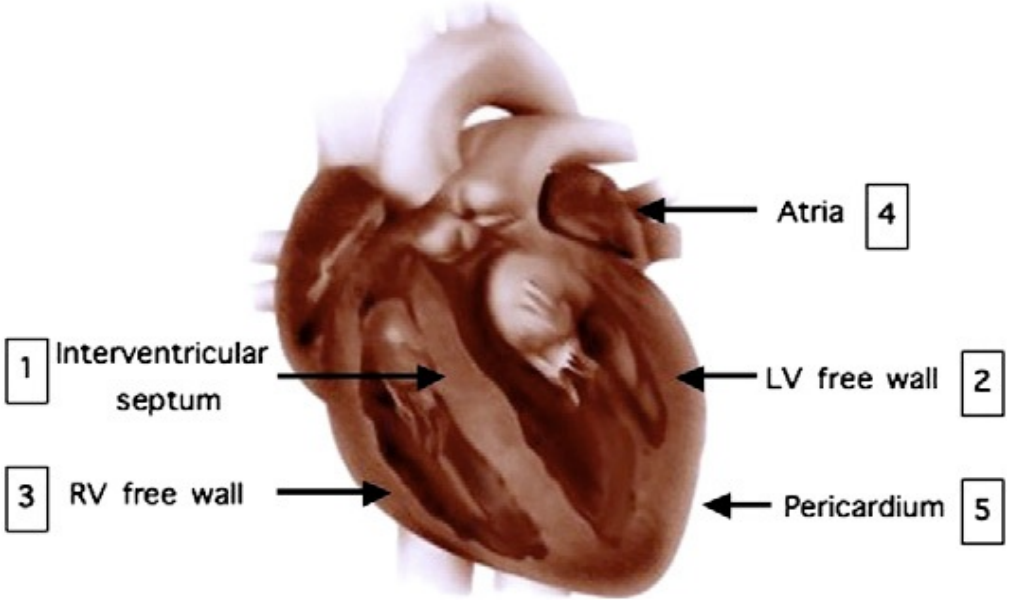
Figure 1


Atria
4
1
Interventricular septum
LV free wall
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RV free wall
Pericardium
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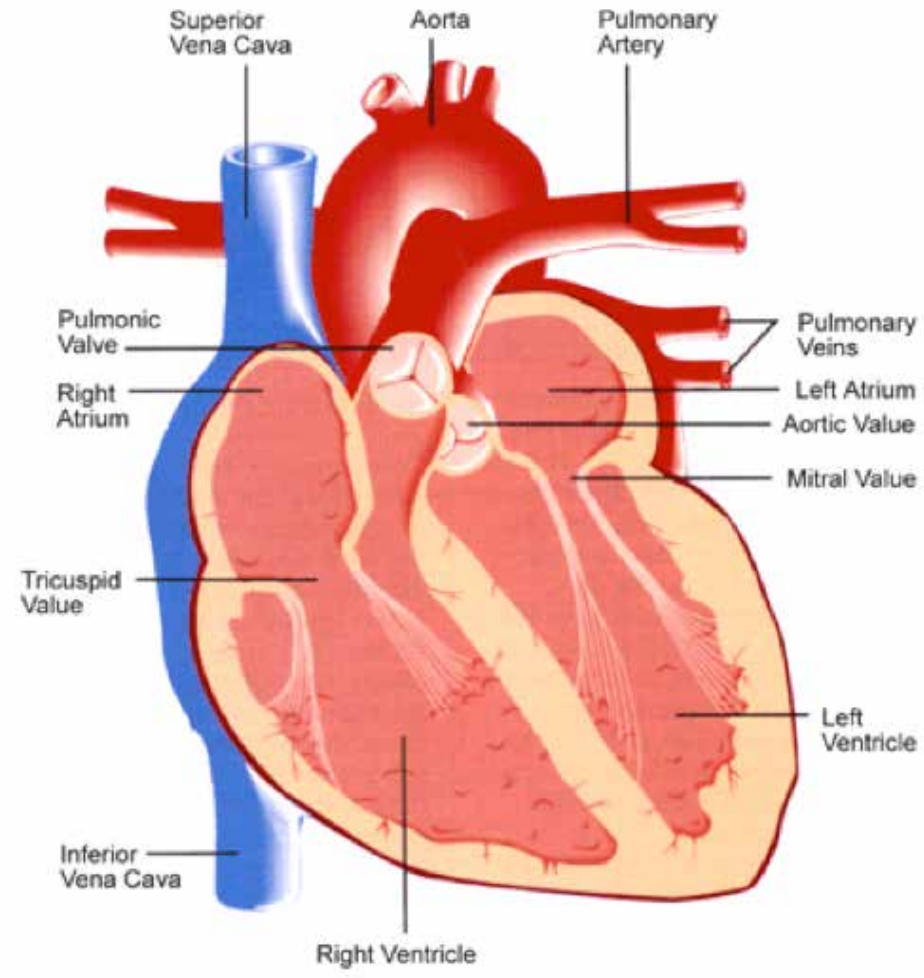

Superior Vena Cava
Aorta
Pulmonary Artery
Pulmonic Valve
Pulmonary Veins
Right Atrium
Left Atrium
Aortic Value
Mitral Value
Tricuspid Value
Left Ventricle
Inferior Vena Cava
Right Ventricle

Figure 2:

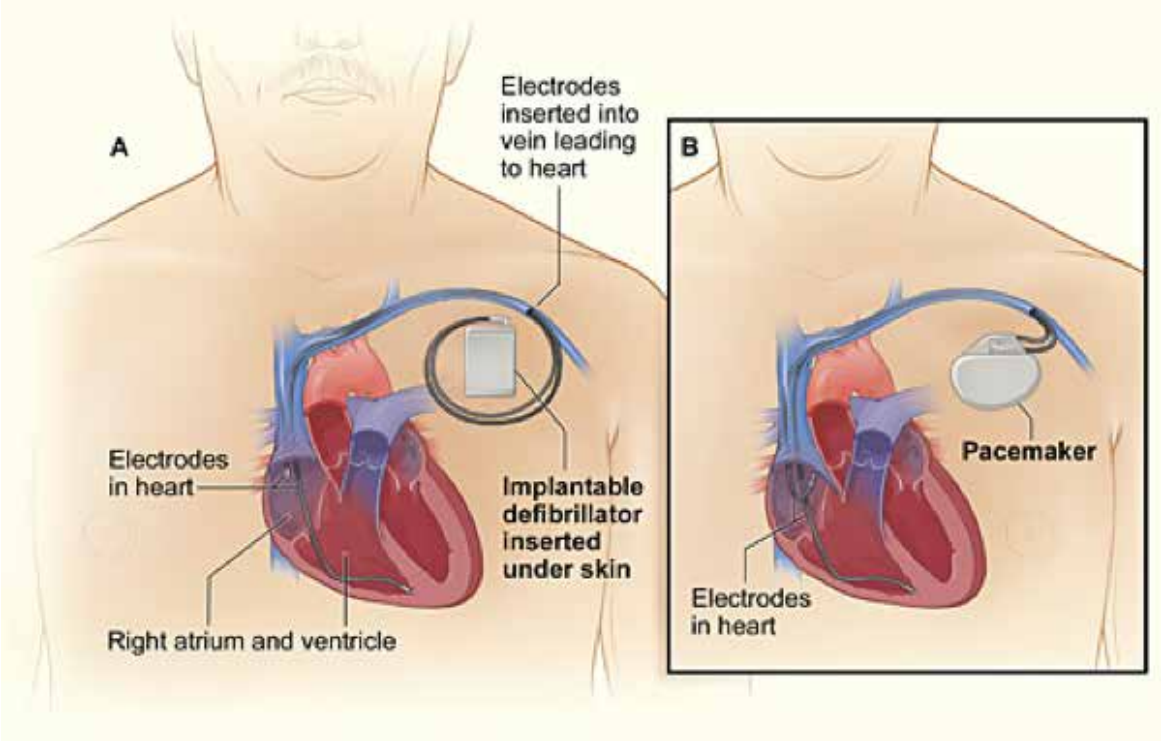
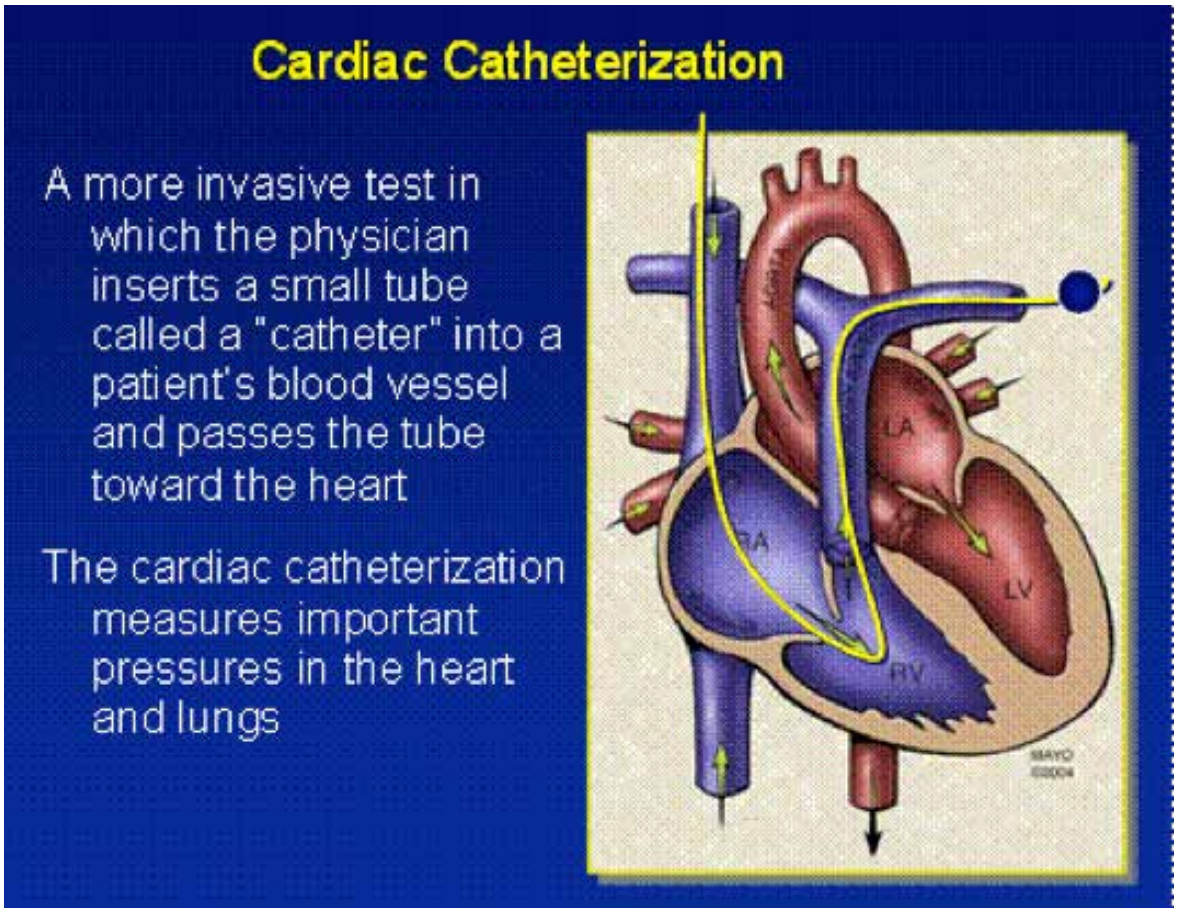
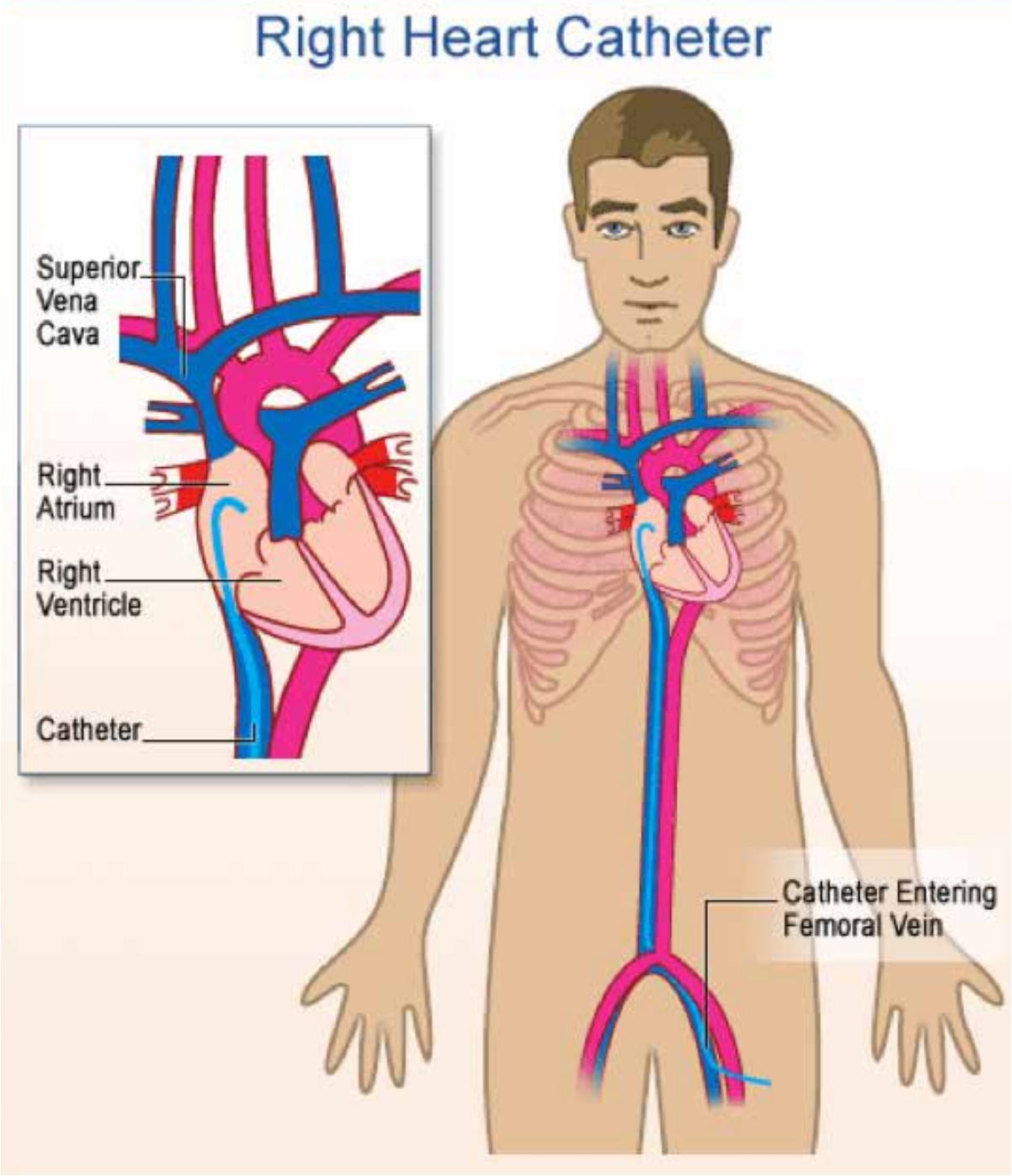


Figure 3a and 3b: Cardiac Catheterization




Right Heart Catheter
Superior Vena Cava
Right Atrium
Right Ventricle
Catheter
Catheter Entering Femoral Vein

Introduction

Sarcoidosis is a disease process that can affect multiple organ systems in the body. The kidney is one organ that can be involved, though such involvement is rare. A diagnosis of kidney involvement requires the documentation of sarcoidosis elsewhere in the body.

This section reviews the incidence, clinical features, prognosis and treatment of kidney involvement in sarcoidosis. The kidneys can be involved either directly, through alteration of kidney function, or indirectly by elevated serum calcium levels (hypercalcemia).[1]

Incidence

Less than 1% of patients with sarcoidosis will experience symptoms of sarcoidosis in the kidney.[2] However, at the time of autopsy, up to 26%[3] of patients will show evidence of kidney involvement with sarcoidosis. In addition, up to 10% of patients with sarcoidosis have increased calcium levels in the blood. The most common finding in patients with sarcoidosis is increased levels of calcium in the urine (hypercalciuria).

Symptoms and Signs

The urinary tract includes the kidneys, the bladder, ureters (tube-like structures) that connect the kidney to the bladder, and the urethra (another tube-like structure from the bladder through which urine flows to exit the body). (Figure 1) Specific symptoms of sarcoidosis in the kidney depend on the location and the severity of involvement. For example, obstruction of the urinary tract system may result in pain in the back, side, or in the groin. Blood tests may reveal an increase in serum creatinine (a serum marker for kidney function). Urine may show evidence of albuminuria (loss of protein into urine), hypercalciuria (elevated calcium levels in urine) or kidney stones.

Diagnosis

When a physician suspects that sarcoidosis is affecting a patient's kidneys, various tests are considered. These include urine tests (to look for protein leaking through kidneys), blood tests (to measure markers of kidney function) and perhaps a kidney biopsy. The classic kidney biopsy finding for sarcoidosis is the presence of granulomas. However, other conditions may also be identified, including mycobacterial infections, fungal infections, malignancy and autoimmune disorders that can have similar findings.[4] These other conditions must be excluded before sarcoidosis can be confirmed. To establish a firm diagnosis of renal sarcoidosis, a typical clinical pattern must be established that includes evidence of other organ involvement together with a kidney biopsy that shows evidence of granulomas.

Treatment and Prognosis

The usual treatment for renal sarcoidosis is high-dose oral prednisone which is gradually decreased over weeks or months. Most patients respond well to steroids. Treatment with steroids may be repeated if symptoms or signs of the disease recur. In rare cases, the disease may not respond to steroids. In such instances, other medications that suppress the body's immune system may be used. These can include methotrexate, azathioprine, or other drugs. Additional information about medications that may be used to treat renal sarcoidosis can be found in Chapter 5.

Hypercalcemia

Sarcoidosis can increase the body's total calcium in a variety of complex ways. For example, the intestines may increase the amount of calcium that can be taken up from food. Exposure to sunlight can increase vitamin D levels that can also increase the absorption of calcium. Calcium is then processed by the kidneys. This can lead to an excess amount of calcium in the urine, the formation of calcium stones, and the risk of kidney failure. Approximately 1 to14% of patients with sarcoidosis may have renal stones.[5]

Symptoms: The symptoms and signs of hypercalcemia include frequent urination, increased thirst, pain in the side near the back (flank), weakness, loss of appetite, stomach pain, constipation, depression, drowsiness, and impaired thought processes.

Treatment: Steroids are effective in treating hypercalcemia and calcium stone formation. Once elevated calcium levels are controlled, the detrimental effects of calcium on the kidney are controlled as well. In addition, patients will also be asked to decrease the amount of calcium and vitamin D in their diets and to drink plenty of fluids. Major dietary sources of vitamin D are fish, liver, and egg yolk.

Conclusion:

Sarcoidosis affecting the kidney is rare, but it can be a serious complication of the disease. If diagnosed early, this condition can be treated with steroids or other anti-inflammatory drugs and generally has a good prognosis.

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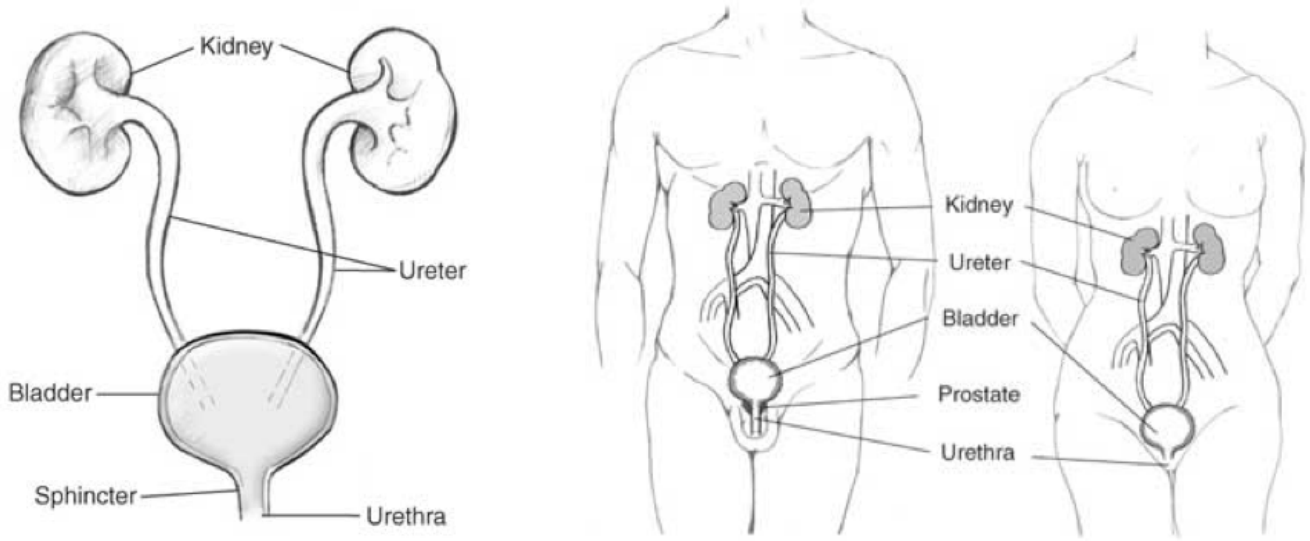
Figure 1: The Urinary tract and its position inside the human body.



Introduction

The liver is a vital organ located on the right side of the abdomen just under the ribs. (Figure 1) The liver has many responsibilities and functions. It makes proteins that are important for different activities in the body. It produces and excretes bile into the intestines that help absorb important nutrients from food. It also removes the toxins absorbed from the intestines and works to break down and eliminate different medications from the body. In addition, the liver plays an important role in the immune defense system.

Granulomas of sarcoidosis can be seen in up to three-quarters of patients diagnosed with sarcoidosis who undergo liver biopsies. Most of these cases do not require treatment and usually have a good outcome. African Americans tend to experience liver involvement with sarcoidosis more frequently than Caucasians.[1-4]

Below is a list of medical terms commonly used when discussing liver involvement with sarcoidosis:

Hepatic – Of or related to the liver.

Jaundice - Yellow discoloration of the skin or eyes.

Pruritis - Itching.

Bile – Alkaline fluids or liquids made by the liver, stored in the gallbladder and excreted into the intestines to aid in the digestion and absorption of nutrients from food.

Hyperbilirubinemia - Elevated bile (bilirubin) levels in the blood.

LFT - Liver Function Tests – Groups of blood tests that check the condition and function of the liver.

Symptoms and Signs

Most patients with liver involvement usually have no signs and do not complain of symptoms related to their liver. Some patients may have non-specific symptoms such as fatigue, low grade fever, abdominal discomfort or pain. Patients might notice yellow discoloration of their skin or the white of their eyes (jaundice) and may experience itching (pruritis). Yellow discoloration and itching are symptoms related to increased blood levels of a substance called bilirubin. Patients who experience these signs or symptoms should report them to a physician if they develop. The liver and possibly the spleen of these patients might be enlarged and may be felt by a physician during an examination of the abdomen.[1-4]

Diagnosis

Evaluating for possible liver involvement with sarcoidosis begins by asking the patient questions about signs or symptoms that may be related to liver involvement. Liver Function Tests (LFT), blood tests related to the liver, may then be ordered. These tests measure the levels of proteins produced by the liver as well as certain chemicals related to bile production and excretion. This information makes it possible for physicians to determine how the cells within the liver have been affected. About one-third of all sarcoidosis patients may show some abnormalities on their liver function tests. For patients who have liver involvement with sarcoidosis, the most common abnormal blood test is an elevated level of an enzyme called alkaline phosphatase.

If the results of liver function tests are abnormal, additional tests may be ordered to ensure that nothing else is causing the abnormalities. An ultrasound or CT (Computerized Tomography) scan of the liver may give more information on the condition of the liver. An MRI (Magnetic Resonance Imaging) of the liver may also be considered. Occasionally, a liver biopsy is performed to rule out other possible causes of abnormal liver function and to determine the extent of liver involvement with sarcoidosis.[1,3,4]

Treatment

Liver involvement with sarcoidosis does not always require treatment. There are no standard recommendations for when to treat liver involvement. A physician may decide that the best option may be to watch the situation without treatment. However, a decision to treat the condition will generally depend on the severity of the patient's symptoms (fatigue, itching and jaundice) and/or any identified abnormalities such as high liver enzymes. Generally, a decision to start treatment will be made if symptoms of liver involvement or LFT results are significantly abnormal, or if the sarcoidosis granulomas are affecting the function of the liver.

If treatment is needed, options may include medications such as prednisone, methotrexate, azathioprine, and ursodeoxycholic acid. Ursodeoxycholic acid reduces the formation of gallstones and has been reported to improve liver sarcoidosis in a few cases. Additional information about medications that may be used in liver sarcoidosis can be found in Chapter 5.

Possible complications from liver involvement with sarcoidosis include cirrhosis, portal hypertension and ascites. Cirrhosis is the term used to describe scarring of the liver to such a significant degree that normal functions of the liver are impaired. Scarring of the liver is irreversible, and a patient with cirrhosis may need a liver transplant. Portal hypertension is a condition in which the blood pressure in the veins that drain into the liver is high. This usually occurs in patients with cirrhosis or when a large lymph node presses on and blocks the flow of blood in the portal vein. (Figure 2) Patients with portal hypertension may develop swelling in the legs. They may also experience swelling of the abdomen caused by the accumulation of fluid inside the abdomen (ascites). Some patients might also notice enlarged and visible veins on their abdomen.

Certain medications used to treat sarcoidosis involving other organs may also have potential side effects and toxicities. Routine liver function tests or other liver tests may be performed on patients to monitor for possible toxicity to the liver from these medications. If signs or symptoms of liver toxicity are discovered, changes may be required in either the medications used or the dosage of a medication prescribed for the patient.

Summary

Most cases of liver involvement with sarcoidosis are asymptomatic. For patients with liver involvement, the outcome is usually good and no specific treatment is required. For those who need treatment, a number of medications are available. Potential but uncommon complications from liver involvement with sarcoidosis include scarring of the liver (cirrhosis), portal hypertension and ascites.

Resources

www.stopsarcoidosis.org

www.nhlbi.nih.gov

www.lungusa.org

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2. Kennedy PT, Zakaria N, Modawi SB, et al. Natural history of hepatic sarcoidosis and its response to treatment. Eur J Gastroenterol Hepatol 2006; 18(7):721-6

   - The authors of this article reviewed all cases of liver involvement with sarcoidosis at their institution. They describe the presentation and patient response to treatment.

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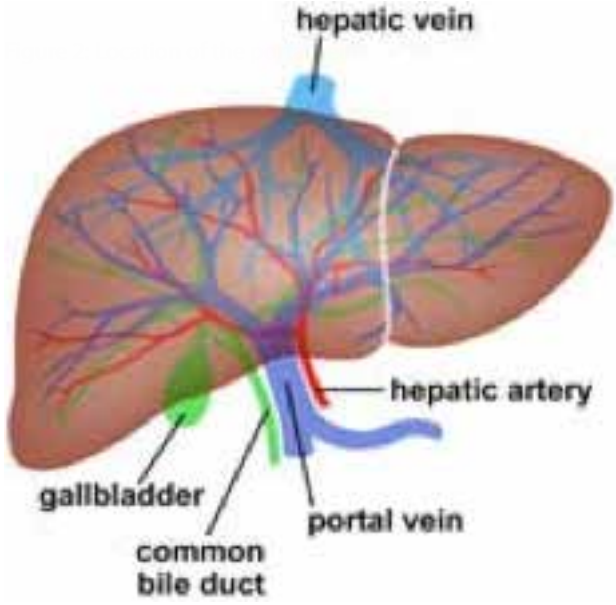
Figure 1: The location of the liver



Introduction:

The pulmonary system includes the entire respiratory tract. It consists of the sinuses, throat, airways, and lungs. It is the organ system most commonly affected by sarcoidosis. More than 90% (9 out of 10) sarcoidosis patients have some form of pulmonary involvement.[1] Pulmonary sarcoidosis may lead to symptoms such as cough, chest pains, and shortness of breath. In some cases, sarcoidosis patients experience no symptoms even when the pulmonary system is involved.

Symptoms:

Symptoms of pulmonary sarcoidosis vary greatly from person to person. In about half of all cases, patients have no symptoms and the diagnosis of pulmonary sarcoidosis is considered only when a chest x-ray is obtained for other reasons (such as an annual physical exam or a work physical).

When symptoms are present, the type and severity depend on many factors such as age, race, ethnicity and the degree and location of disease involvement. Common pulmonary symptoms include shortness of breath (also called dyspnea), chest pains, and/or a dry cough. In a small percentage of patients, major symptoms may include recurrent sinus infections, hoarse voice, nasal stuffiness or facial swelling[2]. This uncommon presentation of sarcoidosis is called 'sarcoidosis of the upper respiratory tract' or SURT.

When dyspnea is a symptom, it is usually first noticed during exercise or exertion. In advanced cases, dyspnea may occur even at rest. Chest pains may be experienced in a single location or may occur throughout the chest. Typically, patients will notice sharp or 'stabbing' pains in the chest which may increase in intensity when they move or breathe deeply. Coughs are typically described as dry and hacking. These coughs may also be associated with wheezing. When patients with asthma develop pulmonary sarcoidosis, they may cough up mucus in a manner typical of their asthma attacks. Although acute presentations (presentations with abrupt onset) of pulmonary sarcoidosis are possible in some patients, the development of symptoms is usually slow and progressive, occurring over a period of weeks or months.

Diagnosis:

The diagnosis of pulmonary sarcoidosis relies on a review of the patient's medical history, x-ray findings, and/or a respiratory system biopsy that shows the classic abnormality, a non-caseating granuloma. Testing to exclude other diseases that can look like sarcoidosis such as certain infections, cancers, or inflammatory diseases may also be needed.[1]

Abnormalities are commonly seen on chest x-rays. These abnormalities are often classified into different "stages" which describe the degree of chest involvement. Chest x-rays that illustrate the various stages of sarcoidosis are shown in Figure 1. These stages may be helpful in determining whether treatment is needed. When a chest x-ray does not provide adequate information, a CT (computed tomography) scan may provide more detail about changes occurring in the chest. For patients with SURT, a CT of the sinuses and/or neck may be ordered.

Pulmonary function studies ("breathing tests") are done to help determine the degree of lung involvement with sarcoidosis. No findings on pulmonary function studies are specific for sarcoidosis alone. Changes may be seen that look similar to an obstructive lung disease (such as asthma or emphysema) or a restrictive lung disease (such as pulmonary fibrosis or lung scarring). In other cases, pulmonary function testing may be normal despite an abnormal x-ray or worrisome pulmonary symptoms.

A diagnosis of sarcoidosis usually requires a biopsy. This test may reveal non-caseating granulomas and exclude other conditions such as infections, cancers, or other inflammatory diseases. In instances where a biopsy from another part of the body discovers the presence of sarcoidosis, a respiratory tract biopsy may not be necessary. Most commonly, doctors will perform an outpatient procedure called bronchoscopy to sample tissues from the lung. Other tests that may be considered include bronchoscopy with ultrasound. A mediastinoscopy, another internal visualization procedure, may also be recommended. Additional information about these procedures can be found in Chapter 3.

Very rarely, a surgical lung biopsy performed with general anesthesia may be necessary. In this procedure a surgeon makes a small incision in the chest wall and directly removes a small sample of lung tissue. It is not uncommon for patients with pulmonary sarcoidosis to require more than one type of procedure.

Treatment

Most cases of pulmonary sarcoidosis require no therapy. The physician may decide to review x-rays, breathing tests (pulmonary function studies), and/or patient symptoms to determine whether treatment will be required. In other cases, the physician may recommend immediate treatment. Generally, treatment for pulmonary sarcoidosis is indicated whenever symptoms of breathlessness, cough, or chest pains are significant enough to interfere with the patient's daily life. Also, some physicians will recommend treatment for patients even when symptoms are not present. For example, if breathing tests indicate severe or worsening lung function or chest x-ray abnormalities suggest that the disease is not likely to go away spontaneously, treatment may be recommended.

The treatment of pulmonary sarcoidosis usually focuses on relieving the patient's symptoms, improving breathing function tests, and/or improving x-ray abnormalities. Treatment may include the use of inhalers similar to those used for asthma or emphysema. It may also require medications given either as a pill or as an intravenous (IV) infusion. Options for pulmonary sarcoidosis therapy include steroids or immunosuppressant medications. In general, most patients with pulmonary sarcoidosis who require therapy must be treated for about 2 years. Some patients who have progressive or persistent symptoms, however, may require life-long therapy. In severe cases, lung transplantation may be necessary. Additional information about lung transplantation can be found in Chapter 18.

It is important to note that treatment of pulmonary sarcoidosis does not necessarily change the outcome of the disease. Patients may improve, remain stable, or continue to worsen despite treatment. However, treatment is usually helpful at improving both the patient's symptoms as well as the results of breathing function studies, and x-ray changes.[3]

Resources

http://www.thoracic.org/sections/education/patient-education/patient-information-series/index.cfm
A good patient-centered overview of the diagnosis, treatment, and prognosis of sarcoidosis.

http://www.stopsarcoidosis.org/
A good site for patient-centered support and information.

http://www.nhlbi.nih.gov/health/dci/Diseases/sarc/sar_whatis.html
The National Heart, Lung, and Blood Institute of the National Institutes of Health website on sarcoidosis.

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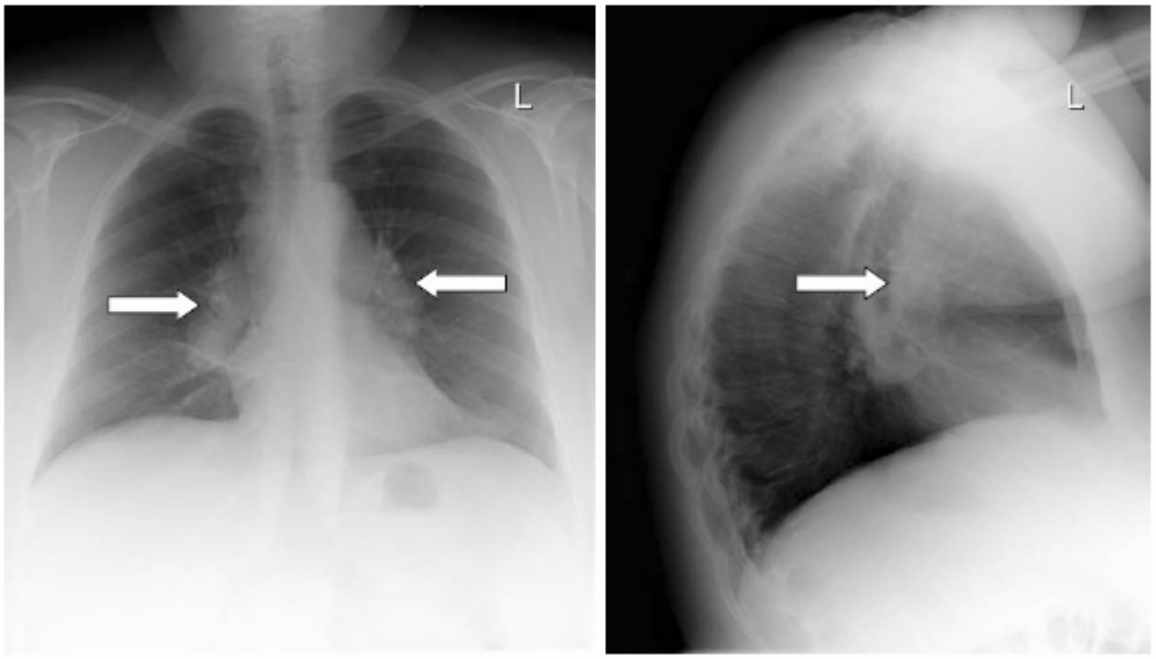
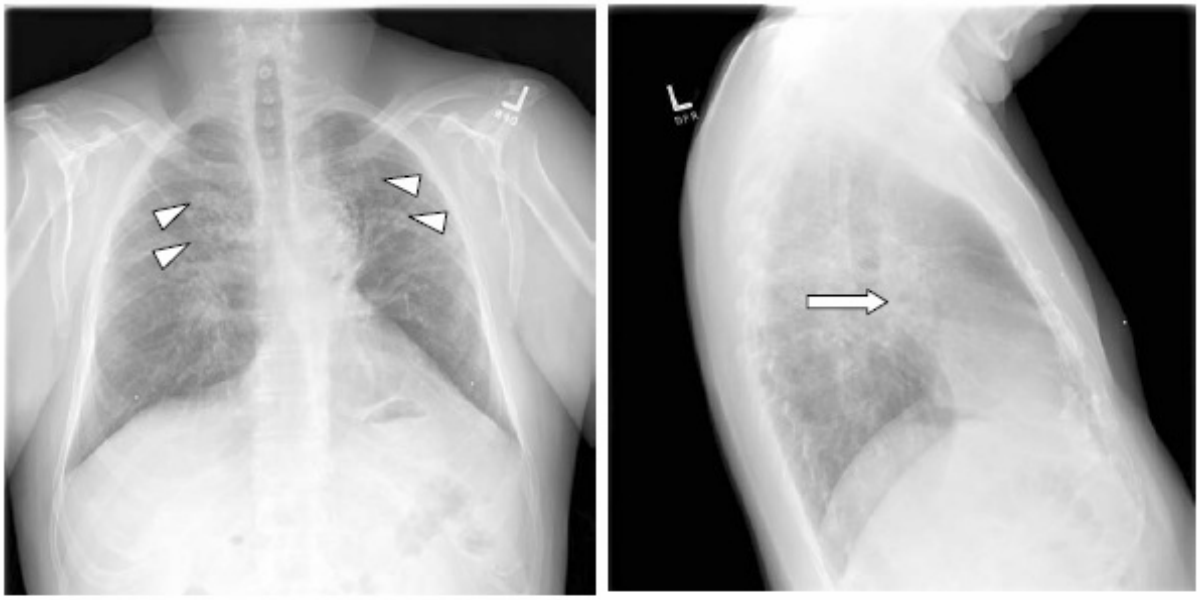
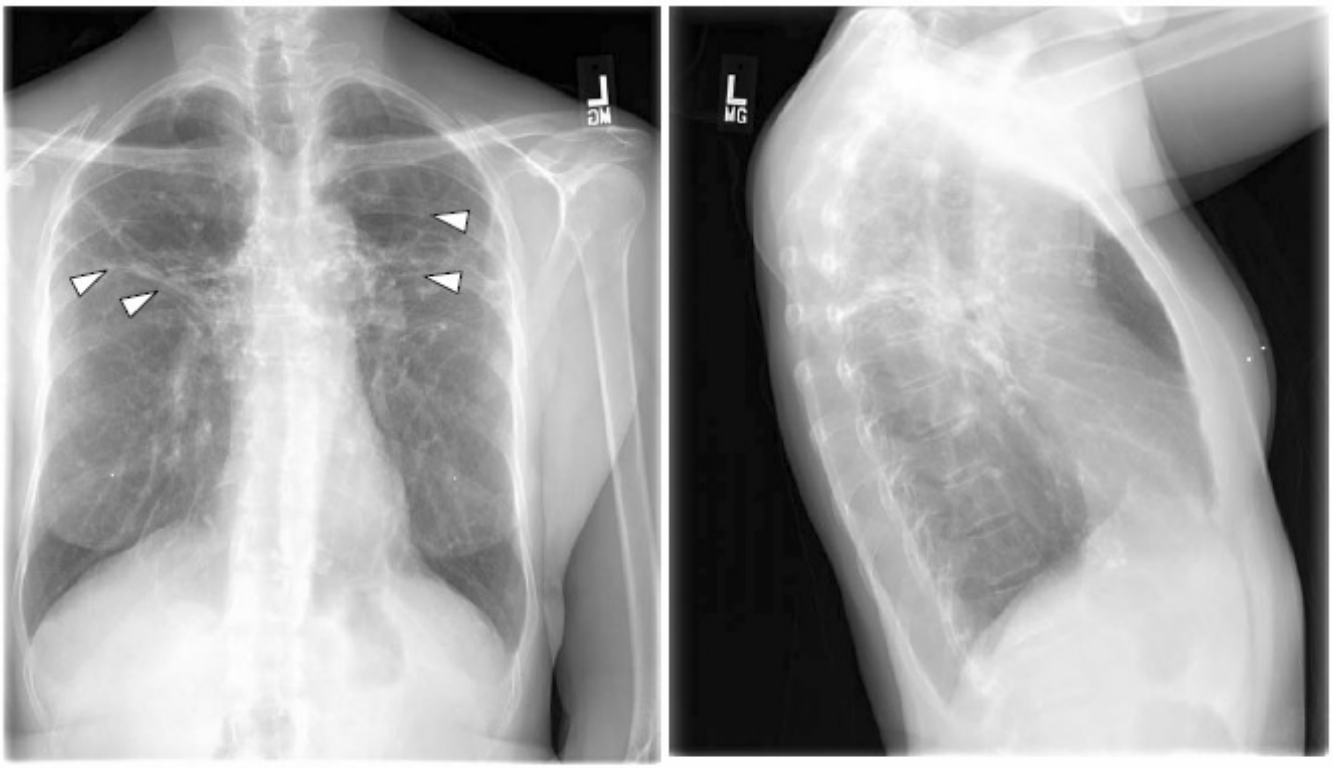
Figure 1: Radiographic stages of sarcoidosis



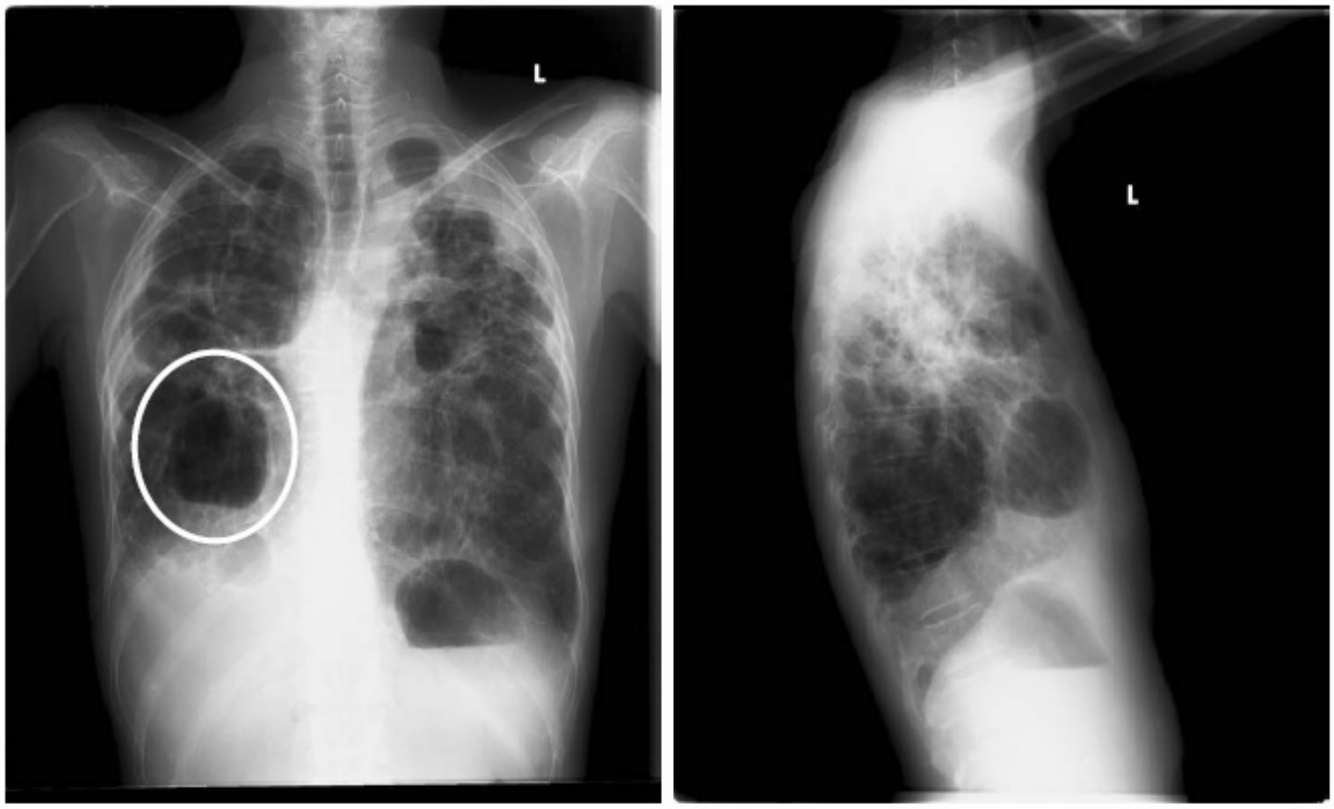
Stage I pulmonary sarcoidosis. Enlarged bilateral hilar and mediastinal lymph nodes (white arrows).



Stage II pulmonary sarcoidosis. Upper lung infiltrates (white arrowheads) along with enlarged bilateral hilar/mediastinal lymph nodes (white arrows).



Stage III pulmonary sarcoidosis. Upper lung infiltrates (white arrowheads) without enlarged lymph nodes.



Stage IV pulmonary sarcoidosis. Destruction of the normal lung architecture with cavity formation (open circle).

Introduction:

Sarcoidosis affects many organ systems in the body, including the lymphatic system and the spleen. These organs are part of the immune system that work continuously along with white blood cells to remove infections, foreign substances, and inflammations from the body. The lymphatic system is made up of a collection of lymph nodes (small bean-shaped collections of immune cells) that are connected by lymph ducts located in different parts of the body. These nodes serve as the first line of defense against many infections and inflammations. The spleen is located in the left upper part of the abdominal cavity, under the ribcage. (Figure 1) It is an organ that controls inflammation and removes infections from the blood.

Lymph nodes:

Any lymph node in the body can be affected by sarcoidosis, though some are more commonly affected than others. Lymph nodes become swollen when they are affected by sarcoidosis. When a lymph node is sampled and examined under the microscope, the inflammation that is typical of sarcoidosis (non-caseating granuloma) can be seen.

The lymph nodes that are typically affected from sarcoidosis can be divided into two groups:

1) Superficial or peripheral lymph nodes, and

2) Intrathoracic or mediastinal and hilar lymph nodes.

Superficial lymph nodes typically affected by sarcoidosis are located in the neck, behind the ear, in the axilla (armpit), and in the groin. When swollen, these lymph nodes can be felt through the skin. Swelling of these lymph nodes occurs in up to 35% of people diagnosed with sarcoidosis. Unlike lymph node swelling due to an infection, superficial lymph node swelling from sarcoidosis is soft and painless. Swelling of the lymph nodes is usually found in the same area on both sides of the body. For example, if the left groin lymph node is swollen from sarcoidosis, similar lymph node swelling will usually be found in the right groin as well. These lymph nodes can be helpful in making the diagnosis of sarcoidosis, but they rarely cause a problem that requires further clinical attention.

Intrathoracic lymph nodes are located inside the chest and around the lungs. These lymph nodes cannot be felt by the fingers and can be detected only with imaging tests such as a chest radiograph, CT scan, or a gallium scan.[1] These intrathoracic lymph nodes are subdivided into mediastinal, hilar and bronchial lymph nodes. Mediastinal lymph nodes are located in the center of the chest behind the breast bone. Hilar lymph nodes are located just outside both lungs near the point where they connect with the trachea, or main breathing tube. (Figure 2) These lymph nodes can be enlarged in from 50 to 90% of people diagnosed with sarcoidosis.

Symptoms of lymph node involvement may include chest pain. When these lymph nodes become enlarged, chest pain may be the first symptom of sarcoidosis noticed by the patient. To support a diagnosis of sarcoidosis, these lymph nodes can be reached by procedures such as mediastinoscopy or bronchoscopy. In some cases, if the physician determines that both hilar

lymph nodes are swollen and also has other specific findings that indicate the illness, a biopsy may not be needed to make a diagnosis of sarcoidosis. In about 80% of people, intrathoracic lymph node swelling eventually subsides.[2] A recurrence of enlargement of lymph nodes is seen in 15% of people with sarcoidosis.

Spleen:

The spleen can be affected in from 15 to 40% of people with sarcoidosis. When a sample from the spleen is taken for a biopsy, the typical non-caseating granulomas of sarcoidosis may be seen during microscopic examination. For the most part, spleen involvement does not cause significant problems for the patient. In a small percentage of patients, however, the spleen may become enlarged. The patient may experience symptoms such as pain and discomfort in the left upper part of the trunk, immediately below the rib cage. In some cases, the primary symptom may be fatigue. Rarely, the spleen may become so enlarged that it pushes against the stomach, which is located next to the spleen. This can cause a decrease in the patient's appetite and in his or her ability to eat normal amounts of food. Also, blood cells that are filtered through the spleen may be affected and cause anemia (reduction in red blood cells), leukopenia (reduction in white blood cells), and thrombocytopenia (reduction in platelets). Red blood cells help to carry oxygen to different parts of the body, white blood cells help fight infections, and platelets help stop bleeding. Treatment for this form of sarcoidosis may include corticosteroids and close monitoring of blood cell counts and spleen size. On some occasions, if medication does not decrease the size of the spleen, improve the blood cell counts, or reduce symptoms such as fatigue, surgical removal of the spleen may be needed to avoid rupture.[3]

Resources:

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Figure 1. Normal Spleen.

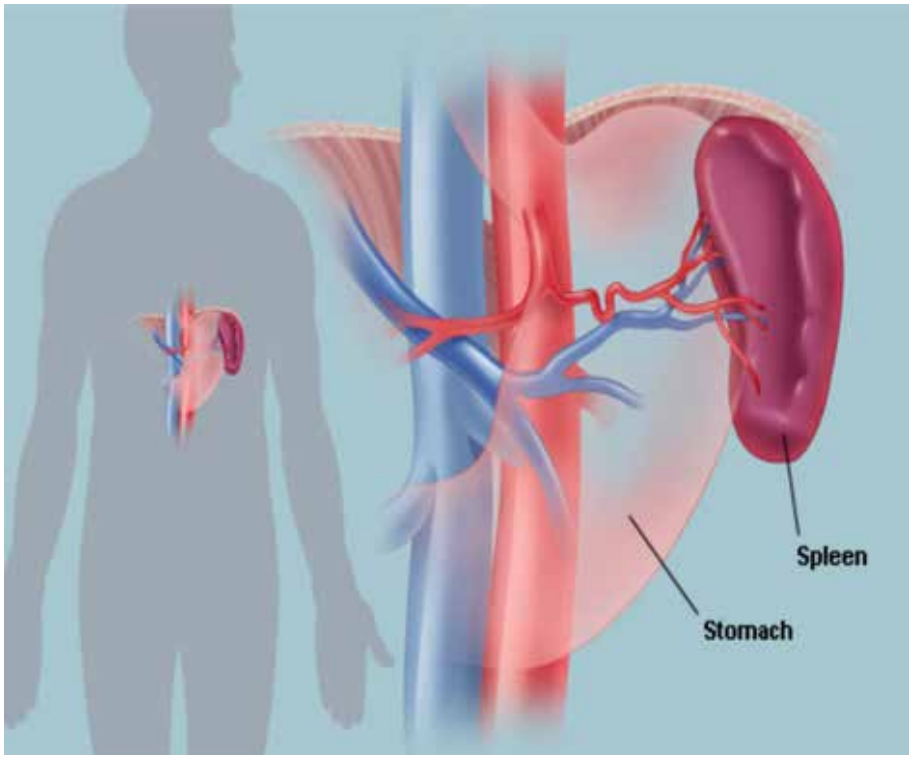
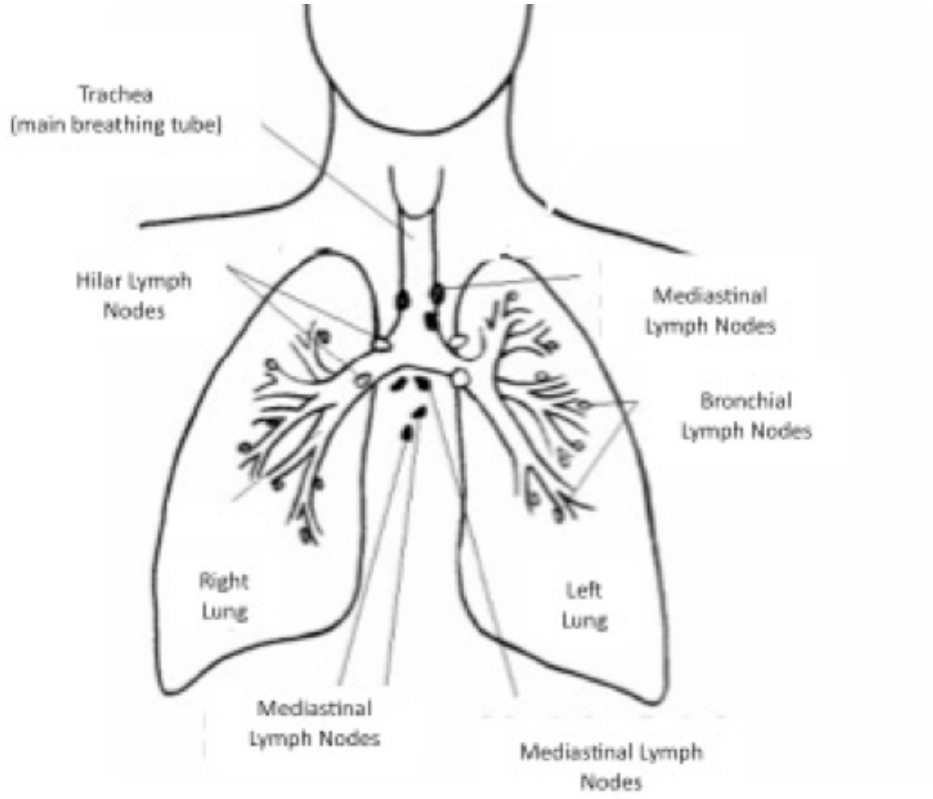


Figure 2. Trachea (main breathing tube), mediastinal lymph nodes, and hilar lymph nodes.



Introduction

Sarcoidosis can involve virtually every organ in the body. Areas in the musculoskeletal system that can be affected by this disease include the muscles, joints, and bones. This section will discuss how sarcoidosis can affect the musculoskeletal system.

Muscle

Although many patients with sarcoidosis have involvement of their muscles with the disease, only a small percentage of those patients will experience any clear symptoms.[1] The different forms of muscle involvement in sarcoidosis are described below.

Chronic myositis is a long-term involvement of the muscles that is caused by sarcoidosis. It is the most common form of symptomatic muscle involvement related to sarcoidosis. People with this kind of sarcoidosis experience progressive weakness in their muscles that occurs over a period of months to years. This condition is more common in women than men. It usually affects muscles of the arms and legs closer to the center of the body rather than muscles nearer the extremities. This can make it difficult for the affected individuals to climb stairs, get up from a chair, or use their arms above the level of the head. As a result of longstanding weakness, muscles become smaller, or atrophy. Medical professionals find it helpful to examine a small piece of a patient's muscle under a microscope to more effectively diagnose possible muscle involvement due to sarcoidosis. When such muscle involvement is discovered, it can been treated with corticosteroids, such as prednisone, or with other agents that suppress the immune system, such as methotrexate and azathioprine.[2] Additional information about medications that may be used to treat musculoskeletal sarcoidosis can be found in Chapter 5.

Nodular tumorous sarcoidosis is a rare form of muscular sarcoidosis that causes lumps to form within the muscle. People affected by this disease usually have multiple masses form in their muscle tissue. The size of these masses can vary widely. Some may be the size of a pea while others can be larger than a softball. The most common symptoms of this disease include weakness and pain. Treatment of this type of sarcoidosis is not standardized because it is so rare. Some patients have reportedly improved after surgical removal of the masses. For other patients, corticosteroids have been used to treat this condition.[2]

Acute myositis may be the first symptom of sarcoidosis. It may also be related to chronic myositis sarcoidosis. Symptoms of this form of sarcoidosis include muscle aches, joint pains, and rash. Blacks and women are more commonly affected by this disease than others. Shoulder and hip muscle groups are more typically impacted by this disease. Blood tests of muscle enzymes can be used to monitor the progress of the disease. Corticosteroids such as prednisone are used for treatment. While the length of treatment is individualized based on each patient's symptoms, treatment is usually recommended for at least one year to help prevent recurrence.[2]

Granulomatous myositis occurs more commonly in sarcoidosis but has also been reported in other diseases that include rheumatoid arthritis, scleroderma, tuberculosis, and dermatomyositis. While it is associated with the same type of granulomas seen in sarcoidosis, it may also occur with no other systemic involvement or association to any disease (including sarcoidosis). Symptoms generally include weakness, pain, and weight loss.[2]

Joints

Sarcoidosis can affect the joints in different ways. Many patients with this disease have arthralgias (aching of the joints), without signs of swelling.[3] Immune-mediated inflammation of the joints with frank swelling is called sarcoidosis-associated arthritis. When the arthritis lasts for weeks to months, it is labeled "acute." If the arthritis lasts for a longer period of time, it's called "chronic." Types of sarcoidosis that affect the joints are listed below.

Acute polyarthritis is common and may be a presenting symptom of sarcoidosis. Acute polyarthritis of sarcoidosis is frequently seen accompanied by fever, painful red lumps on the legs (erythema nodosum), and bilateral hilar lymphadenopathy (large lymph nodes between the lungs that can be observed by chest X-ray). The triad of acute arthritis, erythema nodosum, and bilateral hilar lymphadenopathy is known as Lofgren's Syndrome. (Additional information on this syndrome can be found in Chapter 2.) Acute polyarthritis of sarcoidosis is usually symmetric and involves the ankles and small joints of the fingers, wrists, and knees. Symptoms include pain, swelling, and tenderness of the joints. The prognosis for acute polyarthritis of sarcoidosis is very good. Most patients experience a spontaneous resolution of their symptoms within two months.[4] Treatment with anti-inflammatory medications and corticosteroids may be prescribed if the patient's symptoms are severe or cause functional limitations.

Chronic recurrent arthritis related to sarcoidosis occurs in less than five percent of people diagnosed with sarcoidosis.[5] When it occurs, it is frequently associated with lupus pernio (a raised skin lesion), chronic uveitis (eye involvement), and pulmonary (lung) sarcoidosis.[3] Sometimes a biopsy of the synovium (tissue lining the inside of the joint), must be taken to exclude other causes of the arthritis, such as infection. Chronic recurrent arthritis related to sarcoidosis has a progressive course that may result in deformity and functional limitation. Unfortunately, chronic recurrent arthritis related to sarcoidosis does not respond well to treatment even when anti-inflammatory medications, corticosteroids, and other agents are used.

Bone

Osseous sarcoidosis, or sarcoidosis involving the bones, can be either symptomatic or asymptomatic. When symptoms are present, patients complain of pain and swelling between the joints. This condition is more common in blacks and women. Osseous sarcoidosis is associated with longstanding sarcoidosis that affects multiple organs, usually the lungs, skin and eyes. It typically involves the small bones of the hands and feet. X-rays may be helpful in diagnosing osseous sarcoidosis. When this disease is present, cysts, or hole-punched areas, may be seen on the x-ray image. Treatment to help decrease symptoms of this condition may include corticosteroids, anti-inflammatory medications, methotrexate, and azathioprine. While treatment may relieve symptoms, it is generally not effective in preventing the progression of the disease.[2]

In addition to direct involvement of the bones, osseous sarcoidosis may also lead to a thinning of the bones (osteopenia or osteoporosis). There are many causes for this condition, possibly including corticosteroid therapy. Treatment may include prescribing bone-protecting medi-

cines and/or calcium and vitamin D. These medications are used cautiously in patients with sarcoidosis as they can increase absorption of calcium from the digestive tract and possibily lead to the formation of kidney stones. The effect of sarcoidosis on the kidneys and calcium metabolism are discussed in Chapter 10.

Conclusion

Sarcoidosis can involve most organ systems of the body, including the musculoskeletal system. People with this condition may be either symptomatic or asymptomatic. Patients affected by sarcoidosis of the musculoskeletal system generally have a good prognosis. However, it is important to realize that the potential exists for decreased functionality, disability, and deformity resulting from musculoskeletal sarcoidosis. Treatment of most musculoskeletal components of sarcoidosis includes corticosteroids, anti-inflammatory medications, methotrexate, or azathioprine.

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   - In this review article, researchers from the University of Alabama in Birmingham suggest that extrapulmonary manifestations of sarcoidosis are not uncommon. An awareness of these findings and using MRI and other tools to help determine their presence plays a key role in treatment.

2. Zisman DA, Shorr AF, Lynch JP. Sarcoidosis Involving the Musculoskeletal System. Seminars in Respiratory and Critical Care Medicine 2002; 23:555-570

   - The authors, researchers from the University of Pennsylvania School of Medicine, describe sarcoid manifestations in the musculoskeletal system in depth. The focus of this article is sarcoidosis involving the bone, muscle, and joints. A full review of the clinical manifestations, epidemiology, and treatment options are described.

3. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. The New England Journal of Medicine 2007; 357:2153-65

   - This article, written by researchers at Mount Sinai School of Medicine in New York, describes recent updates in identifying and treating sarcoidosis. Although much work has been done to better diagnose and treat sarcoidosis, many pitfalls still exist. These challenges are described in the article.

4. Torralba KD, Quismorio FP. Sarcoidosis and the Rheumatologist. Current Opinion in Rheumatology 2009; 21:62-70

   - This review article by authors from the Keck School of Medicine, University of Southern California, describes the difficulties facing rheumatologists regarding the diagnosis and treatment of sarcoidosis. Extrapulmonary manifestations of sarcoidosis can mimic other rheumatologic diseases thus making management more complex.

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   - This article describes the various extrapulmonary manifestations of sarcoidosis. It focuses specifically on the neurologic, cardiac, and renal manifestations of sarcoidosis as they can be life- threatening.

Introduction

Sarcoidosis can affect various organs in the body, including the lungs, skin, eyes, lymph nodes, spleen, and the heart.[1] In rare instances, sarcoidosis can also affect the genital tract. Sarcoidosis and tuberculosis can have similar presentations. Physicians must be especially careful to differentiate between sarcoidosis and tuberculosis, as treatment for the two conditions is very different. Also, tuberculosis of the female genital tract has a different prognosis for future fertility.

Symptoms and Signs

Patients with genital sarcoidosis are more likely to present with symptoms typically associated with sarcoidosis involvement of the lungs and eyes.[2] Because the symptoms and onset of this disease can be subtle, an awareness of other health-related findings of sarcoidosis for the patient is important.

Sarcoidosis of the female genital tract is rare. When it occurs, the uterus is the most common site for the disease. Sarcoidosis has also been reported in the vulva, fallopian tubes, cervix, and the ovaries.[3] (Figure 1) While this article focuses on the female genital tract, sarcoidosis has also been reported in the male reproductive tract, affecting the testes, scrotum, prostate, and epididymis. (Figure 2) Sarcoidosis in the male reproductive system may cause male infertility and erectile dysfunction.

In addition to direct involvement, sarcoidosis can indirectly affect the urogenital tract through its effect on the pituitary gland, a small gland located at the base of the brain.

Cutaneous Gynecologic Effects

For patients with genital sarcoidosis, the skin of the urogenital areas may be involved and should be examined. Additional information about skin involvement from sarcoidosis can be found in Chapter 16.

Direct Gynecologic Effects

Sarcoidosis of the female genital tract can affect the uterus, fallopian tubes, vulva, endometrium, cervix, or the ovaries. Several case reports of this disease outline the obscurity of sarcoidosis in the female genital tract. Menzin and colleagues reported a patient diagnosed with pulmonary sarcoidosis as well as a pelvic mass. Surgical findings later showed inflammatory nodules consistent with sarcoidosis within the pelvic mass.[4] Boakye et al. reported a 47- year old woman with a 16-year history of pulmonary sarcoidosis. This patient presented with persistent lower abdominal pain. When both fallopian tubes were removed and examined, sarcoidosis was identified.[5] Uterine sarcoidosis can present with varying symptoms that may include chronic pelvic pain, infertility, abnormal uterine bleeding, and persistent vaginal discharge.[2] Sarcoidosis of the fallopian tube may cause lower abdominal pain and lead to infertility. Sarcoidosis of the vulva is rare and most frequently presents with involvement of the skin.[6] Ovarian involvement can cause painful menstrual cycles for the patient. It may also present as a mass raising concern

for tumors. Involvement of the endometrium is reported more frequently in post-menopausal women than in pre-menopausal women, but the presenting symptom of vaginal bleeding is the same.

Most women with sarcoidosis do not undergo an exam of their pelvic organs. Scarring and inflammation of pelvic organs due to sarcoidosis may therefore go undetected, especially in women who are having trouble with fertility.[4]

Indirect Gynecologic Effects

Sarcoidosis can also have indirect effects on the female genital tract. Female sex hormones related to the genital tract are the follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH controls ovulation while LH controls estrogen. When sarcoidosis affects the pituitary gland, changes in these hormones may cause numerous symptoms that can affect the female genital tract.

Sarcoidosis of the brain can cause endocrine disorders in 0.5 to 1.3% of patients.[7] Signs and symptoms in patients with central nervous system sarcoidosis may include a loss of, or decrease in, sexual drive, inability to maintain an erection, decreased secondary sex changes, and amenorrhea (no menstrual cycles).[7] Sarcoidosis can indirectly affect the female genital tract by invading the pituitary gland and causing disruption of the menstrual cycle, which, in turn, can affect fertility.

Sarcoidosis has also been reported to cause spontaneous flow of milk from the nipple in a female who was neither breastfeeding nor pregnant. This patient was found to have elevated hormone levels of prolactin (a hormone which causes milk production). Imaging studies showed lesions in two parts of this patient's central nervous system which corresponded to inflammatory nodules of sarcoidosis.[7]

Conclusion

The cause of sarcoidosis is unknown and diagnosis of the disease can be difficult. The diagnosis is typically based on the identification of non-caseating granulomas within the affected organ as well as the exclusion of other potential causes such as tuberculosis or fungus infections. The primary treatment for sarcoidosis is corticosteroids. Sarcoidosis of the female genital tract is rare. Since sarcoidosis affects females more than males, women with sarcoidosis should be aware of the unusual presentations discussed in this Chapter. If sarcoidosis is initially detected in the female reproductive organs, a thorough investigation should be initiated to determine if other organs are also involved.

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Figure 1:

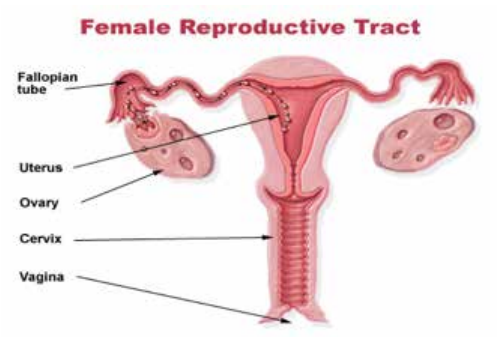
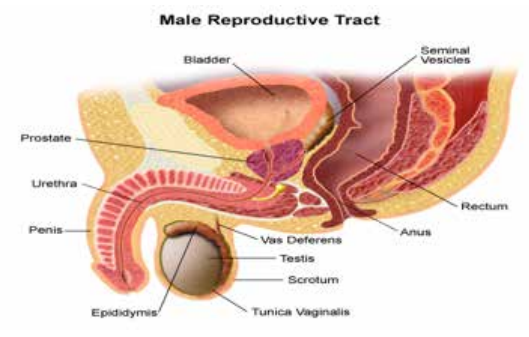


Figure 2:



Sarcoidosis is a chronic multi-system disease that may be systemic (involving other organs), cutaneous only (skin), or a combination of both in some patients.[1,2] Skin involvement is present in about 30% of patients with this disease. In 20% of patients with cutaneous sarcoid, skin symptoms appear before systemic disease begins. In approximately 50% of cases, skin lesions appear simultaneously with other organ involvement. For some patients, cutaneous lesions are the only manifestation of the disease. A glossary of terms used to describe some of the more common skin lesions can be found at the end of this section.

Signs and Symptoms

Skin lesions are divided into specific and non-specific lesions. Specific lesions show non-caseating granulomas when examined under the microscope, while non-specific lesions do not. Specific lesions include papules, plaques, and scarring. The most common nonspecific skin lesion of sarcoidosis is erythema nodosum . However, erythema nodusum is not seen only as a symptom of sarcoidosis. It can also be caused by exposure to a number of other agents, including medications, infections, and inflammatory diseases.

Specific Lesions

Specific lesions -- that is, those which demonstrate classic granulomas on biopsy -- can vary in appearance and location. The most common specific lesions are red brown papules and plaques that may have an "apple jelly" color. These lesions are most commonly found on the lips, face, neck, and chest or back. They are usually numerous, symmetric (appearing on both sides of the body), and firm to the touch. Generally, they do not cause any specific symptoms. Less common presentations include alopecia (hair loss), ulcerations, ichthyosis, hypopigmented patches, nodules, and erythema multiforme. Other variants of sarcoidosis of the skin include Darier Roussy (sarcoidosis with subcutaneous nodules) and lupus pernio. Scars from prior trauma, surgery, tattoos, or even blood drawing may become infiltrated with sarcoidosis lesions that may be tender and red to violet in color. (Figure 1)

Plaques of sarcoidosis are generally more persistent than other cutaneous forms and are associated with a more chronic course of the disease. In contrast with lupus pernio, plaques do not seem to be associated with uveitis (additional information can be found in Chapter 8) or bone cysts (additional information can be found in Chapter 14).[3] Cutaneous sarcoidosis lesions may be mistaken for granulomatous rosacea papules, basal cell carcinomas, plaques of psoriasis, granuloma annulare, discoid lupus, Kaposi's sarcoma, or normal scar tissue.

Papular and macular sarcoid lesions are generally asymptomatic. They may resolve spontaneously, leaving no visible mark on the patient's skin. However, scarring may occur. Plaque-type sarcoid lesions are generally round to oval with central atrophy. They also have a characteristically infiltrated-rubbery texture. Those scaly plaques may be mistaken for psoriasis or hypertrophic lichen planus. Often they are found on both sides of the body, over the chest, back, arms or legs, but may also involve the face, scalp, or neck. When infiltrated with telangiectatic (spider-like) blood vessels, the plaques may resemble a basal cell carcinoma. These lesions are

called angiolupoid sarcoidosis. Plaque-type sarcoidosis patients generally have more severe systemic disease than patients with papules and macules of cutaneous sarcoidosis.

Subcutaneous nodular lesions, called Darier-Roussy sarcoidosis, are usually painless, firm and may resolve spontaneously. They usually present at the start of the disease process in patients with generally less severe systemic disease.

Lupus pernio occurs with a higher frequency in African-Americans and Puerto Ricans than in Caucasians and is a distinct variant of cutaneous sarcoidosis. It is characterized by purple-red papules, nodules and plaques on the central face, ears, and lips. It can also be seen on the hands, fingers, and toes and is associated with sarcoidosis of the lungs in up to 75% of patients. It is seen mostly in African-American females with long-standing systemic disease and also in patients with uveitis and bone cysts. The course of this disease is chronic and can be cosmetically disfiguring. When lupus pernio involves the nasal rim, the physician should also look for involvement of the respiratory tract and lungs.

Non-specific Lesions

Non-specific lesions are thought to be reactive in nature. This condition is most commonly demonstrated as erythema nodosum, painful red raised bumps that appear on the legs or arms. This type of lesion usually resolves on its own. When it is seen with sarcoidosis, it may be a sign of acute sarcoidosis and a benign clinical course.[3] Ichthyosis, a condition which most commonly affects the legs, appears as fish like scales on the skin. They are typically white to dirty brown, and irregular in shape. This condition must be differentiated from an inherited version of the disease called ichthyosis vulgaris. Sarcoidosis can also involve the mouth, including the salivary glands, mucosa, tongue, and the palate (roof of the mouth). Finally, nail changes may also be seen. These changes may include onycholysis, clubbing and hyperkeratosis.

Diagnosis

A skin biopsy of a suspected lesion is required for a full diagnosis of cutaneous sarcoidosis. However, with a biopsy comes the risk of further sarcoidal infiltration of the biopsy scar. Whenever possible, the biopsy will be performed in a less cosmetically sensitive site – that is, in a location not obviously visible on the patient's body. A positive skin biopsy may preclude the need for more aggressive diagnostic procedures, such as a biopsy of a lymph node, muscle, or lung. When a skin biopsy returns a positive result for sarcoidosis, the patient will need further testing to check for the possible involvement of other organs.[1]

Treatment

Some cases of cutaneous sarcoidosis will clear up independently and without treatment. Treatment may, however, be needed to prevent the development of disfiguring scars. Treatment of cutaneous sarcoidosis may include topical (on the surface) and intralesional (injections) steroids, oral anti-malarial medications, or oral steroids.

Potent topical steroids, with or without occlusion, may be all the patient needs to treat individual lesions. Intralesional steroid injection may be used to help flatten lesions that do not respond to topical treatment. These injections may also be used as an additional treatment along with topical medications. When a patient experiences widespread or unresponsive lesions, oral anti-malarial medications such as hydroxychloroquine and chloroquine can be used with proper monitoring that includes eye examinations before and during therapy.

Generally, oral steroids are reserved for patients with systemic involvement of sarcoidosis. Other oral agents that may be helpful include thalidomide and TNF inhibitors. If oral steroids fail to properly treat the condition, immunosuppressive agents such as methotrexate and azathioprine may be needed.

Glossary:

Alopecia: Hair loss

Angiolupoid: An eruption consisting of a small, red, oval, infiltrated rubbery plaque with small blood vessels over the surface.

Basal cell carcinomas: A type of skin cancer that is often glassy or pearly in appearance with small blood vessels over the surface.

Clubbing: A proliferative change in the soft tissue about the distal fingers and toes without boney changes.

Discoid lupus: A type of lupus (a connective tissue disease) consisting of a superficial inflammation of the skin marked by red papules up to 3-4cm in size and covered with a scant amount of adherent scale.

Erythema multiforme: A symptom complex that develops secondary to many different stimuli characterized by red, hive-like to blistering lesions which usually present in a symmetrical distribution. Lesions may be Individual, target-appearing, vesicles/blisters, papules or plaques.

Granuloma annulare: A rash consisting of hard, reddish nodules arranged in a circle which enlarge until they form a ring.

Granulomatous rosacea papules: Rubbery red bumps usually distributed on the central face

Hyperkeratosis: Thickening of the outer layer of skin.

Hypertrophic lichen planus: A type of lichen planus with thicker plaques and papules than seen with "regular" lichen planus

Hypopigmented: Decreased pigmentation

Ichthyosis: Any of several generalized skin disorders characterized by dryness, roughness and scaliness due to a thickening of the outer layer of skin as a result of excessive production or retention of keratin (a principle constituent of skin, hair, and nails)

Kaposi's sarcoma: A type of malignancy principally involving the skin, although visceral lesions may be present. Seen in AIDS patients but the classic type is also seen in elderly Jewish, Italian, and Greek males (Mediterranean and Middle eastern)

Lupus pernio: Cutaneous sarcoidosis consisting of chronic, persistent, violaceous skin lesions with a predilection for the central face.

Nodules: Solid skin lesion larger than 5mm.

Occlusion: The act of covering a site.

Onycholysis: Separation, complete or partial, of the nail plate from the nail bed.

Papules: Solid skin lesion smaller than 5mm.

Plaques: Circumscribed, elevated, superficial, solid skin lesion greater than 5mm., often formed by the confluence of papules.

Psoriasis: A chronic, hereditary, recurrent, inflammatory skin condition with red macules, papules, and plaques covered with silvery scale.

Subcutaneous: Below the skin.

Telangiectatic: Pertaining to small superficial blood vessels, e.g., spider veins.

Ulceration/ulcer: A focal loss of epidermis and dermis; ulcers heal with scarring.

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Figure 1: Sarcoidosis skin lesions often grow on tattoos. This photograph shows an example of this. (M. Judson)

CHAPTER 17: DISABILITY AND REHABILITATION
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Introduction

Shortness of breath and fatigue are among the most common symptoms reported in patients with sarcoidosis.[1] Patients frequently report feelings of exertion or fatigue when performing the normal activities of daily living. This chapter will discuss the possible mechanisms underlying these observations. Possible strategies for handling these problems will be also identified.

Exercise Tolerance and Fatigue

Exercise tolerance is often limited in patients with sarcoidosis.[2] It may be more difficult for these individuals to perform various physical activities such as walking or climbing stairs when compared to healthy people of the same age. Patients typically lack energy which is sometimes aggravated by feelings of depression. An important factor contributing to de-conditioning in these patients is muscle weakness.[3] Also, patients frequently offer leg complaints or fatigue as the reasons why they discontinue high-intensity exercise activities such as brisk walking or climbing stairs.

Sarcoidosis may cause or contribute to muscle symptoms in several ways. In some patients, muscles are directly affected by sarcoidosis. This can cause changes in the muscle that influence their function. In addition, corticosteroids, a medication that may be used to treat sarcoidosis, can have a negative influence on muscle function. A physically inactive lifestyle is another important factor that can lead to muscle weakness and de-conditioning. If the patient associates performing daily physical activities with symptoms such as 'heavy legs' and breathlessness, then these activities may be avoided. The resulting muscle weakness and de-conditioning will then increase the number of symptoms the patient observes when he or she performs normal activities. This situation can draw people into a vicious cycle of ever-increasing inactivity and de-conditioning. This can lead to a further worsening of the symptoms in the patient. At some point, the patient comes to believe that he or she is no longer able to perform exercise.

Breathlessness

Shortness of breath is, in part, explained by impairment of the lungs. However, breathlessness can also be due in part to the patient's de-conditioning process. Weak muscles quickly start to produce waste products during exercise. These waste products stimulate breathing during physical activity and increase symptoms of breathlessness. In some patients, the respiratory muscles (which are responsible for air flow into and out of the lungs) are also impaired. This can increase the patient's respiratory symptoms, especially during exercise, because of the onset of fatigue in the respiratory muscles.

Reconditioning

It is very important for patients to reverse the vicious cycle of deconditioning. Research has shown that following a structured exercise program leads to increased muscle function and

exercise tolerance in healthy persons and other patient groups with chronic diseases (for example chronic lung and heart patients).[4] Patients feel stronger and gain more self-confidence. They then feel more willing and able to perform daily life activities. Consequently, regular exercise has a positive influence on a patient's feelings of well-being and his or her overall quality of life. Mood status can improve and depressive feelings can be reduced.

Training methods typically used in these programs include walking (or running), stationery cycling, stair climbing and resistance exercises. Appropriate exercise programs generally consist of 2 to 3 training sessions per week that continue for at least three months. These sessions must be at least partially supervised by a skilled physical therapist who has experience training patients with a respiratory impairment. When exercising at an appropriate intensity, it is normal and sometimes necessary for patients to experience feelings of breathlessness and fatigue both during and after the exercise. These feelings are an immediate consequence of the training stimulus at the site of both the muscles and the cardiorespiratory system.

Ideally, exercise training will be embedded within a multidisciplinary pulmonary rehabilitation program. Such a program should also include nutritional interventions, psychosocial support and occupational therapy focusing on activities of daily life. Education sessions can also enhance the patient's understanding of the disease and the self-management steps that he or she should take.

Maintenance

To maintain the beneficial effects of exercise training after the program is complete, patients should incorporate adequate physical activity into their daily lives.[5] To achieve this goal, medical professionals recommend that patients develop some routine habits that involve physical activity (e.g. a daily walk, a regular cycling tour, etc.). Even when not following a structured exercise training program, it is important for patients to adopt a physically active lifestyle. Regular walking or other moderate-intensity activity is associated with reduced rates of cardiovascular disease and all-cause mortality. Furthermore, a moderate improvement in cardiorespiratory fitness that is associated with regular physical activity can reduce the symptoms of fatigue and breathlessness that patients might otherwise experience during physical activity.

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Introduction

For most sarcoidosis patients, the disease will either go into remission on its own or be controlled with medications. For a few patients, the disease will advance to organ failure. Such failure occurs most commonly to the lung or the heart. This organ failure can take place despite medical therapy.[1] For these patients, organ transplantation is an accepted treatment option that can prolong and improve their quality of life.

Though some sarcoidosis patients develop severe organ dysfunction, the number that does not respond well to medical therapy is relatively small. Approximately 10% of sarcoidosis patients will develop progressive scarring of the lung that leads to respiratory failure.[1] Less often, progressive weakening of the heart muscle or scarring of the liver tissue can lead to the failure of these vital organs. A recent UNOS (United Network for Organ Sharing) report showed that about 3% of lung transplants and less than 1% of heart and liver transplantations were performed in patients with sarcoidosis.[2]

In general, the decision to perform an organ transplant is made when physicians determine that the risk of death from severe single organ failure is greater than the risk of organ transplantation. Organ transplantation is a complicated and demanding procedure. It should be used only as a final option for patients who have failed other forms of intensive medical therapy. Once a patient is referred to a transplant center, a multispecialty team will evaluate the transplant candidate's condition to determine whether an organ transplant is the best treatment option. During this evaluation, doctors may find other medical problems that could affect the success of the transplantation. These can include other diseases such as active hepatitis, some types of cancer, continued tobacco use, or HIV infection.

This section will discuss issues related to lung, heart, and liver transplantation for advanced organ problems due to sarcoidosis.

Lung Transplantation

The prognosis for patients with sarcoidosis only in the lungs is generally good, though this depends on the stage of the disease. A very small number of patients may go on to develop chronic lung disease from sarcoidosis and may even develop respiratory failure.[3] Sarcoidosis rarely results in death. When it does, the most common cause of death in the United States for patients with sarcoidosis is lung failure. Some specific risk factors have been identified for the development of advanced lung sarcoidosis. Black people (African Americans, sub-Saharan Africans, etc.) are at higher risk, as are patients with a need for supplemental oxygen and extensive scarring of the lungs.[3,4] High pressure in the blood vessels in the lungs (pulmonary hypertension) is also a poor sign, especially when signs and symptoms of heart failure are also present. Pulmonary hypertension in sarcoidosis markedly worsens the likelihood of survival. In one recent study of sarcoid patients with pulmonary hypertension, 2- and 5 year survival rates were 74% and 59%, respectively. In sharp contrast, 5-year survival among sarcoid patients without pulmonary hypertension was 96.4%.[4] Lung transplantation has become a surgical option for

patients who develop respiratory failure that does not respond to medical interventions. This complex procedure may become necessary even earlier for patients diagnosed with pulmonary hypertension.

Eligibility for lung transplantation depends on a patient's symptoms and breathing status. This status is measured by pulmonary function tests. Another eligibility factor is the presence of pulmonary hypertension. Some signs and symptoms of lung failure include shortness of breath during normal activities, repeated coughing of blood, increased use of oxygen, chest pain, fainting, and leg swelling. If these symptoms are present and do not improve with medication, lung transplantation may be considered. In most cases, the patient must first be referred to a transplant center for evaluation. Evaluation testing includes an assessment of the patient's ability to exercise, breathing capacity, the amount of oxygen needed, heart studies and x-rays. A heart catheterization may also be needed to check for high blood pressure in the heart and for any blockage of the heart's blood vessels. Guidelines for considering a patient for transplantation include severe limitation in the ability to exercise, together with any of the following: The need for oxygen at rest, pulmonary hypertension, or high pressure in the right side of the heart.[4]

After evaluating these factors, the transplant team will decide if a transplant is both appropriate and possible. Patients with high pressure in the lungs or repeated lung infections may need both lungs transplanted. For older patients or patients who have had prior chest surgery, a single lung transplant may be the best option. A combined heart and lung transplant is sometimes needed when both the heart and the lungs are affected by sarcoidosis. If the transplant team decides that a transplant is appropriate and the patient agrees to the procedure, the transplant candidate's name is placed on the national waiting list for a donor organ. The medical team must be able to reach a transplant candidate at all times in the event a donor organ becomes available.

The United Network of Organ Sharing (UNOS) manages the transplant candidate list. This group works with transplant centers and local organ procurement organizations (OPO) to match listed patients with donors. The lung allocation score system (LAS) was started in 2005. Every patient on the lung transplant list is assigned a lung allocation score. The LAS is calculated on the basis of medical information gathered during evaluation testing. This assessment includes the results of the breathing tests together with heart and blood testing. It also includes information about the patient's other medical history. The allocation score assigned to each patient ranges from 0 to 100. This score indicates the severity of the patient's disease and the chances of success following transplantation. Along with the LAS, the blood type, lung size, presence of antibodies in the blood, the patient's distance from the transplant hospital and the hospital where the lung donor is located are also considered. A candidate with a higher LAS is given higher priority when a compatible lung becomes available.

By offering lungs to candidates based on the LAS instead of the older first-come, first served system, lungs are offered first to candidates who have the most urgent need and who will have the best chance of success after transplantation. The waiting time can vary from a few weeks to few months. Wait time is considered as a factor in the allocation decision only when two candidates have the same LAS. The LAS score is updated every six months or whenever the candidate's medical status changes.

While on the waiting list, transplant candidates are required to enroll in an outpatient pulmonary rehabilitation program. This program improves their physical conditioning before

the transplant surgery, and their ability to recover afterwards. A lung patient can expect to be in the hospital for 15 to 21 days, but a longer stay may be necessary. Survival after lung transplantation for sarcoidosis is about 78% after one year, 61% at three years and 49% at five years.[4] These results are similar to those for patients receiving transplants for other diseases. After a transplant, sarcoidosis might return in the transplanted organ. However, this does not seem to limit the patient's lifespan or increase the number of problems he or she faces.

Heart Transplantation

The heart can be affected by sarcoidosis in up to a third of the cases, but only a small number of patients (2-5%) will show signs of heart failure. The survival rate for patients with obvious symptoms and signs of heart failure is poor. That rate may be as low as 10% at five years in patients without treatment. However, it may improve to from 60 to 90% if steroid treatment is started before cardiac function declines.[5]

Treatment for heart disease from sarcoidosis is similar to treatments for heart failure from other causes or for cardiac rhythm problems. Medication to treat the sarcoid, such as steroid (prednisone) or other immunosuppressant drugs, may also be used to decrease inflammation. If the heart continues to worsen despite treatment with medications – that is, if the patient experiences severe heart failure -- then heart transplantation may be considered. Only a very small number of patients have been given a heart transplant for sarcoidosis. From 1987 to 2005, only 65 patients received heart transplants for sarcoid related heart disease in the United States.

To determine if a heart transplant is indicated, medical professionals will first evaluate the patient. They will look for any other medical problems that may need to be treated before a heart transplant can be performed. If the patient has a history of cancer within the past two to five years depending on type, an HIV infection or an active hepatitis B infection, heart transplant will not be considered. Poor psychosocial support or a history of failing to follow a doctor's medical therapy recommendations are also factors that are considered when determining a patient's eligibility for transplant surgery.[4] If the transplant team decides that a heart transplant is appropriate, the center will place the candidate's name on a nationwide waiting list. About 4,000 people are waiting for a heart transplant in the United States. Unfortunately, there are not enough donor hearts available for every person in need, and some patients die while waiting for a transplant. Each year, only about 2,000 donor hearts become available for transplants. While transplant candidates are on the waiting list, the medical team monitors their condition and modifies treatment as needed. The transplant team may remove a candidate from the waiting list if a significant medical condition develops, such as a severe infection or stroke. The patient's name will be placed back on the waiting list if warranted following recovery.

If medical treatment for the patient does not adequately support vital organ function while he or she is waiting for a donor heart, doctors may recommend that a device be placed inside the body to help support the heart. These support devices are known as ventricular assist devices (VADs). The VAD can serve as a bridge to heart transplant by increasing the amount of time a candidate can wait for a donor heart. When a donor heart becomes available, the donor-recipient matching system considers a variety of factors to make a match. These include: the medical urgency of recipients, blood type (A, B, AB or O), antibodies the candidate patient may have developed while waiting, the size of the donor organ, and time spent on the waiting list.

Heart transplant surgery usually lasts for about four hours. Recovery often requires a one to two week hospital stay. Recipient survival rates vary, but the overall survival rate for heart

transplants is nearly 90 percent after one year and 72 percent after five years.[2] Survival rates for patients transplanted due to sarcoidosis are similar to, or better than, patients transplanted for other conditions. After transplant surgery, sarcoid granulomas may return. However, little is known about how this affects long- term patient survival.

Liver Transplantation

Liver involvement with sarcoidosis occurs in most cases without signs or symptoms. Generally, the prognosis for patients with sarcoidosis of the liver is good even without treatment. When treatment for liver sarcoidosis is required, available options are similar to those used for sarcoidosis involving the lung and heart. In rare cases these treatments do not stop the disease. Patients may develop cirrhosis, a severe scarring of the liver, to the point where normal functions of the liver are impaired and the liver fails. This condition is not reversible and the patient may then require liver transplantation. As with other organ transplants, the decision to transplant is based on an evaluation of liver function and the patient's general health status. Evaluation of liver function includes liver function tests (LFT), clotting times (INR) and other testing to determine if a liver transplant is appropriate and likely to succeed. If a decision is reached that a liver transplant is indicated and the patient would benefit from the procedure, the center places the candidate's name on a nationwide waiting list. About 17,000 Americans are currently waiting for a liver transplant. Each waiting patient is given a score that helps determine his or her urgency of need and assigns priorities for liver transplants. This score is called the MELD (Model for End-Stage Liver Disease). This scoring system for determining the severity of liver disease is used for patients 12 years old and older. This numerical scale ranges from 6 (less ill) to 40 or more (gravely ill). The score helps doctors prioritize treatment by predicting how urgently a person will need a liver transplant in the next three months. Patients with higher scores are given a higher priority if a compatible donor with same blood type becomes available.

The MELD score is calculated using three routine labs test results: Bilirubin, which measures how effectively the liver excretes bile; INR which measures the liver's ability to make blood clotting factors; and creatinine, which measures kidney function. The only priority exception to MELD scoring are patients who have acute (sudden and severe onset) liver failure. However, this is infrequent with sarcoidosis. A liver for transplantation may come either from a donor who has died or from a living donor. Living donors may be able to donate a part of their liver. Candidates for this type of donation include family members or people who are not related but who are a good match to the patient. This procedure is called a "living donor transplant." People who donate a portion of their liver can lead healthy lives with their remaining liver. The waiting time for a liver transplant varies widely. Blood type, body size, severity of illness and availability of donor organs can all affect the waiting time. While a patient is on the waiting list, the transplant team maintains contact with the candidate and adjusts the MELD score as needed to reflect any changes in his or her medical condition. After the transplant surgery, most patients recover in the hospital for up to three weeks.

The five-year survival rate for liver transplant patients is about 75 percent. Patients who receive livers from living donors have a slightly higher survival rate than patients whose transplants came from deceased donors.[6] As with lung and heart transplants, sarcoid may return after a liver transplant, but it does not usually affect the outcome.

Renal Transplantation

Only about 0.7% of patients with sarcoidosis will develop symptomatic kidney disease.[1] Signs of sarcoidosis of the kidney include high amounts of calcium in the urine (hypercalciuria) and high calcium in the blood (hypercalcemia). As a result, kidney stones may form. Calcium deposits in the kidney may sometimes be severe enough to cause kidney failure. Direct kidney involvement (nephritis) from sarcoidosis is rare. Most cases of kidney involvement respond well to treatment with steroid or other immunosuppressive drugs. However, in the rare cases in which the kidney fails, kidney transplants have been performed.

The kidneys remove excess fluid and waste from the blood. When the kidneys lose their filtering ability, dangerous levels of fluid and waste build up in the body. This condition is known as kidney failure. Dialysis can be used as an artificial replacement for kidney function to remove the excess fluid and waste materials. This procedure can be provided as a chronic treatment for renal failure. It may also be used as a short-term "bridge" treatment until a kidney transplant is performed. As with liver transplants, a donor kidney can come from either a deceased or a living donor. In both cases, the key to success is seeking the closest possible blood and tissue matches. Family members do not always provide the best match. Medical teams perform tests to ensure that the donor kidney matches the recipient's tissue type (HLA matching) and blood type (ABO matching). This careful matching helps reduce chances that the body will reject a new kidney. Possible transplant candidates are also evaluated for any significant heart, lung or other diseases, such as cancer, which may make a transplant less beneficial.

Only one donated kidney is needed to replace two failed kidneys. This makes living-donor kidney transplantation a viable option. If a compatible living donor is not available for a kidney transplant, the center will place the candidate's name on a waiting list to receive a kidney from a deceased donor. The wait time for a kidney transplant may be as long as a year or more. Kidney transplant surgery takes about three hours. During surgery, the donor kidney is placed in the lower abdomen. Blood vessels from the donor kidney are connected to arteries and veins in the recipient's body, and the ureter from the donor kidney is connected to the recipient's bladder. The kidney then begins to filter and remove wastes and produce urine. After receiving the new kidney, the patient generally recovers in the hospital for seven to ten days. Survival for kidney transplant patients with sarcoid is similar to that of patients who undergo kidney transplantation for other reasons. Sarcoidosis may recur in a transplanted kidney, but such a recurrence does not decrease the patient's life span or affect the rate of complications.

Life after Transplant

Living with an organ transplant is a "gift that keeps on giving" throughout the life of the recipient. Maintaining good organ function is a lifelong process. It demands that patients remain constantly aware of their condition and take steps to prevent rejection. Medications must be taken to prevent the recipient's immune system from attacking the transplanted organ as a foreign object (rejection). Other medications to prevent side effects of the anti-rejection medications, such as infection, will also be required. Frequent contact with the transplant team, including face-to-face visits, is essential. Patients may find it hard to adjust to lifestyle changes they must make because of the organ transplant. These often include adjustments in their diet and patterns of exercise. Cardiac and pulmonary rehabilitation programs can help patients adjust to these changes. These programs can also help patients regain their physical strength and improve their overall quality of life.

What are the side effects of an organ transplant?

The most common side effects of a transplant are caused by the medications used to treat or prevent rejection. These can include infection, fluid retention, raised blood pressure, headaches, diarrhea and nausea. The severity of these side effects varies among patients.

What lifestyle changes are associated with organ transplants?

Most patients can return to a normal or near-normal lifestyle from six months to a year after a successful organ transplant. When practical, transplant recipients should avoid exposure to people with infections. A balanced diet, regular exercise and consistent use of prescribed medications are all important ways for these patients to stay healthy.

Rejection of the donor organ

The immune system of the organ transplant recipient may consider a donor lung, heart, liver or kidney as a foreign object that is not supposed to be in the body. When this happens, the immune system attempts to attack the donor organ. All patients who receive an organ transplant are given immunosuppressant medications that suppress this defensive action of the immune system. However, some recipients still experience signs of rejection during the first year after transplantation. The rejection rate varies depending on the organ transplanted. To determine if a patient's body is rejecting a new organ, biopsies (tissue samples) are taken from the donor organ for several months after the transplant, then on an as-needed basis later. Because rejection is most likely to happen in the early weeks and months after transplantation, the frequency of biopsies is greatest during that period.

Infection

Immunosuppressant medications decrease the body's ability to fight certain types of infection such as viruses and fungus. In the first few weeks after a transplant, infections from bacteria are common. These infections are especially common for lung transplant recipients. Two to six months after transplant, viral and fungal infections become a major concern. To prevent or minimize serious infections after a transplant, anti-viral and anti-fungal medications are routinely prescribed. These medications are given for three to six months after the transplant depending on the program of the transplant center.

Common Medications after Transplant and Side Effects

Immunosuppressant medications used after transplant surgery may include cyclosporine, tacrolimus, prednisone, imuran or mycophenolate mofetil. Common side effects associated with cyclosporine or tacrolimus include high blood pressure, kidney problems, hand tremors, excessive hair growth, headaches, and burning or prickly sensations in the hands and feet. Side effects of prednisone include diabetes mellitus, fluid retention, calcium loss from bone, mood swings and stomach irritation. Imuran or mycophenolate can cause liver injury and a low white blood-cell count. All of these possible side effects can be reduced by adjusting dosage and monitoring the patient's blood drug levels. When patients form a lifelong partnership with their transplant team and are pro-active about optimizing their health, they can usually overcome the problems that can commonly arise after transplant.

Cancer

The long-term use of immunosuppressants can increase cancer risk. The most common cancers that occur after organ transplant include skin cancer and lymphoma.

Conclusions

Organ transplantation is a viable treatment option for patients with severe organ failure due to sarcoidosis. The survival rate following transplant surgery is similar to the rate for transplants performed for other diseases. Sarcoidosis has occasionally been seen in the transplanted organ, but the long-term outcome for patients when this occurs does not appear to be negatively affected.

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Advanced sarcoidosis is a significant challenge for patients and health care providers. As treatments for curing the disease or prolonging life become less helpful, medical professionals may turn to optimizing the quality of life (QOL) and easing symptoms as primary treatment goals.

Information is limited about how patients with advanced sarcoidosis will respond to therapies aimed at reducing symptoms. However, information gathered from patients with other types of chronic lung disease may offer some helpful guidance. Patients with chronic lung disease experience a significant impact on their quality of life (QOL) from the lung disease itself. For example, patients suffering from interstitial lung disease (a condition in which the lungs are damaged and become stiffer that normal) commonly have breathing complaints along with other symptoms that can cause concern. These symptoms include fear, social isolation, anxiety and depression. Not only do their breathing symptoms limit their activity and comfort, but an awareness of their decreased independence and ability to participate in normal social activities can also affect their QOL. If symptoms of the disease are controlled, the patient's quality of life may improve.

Palliative care and hospice are underutilized resources for helping patients with advanced, life-limiting chronic diseases other than cancer. The goal of palliative care is to anticipate and prevent or relieve the symptoms related to an underlying disease or disorder and the suffering they may cause. This type of specialized care addresses not only the physical, but also the spiritual and emotional needs of the patient and his or her family and friends. Hospice provides palliative care and support to the patient and his or her family during the dying process. Hospice care can be delivered in a variety of locations, including a hospital, a hospice center or the patient's home. Hospice services are provided by a multidisciplinary team of medical and other professionals. Members of this team include physical therapists, clergy, social workers, nurses, volunteers and physicians.

End-of-life care requires careful attention to the decision-making process surrounding the patient's care and preparation for the patient's death. Patients with sarcoidosis, family members and physicians must maintain a focus on quality of life issues as the goals of medical management shift from curative to palliative management therapies. Relief of symptoms and hospice care offer patients and families the opportunity to improve the patient's overall quality of life. The patient is given the opportunity to participate more actively in decision making, and is able to die with greater dignity and comfort. The American College of Chest Physicians (ACCP) strongly supports the position that palliative and end-of-life care should be an integral part of the management of patients with chronically progressive pulmonary disease.[1]

Quality of Life Concerns

Quality of Life (QOL) concerns for patients include: physical and mental well-being; relations with other people; social, community, and civic activities; personal development and fulfillment; and recreation. Common symptoms described as affecting QOL include progressive breathlessness, fatigue, dry cough, decreased activity levels, sleep disturbances, loss of independence, decreased libido, social isolation, fear, anxiety, decreased mobility, and depression.

Shortness of breath or progressive breathlessness appears to be the most common and distressing symptom affecting QOL in patients with advanced lung disease.[2] In addition to shortness of breath and cough, patients also very commonly report fatigue. Patients make significant changes in their lives in order to function throughout the day. These may include limitations in physical and social functioning. Over time, the patient may experience significant worsening in QOL, specifically through increasing physical limitations. The love and support that patients with a chronic illness receive from family members and friends may be a great comfort to them. However, concern about the physical, financial and emotional burden placed on family members may add to the patient's stress.

Concerns expressed by patients participating in focus groups included low energy; sleep disturbances and exhaustion; decreased sexual activity; decreased independence (including activities of daily living); and decreased social participation. Patients may become dissatisfied with the drug treatment prescribed for them because they may feel that the side effects are "worse than the disease itself." Patients may also decide to limit their activity out of fear that traveling into public places might expose them to a respiratory illness that could lead to their death. Other comments from patients in focus groups included that they spent a great deal of time "planning ahead" for travel on their various excursions so as not to "overdo it". In addition, patients noted their concerns about finances and the strain they can place on their families. These included a desire to avoid exhausting family savings on their medical care. As one focus group participant noted, "In terms of using up my finances, continuing living is a real concern of mine".[3]

Some patients find that their diagnosis leads to improved spiritual well-being, but overall mental health may still suffer as fear, worry, anxiety, and panic regarding their future mortality is considered. A fear of worsening symptoms and impending death leads many patients to the hope that when death is imminent, symptoms can be controlled and their death will be peaceful. For this reason, any patients who are aware of the expected course of their disease desire and expect more attention to end-of-life issues from their doctor.

Interventions to Improve Quality of Life

As mentioned previously, shortness of breath is a common symptom of end-stage lung disease. Few studies have specifically evaluated treatments intended to improve symptoms in patients with sarcoidosis. However, some of the more commonly used treatments aimed at symptom control (palliation) include oxygen, medications to control shortness of breath or anxiety, and pulmonary rehabilitation. Treating sleep-related breathing disorders (SRBD) may also improve quality of life. Guided imagery, an easy-to-learn therapeutic technique, has been shown to improve QOL in patients with COPD. In addition, energy conservation, pursed-lip breathing, and diaphragmatic training are also widely accepted ways to help treat shortness of breath. However, it is not known if this would help patients with sarcoidosis.

Concerns have been expressed that the use of narcotic medications to treat symptoms of breathlessness could lead to drowsiness and hasten death. Contrary to this belief is evidence that for patients with cancer-related shortness of breath, the use of narcotics may actually increase survival by diminishing both physical exhaustion and psychological distress.[4]

Controlling panic and anxiety in lung disease patients also improves QOL.[2] Panic can cause patients to experience sensations of depersonalization, de-realization, and fear of becoming insane. This impacts QOL by changing the patient's behavior in anticipation of another attack.

Medication can help control these symptoms but the effect of any prescribed drug must be watched carefully. Types of drugs that may be helpful to these patients include narcotics and sedatives. These medications can diminish the symptom of pain or anxiety. However, they may also cause the patient to become overly sedated depending on the dosage prescribed and frequency of use. Titration may be required to optimize the benefits and minimize the side effects of this treatment.

Cough can present either early or late in patients with chronic diffuse lung diseases, including sarcoidosis. Other possible reasons for cough should be identified and treated, including asthma, reflux, and post-nasal drip. Treatment for chronic cough is directed at identifying and eliminating the underlying cause. When a specific cause can be found, targeted treatment may help the patient. However, if the lung disease itself is causing the cough, it may affect the patient's QOL. Cough suppressant medicines may be beneficial and are sometimes recommended for treating cough in certain patients.

Oxygen therapy may help patients with lung disease who also have low oxygen levels in the blood. Patients with diffuse lung disease may have low oxygen levels even with minimal exercise and during sleep. Oxygen therapy is not without its problems as it may worsen QOL in some patients with advanced lung disease. A patient may become self-conscious, embarrassed, and experience social withdrawal with the use of oxygen tubes on his or her face in public. There are also costs associated with having oxygen in the home. Monthly energy costs for a 400-watt oxygen concentrator can vary by region. While many patients may qualify for financial rebates, families may still suffer financial hardship in order to continue oxygen therapy.

The need for oxygen therapy may complicate a patient's life but ideally it should not limit activities, including travel. Visiting family or enjoying vacations continue to be an available option for patients on supplemental oxygen, which most consider positive enhancements to QOL. With careful coordination, scheduling, and sometimes an added cost, patients receiving oxygen therapy can travel freely by car, bus, train, boat, and airplane.[5] Policies for travelling with oxygen equipment vary by bus, rail, or cruise line. Air travel requires coordination and advance planning to arrange for in-flight oxygen. A note from the patient's physician is also required stating the required liter flow-per-minute rate so the airline can calculate how much oxygen will be needed throughout the flight. A web site sponsored by the Airline Oxygen Council of America (www.airlineoxygencouncil.org) offers detailed information on this topic for travelers and healthcare providers. Patients with chronic restrictive lung disease have a high risk of low oxygen levels during flight. With supplemental oxygen, however, a patient's oxygen saturations can be maintained at acceptable levels.

Pulmonary Rehabilitation is recommended for chronic lung disease patients. For patients with idiopathic pulmonary fibrosis (IPF), pulmonary rehabilitation has demonstrated improvement in QOL as early as eight weeks into treatment. Some sustained improvement is evident one year later. Pulmonary rehabilitation can decrease the sensation of shortness of breath and therefore improve the patient's QOL.[6]

The true incidence of sleep-related breathing disorders (SRBD) in patients with restrictive lung disease is unknown. Nighttime low oxygen levels during sleep may be common for patients with diffuse lung disease. Poor QOL may also be associated with overnight low oxygen levels and an abnormal sleep patterns. Poor sleep quality can have a significant impact on patients' quality of life, including symptoms of exhaustion and daytime fatigue. Screening for SRBD is recommended. However, treatment of sleep-related disturbances may not improve QOL or the likelihood of survival.

Home care service can provide support for patients. This care can range from patient assessment through education, counseling, and symptom management. These services can also provide home medical equipment as needed. Shortness of breath for the patient, as well as his or her, independent pursuit of daily activities and QOL do not improve with the use of home health care. However, there does appear to be an increase in caregiver satisfaction when the patient is enrolled in home health services.[7]

End-of-Life Care

Education and preparation of the patient and family about the course of the disease may assist all parties in facing a patient's limited life expectancy. However, the course of a terminal illness can vary, making it difficult to predict when a patient will die. An American College of Chest Physicians Position Statement regarding palliative care in patients offers a thorough appendix full of references for health care professionals, family, and patients.[1]

Patients with sarcoidosis may wish to seek guidance, education and support from their doctor as the disease advances. The physician may be able to provide assistance with decision-making and preparation for end-of-life. This may include medical decisions that can have an impact on the patient's well-being during the dying process. If symptoms of pain, depression, and/or anxiety are present at the time of decision making about medical care, it is believed that these symptoms may affect a patient's preferences for care. Patients should consider discussing this matter with their doctors well before end-stage disease is apparent. End of life issues, while difficult to discuss for some patients, are best explored at a non-critical time. This allows the patient time to consider one's own end-of-life wishes, and then discuss these wishes with a spouse, significant other, family and friends. As the disease advances, end-of-life care that is implemented based on a patient's considered wishes may help ease tension, fear and stress for both the patient and his or her family. The patient is treated with dignity and respect throughout the process. With his or her wishes followed, the patient's family is often relieved of responsibility for making difficult decisions.

Focusing on the QOL during medical treatment should not cease when it is decided that aggressive medical therapy is no longer appropriate. As the disease progresses in the face of maximum medical therapy, a shift in therapeutic goals and alternative management plans should be considered, discussed and implemented. For patients with chronic lung disease, issues and concerns that affect QOL at an early stage of the disease may become magnified as symptoms worsen and limitations on the patient increase. Many patients express insecurity about the dying process, fear losing control over symptoms toward the end of their lives and sometimes express fears of experiencing conscious suffocation. Patients also fear abandonment at the end of life. These concerns can be reduced by addressing these fears and assuring patients that treatment is available to them that can help control their symptoms as they occur.

Palliative care and hospice care provide patients with treatment options that attempt to control symptoms and improve QOL.[8] Palliative care and hospice services are most commonly associated with support for terminal cancer patients. However, hospice services are available to patients regardless of diagnosis, but are underutilized for patients dying with advanced stages of non-malignant lung diseases. Hospice care seeks neither to prolong life nor to hasten death. Rather, its goal is to maximize the comfort, dignity, and QOL of the dying while also offering bereavement support to surviving family members and significant others.

Appropriate hospice referrals are generally made by physicians who consider a specific patient to have a life expectancy of less than six months. However, patients with advanced lung disease often have unpredictable courses. Criteria to refer a lung disease patient to hospice care include a number of considerations. These include: diagnosis of progressive lung disease in which there is a high risk of death from an intercurrent illness; adequate medical therapy that has been used without significant improvement; potential benefits from hospice services for the palliation of distressing symptoms, and a wish to avoid unnecessary suffering.[9]

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Living Healthy with Sarcoidosis

Living daily with sarcoidosis and other long-term health problems may require patients to change their attitude, activities and life-style. Life can become challenging in many ways. The patient's goal -- to live as full and fulfilling a life as possible -- will take courage as he or she faces more questions than answers. Many individuals with sarcoidosis live active and full lives with no lifestyle changes required, while others may need to modify their way of living. Acknowledging the presence of a disease, taking charge and learning as much as possible about it provides a patient with the opportunity to remain in control and to be empowered.

It is important for patients to keep a personal health record. For many, this may be as simple as a record of vaccinations and booster shots. Some individuals may prefer to make journal entries on a regular basis. This might mean making daily, weekly, or monthly entries. It is important for the patient to record all major health problems, surgical procedures and therapy treatments in this journal. Patient should record not only the reasons why tests were given, but also the results of as those laboratory and diagnostic tests as well as information about clinic and office appointments. The patient should be purposeful about recording both negative as well as positive outcomes. This can be especially important if more than one health care provider or clinic is used. If possible, patient should always use the same pharmacy and let the pharmacist know about any over-the-counter medications that are taken. This will help prevent possible negative interactions between the over-the-counter products and the prescribed medications.

Fatigue, malaise, and general weakness are terms used to describe the extreme loss of energy experienced by many patients with sarcoidosis. The fatigue associated with this disease and other autoimmune disorders may become severe enough to be disabling. Pacing one's activities, conserving energy resources and avoiding over-exertion must be made a part of a patient's daily lifestyle. The fatigue a patient can experience may be relieved by taking frequent rest periods. Often, the patient will awaken after a restful night's sleep feeling fit and able to complete a full day's work. However, after only a few hours of normal activity, he or she feels exhausted with is no energy left.

Keeping a diary or journal helps the patient track how energy is expended without realizing it. It may be useful for patients to think of each day's available energy as a dollar, and to think in advance about how that dollar will be spent. One way for patients to help visualize their daily energy reserve is to consider placing ten dimes in a cup. As a normal daily task is completed, such as showering, dressing or making breakfast, a dime is taken out of the cup. When the day's supply of dimes are 'spent', the energy for that day is gone. Borrowing energy from the next day would eventfully lead to bankruptcy. This kind of careful management of one's personal energy may be a hard adjustment for some patients to make.

When an individual is working full-time, frequent rest periods may not be feasible. Coffee and lunch breaks may provide an opportunity to put one's feet up and practice a short relaxation exercise. The ADA (Americans with Disabilities Act), when applied in the work place, requires employers to make efforts to accommodate an employee's disability. Family occasions, shop-

ping, sporting events and vacations may require a lot of energy and special planning to cope with fatigue may be required. Understanding that energy can dissolve rapidly and unexpectedly, will help a patient and his or her family prepare for the low levels should they occur. Patients may find that it helps make family occasions more pleasant and memorable if they take longer resting periods before and after an event.

Anyone with a long-term illness should be watchful for signs of depression. Going through a "grieving process" can help make the adjustment to loss of health easier, not only for the patient but also for the family and friends. The slow deterioration of the patient's health may be a more difficult loss to accept than a sudden loss due to an accident, stroke or heart attack. Often, the slow loss of health is not identified as grieving by friends and family, and inappropriate advice can be given unknowingly.

Other causes of sleep disorders can be related to pulmonary disease, chronic pain, and stress. In sarcoidosis, one or all of these may be present. Once again, a journal may help the patient identify hidden or unrecognized health problems. When patients have a thorough discussion of their depression with their health care provider, they are more likely to have a better understanding of any diagnosis they receive.

Anger is an emotion that can be both beneficial and harmful. How patients deals with it can affect their health and well-being. Anger can also be a part of the grieving process. "Venting" is one form of dealing with anger. Having someone who understands the need to purge feelings of anger can be a helpful part of a good support system.

Mood swings can be one side effect of medications. Key family members and co-workers need to be made aware that medications may contribute to this side effect.

Patients should do some form of daily exercise. Even if this exercises lasts for only two or three minutes at first, it will gradually become longer when done faithfully and on a regular basis as endurance increases. One excellent form of exercise is walking in a warm-water pool. Water provides buoyancy and decreases strain on the body. Physical therapy centers may offer pool time for exercise for a small fee.

The key to success in a program like this is for the patient to never give up! He or she should be advised to live life to the fullest, set goals, and have fun. If the patient becomes tired at just the thought of going to a park, he or she should consider renting a wheelchair or motor scooter for the day. Patients can still have fun. They just have to think outside the box and prepare themselves for their enjoyable activities!

What Is a Support Group?

A support group is a set of people who gather together around a common situation. Groups meet for different reasons. Some provide an opportunity for discussions, others have an educational emphasis while still others help participants meet their goals. Individuals may have many reasons for joining a support group. These settings provide participants with an environment where they can talk about how they feel and know that other people will understand. A participant in a support group can learn how to handle difficult behavior problems from others who have dealt with similar problems. They can be a place to learn coping skills from others who have the same concerns. They can also help participants understand that they are not the only person in the world going through these particular problems. A support group is a place where people can have some time for themselves and their interests and not feel any associated guilt about addressing their personal needs. Support groups can make people feel empowered by helping them acquire new knowledge, skills and growth in self-confidence. They can help reduce stress by allowing people to share information and experiences. Of course, confidentiality can become an important issue for all self-help groups. Groups should discuss the need for confidentiality and everyone should know the group's policy.

There are several ways for patients to find a support group in their area. First, they can check with their local hospital for contact information about local support groups. Local newspapers may include listings throughout the month of groups that meet in the area. The Internet is another great source of information on sarcoidosis and support groups meetings. For example, www.sarcoidosisonlinesites.com includes a state-by-state listing of sarcoidosis support groups as well as a "Doctor Database" that lists physicians who specialize in treating this disease. It also includes a listing for international support groups and doctors. If a patient cannot find local support group for sarcoidosis, he or she can check with a local hospital for groups that have common areas of interest or concern. Sarcoidosis patients can attend a fibromyalgia group or a COPD group meeting. There are also many Internet social networking sites that may be helpful. For example, a number of support groups can be found on Facebook. Another group is Sarcoid Buddies. Their web site is: www.health.groups@yahoo.com/group/Sarcoid-buddies. Before participating in any online support group, be sure to review the "Rules of Conduct" that govern each social networking group to aware of what is and is not allowed. http://health.groups.yahoo.com/group/Sarcoid_Buddies/

How to Start a Support Group

Starting a support group can be as easy as finding a local meeting place, placing a notice in the newspaper and then hoping that people will attend. Completing appropriate background work before starting a support group will contribute to the success of the group. There are many methods of providing support and many questions to ask. For example:

1. Will the group meet primarily to allow patients to discuss disabilities or will the emphasis be on education?

2. Will speakers come to the support group and talk about subjects of interest to the group? Will the group be non-judgmental and accepting of feelings? (The purpose of any support group is to be helpful and supportive.)
3. Can the group avoid extensive advice-giving? It is acceptable to talk about feelings, both positive and negative, within a support group.
4. Where will the group meet? It is recommended that meetings not be held in someone's home. A good location might be a meeting room at the local library. Most libraries have rooms that can be reserved for such meetings and are generally free of charge. A group organizer can also check with a local hospital. A hospital may be able to let the group use a meeting room or even sponsor the group. Other possible locations for meetings include churches, restaurants or coffee shops.
5. How often will the support group meet? How much time and energy will group leaders have available to run a support group? It is generally helpful for a group to have several people who can take turns running the support group to avoid "burnout" of individual participants.
6. Leaders should seek information about how to run a support group, and contact other support groups for information and ideas. Self-help groups can be found on the Internet that provide educational material such as www.howtocare.com and www.addcoach4u.com. The local library can be another source for information about how to start and maintain a support group.
7. What topics will be discussed at support meetings? Some suggestions include: Having Sarcoidosis, The Well Spouse, Physical Symptoms, Medication, Stress, Pain, Low Vision/Hearing Loss, Family, Choosing Medical Care, Grieving, Depression, Your Pharmacist, Alternative Medication.
8. Will the support group have a web site? Will the group exchange phone numbers and e-mail addresses among participants? What safeguards will be needed to protect the people in the support group? The new HIPPA (Health Insurance Portability and Accountability Act) regulations have placed strict guidelines on how medical information can be exchanged. Be sure to read and understand the HIPPA regulations.

Starting a support group requires a lot of thought, time and energy. The help such a group can provide to another person is a special reward unlike any other. Nothing helps a patient more in a support group than to be able to speak to other people, smile at other people, call them by name, be friendly and helpful, be cordial, be genuinely interested in people, be generous with praise, be considerate of the feelings of others, be thoughtful of the opinions of others and be alert to give service. What counts most in life is what we do for others.

Sarcoidosis is a disease with no known cause and no cure. People impacted by this disease will always need a safe, supportive place to exchange information and find out what works best for them.

1. **What causes sarcoidosis**?

   The cause of sarcoidosis is unknown. Many theories about what causes sarcoidosis have been suggested. They include infections, naturally-occurring substances in the environment, and man-made substances. Some examples of these are the bacterium that causes acne, mold in the air, and even photocopier toner. However, none of these has been proven. Mounting evidence suggests that there is not a single cause of sarcoidosis, but many potential causes depending on the immune system of the patient.

2. **Will my children get sarcoidosis if I have it?**

   Probably not. For an African American with sarcoidosis, the odds that a first degree relative (brother, sister, mother, father, child) will contract the disease the disease is 20% (1 out of 5 chance). For Caucasians, the odds are 6% (about 1 out of 20 chance). Both of these probabilities are low. However, these odds are much higher than the chances of individuals in the general population contracting sarcoidosis (20 to 40 per 100,000). Because the odds are so much higher for a patient with sarcoidosis to have a first degree relative who also has the disease, medical researchers believe that a genetic factor probably exists for the development of sarcoidosis.

3. **If I have sarcoidosis, should I check my child to see if he/she has the disease?**

   Because the odds are relatively low for a child of a sarcoidosis patient to develop sarcoidosis, this is not recommended. (See #2 above). In addition, because sarcoidosis rarely occurs before the age of 16, such testing should not be considered in a young child. Diagnostic testing of this kind is only recommended when the child of a sarcoidosis patient displays symptoms that might suggest sarcoidosis.

4. **Can I donate blood if I have sarcoidosis**?

   Yes, you can. There is no recommendation against a sarcoidosis patient donating blood. Sarcoidosis has never been shown to be transferable to others through blood transfusion.

5. **If my spouse has sarcoidosis, can I catch it from him/her?**

   It doesn't appear so. The frequency of both husbands and wives having sarcoidosis is so rare that when it occurs, it is thought to be a coincidence.

6. **What sort of diet should I eat if I have sarcoidosis?**

   There are no official recommendations concerning diet for sarcoidosis patients. However, it makes sense to live a healthy lifestyle that includes eating a healthy diet. This is especially important for persons who take steroids, as fatty and high carbohydrate foods will tend to cause excessive weight gain.

7. Since sarcoidosis can affect any part of the body, how can I be sure that a symptom is not related to sarcoidosis?

It is best to use common sense. If you can relate a symptom to another health problem, then it is probably not related to sarcoidosis. However, if you cannot make such a connection, then sarcoidosis should be considered. For example, if you have a cough, nasal congestion, and fever for two or three days, then you probably have a cold. However, if it lasts two to three weeks, then these symptoms cannot be explained by a cold, and other diseases such as sarcoidosis should be considered.

8. Can I exercise if I have sarcoidosis?

Absolutely. You should try to stay as healthy as possible. However, don't overdo exercise. If you are exhausted by the amount of exercise that you are doing, then your body is telling you that it's too much. On the other hand, it is important to be as active as possible.

9. Does sarcoidosis cause fatigue?

Yes. This is an underappreciated symptom of sarcoidosis. This symptom also usually does not respond well to steroids and other medications used to treat sarcoidosis.

10. I have sarcoidosis. Even though I feel sick, I don't look sick. Sometimes I get frustrated that my employer, spouse, other loved one, friend, or relative doesn't believe that I'm ill. Any suggestions?

Patients with sarcoidosis may develop extreme fatigue as mentioned in answer #9, above. They also may develop significant pain from sarcoidosis. However, they may look well. It is important to educate loved ones, relatives, and employers about sarcoidosis. Such education may involve taking them to a patient support group or referring them to educational resources about the disease.

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