DIAGNOSING AND TREATING THE SARCOIDOSIS PUZZLE

Of unknown origin, sarcoidosis is a form of inflammation which can affect any organ system. Because symptoms are many and varied, it often masquerades as other disorders such as tuberculosis, fungal diseases and some types of lymphoma.

Primarily affecting young adults, ages 20 to 40, sarcoidosis is frequently seen in blonde Scandinavians, red-haired Irish, Japanese, black Americans and West Indians. In the US, black Americans are affected seven to one, and the disease in this population is usually more significant. It also seems to affect more women than men, especially in the US. In a recent statement on sarcoidosis published by the American Thoracic Society, population based incidence rates were 5.9 per 100,000 person years for men and 6.3 per 100,000 person years for women. The lifetime risk for sarcoidosis is .85 percent for US whites and 2.4 percent for US blacks.

Pathologically it appears as noncaseating epithelioid granulomas, with little or no necrosis. It may resolve completely without treatment or proceed to fibrosis. These granulomas occur most often in mediastinal and peripheral lymph nodes, lungs, liver, eyes and skin. Less commonly they appear in the spleen, bones, joints, skeletal muscle, heart and central nervous system.

MULTISYSTEM SYMPTOMS DEMONSTRATE SARCOIDOSIS IS AN ELUSIVE DIAGNOSIS

The diagnostic dilemma is that any organ in the body can be involved and the presentation may vary in each. It may first appear as a simple rash or as sudden death in the more rare cases of cardiac sarcoidosis.

Many patients have no symptoms or only mild, nonspecific symptoms. Initially they may suffer with fever, weight loss and arthralgia. It is believed there is a connection to a dysfunctional immune system. In the recent ACCESS trial (A Case Controlled Etiologic Study of Sarcoidosis), a negative association was that smokers typically do not get sarcoidosis, though this is not well-defined. The trial also uncovered a few positive associations such as mold, mildew, musty odors and agricultural exposure, although the triggers remain unknown.

Pulmonary symptoms. Although sarcoidosis can strike any system, and is often multisystem, the lung is involved in 90 percent of patients with thoracic lymphadenopathy

visible on chest X-rays. Most commonly this appears as a bilateral symmetric hilar and mediastinal lymph node enlargement. However, despite having large thoracic lymph nodes and parenchymal lung disease, the patient may be asymptomatic.

"The patient may feel completely fine – with no cough and no shortness of breath," says Kenneth Knox, MD, assistant professor of medicine and co-director of the IU Center for Sarcoidosis and Immunologic Lung Disease. "But many times, even if the lungs are minimally involved, we will do a bronchoscopy so we can look into the airways and perform washings and small biopsies through the scope. Bronchoscopy with transbronchial biopsies is the preferred method of diagnosis with a high sensitivity."

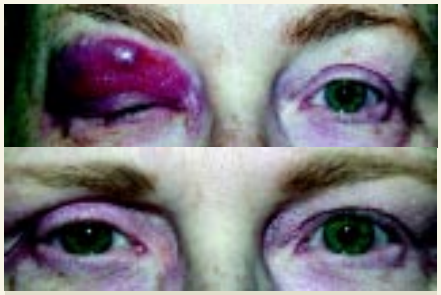
Dermatologic findings. Approximately 25 percent of patients, especially those with chronic sarcoidosis, have skin lesions. These include papules, plaques or subcutaneous nodules. Other rarer forms include scar sarcoid, erythroderma, ulcerations; verrucous or ichthyosifiorm papules; hypomelanotic, psoriasiform plaques and alopecia (hair loss).

"Most patients exhibit multiple firm annular papules or plaques," says Ginat W. Mirowski, DMD, MD, associate professor of oral medicine and dermatology. "The face, eyelids, neck and shoulders are commonly affected. In suspected cases, lesions may appear red, purple-brown or yellow. When lesions are biopsied, typical granulomas are found in the skin. Scar sarcoid occurs when sarcoidal lesions appear within areas of surgical scars or within resolved inflammatory dermatoses."

Several reactive conditions are noted in patients with sarcoidosis. Erythema nodosum first appears as tender red nodules on the shins of young women. Laboratory findings are nonspecific but an elevated erythrocyte sedimentation rate (ESR) is common. Tuberculous skin testing can be falsely nonreactive in these patients.

Hepatic granulomas. Seventy percent of patients, even if patients are asymptomatic with normal liver function tests, have hepatic granulomas. "One of our hepatologists has me follow up with a patient any time he diagnoses granulomatous hepatitis," says David Wilkes, MD, associate professor of medicine, microbiology and immunology, and director of the IU Center for Sarcoidosis and Immunologic Lung Disease. Although this type of manifestation is often seen, it rarely becomes progressive resulting in severe hepatic dysfunction with jaundice.

Ophthalmic issues. Granulomatous uveitis is uncommon, but can be devastating. It is usually bilateral and may cause severe vision loss from secondary glaucoma if it is not treated. Symptoms include blurred vision and photophobia. "Many times we will send people to an ophthalmologist even if they don't have symptoms," says Dr. Knox. "Sometimes there are characteristic changes of the conjunctive or lacrimal glands that could be biopsied very easily and less invasively than bronchoscopy." However, the diagnostic yield is highly variable.



This patient had sudden death from myocardial sarcoid. She also had sarcoid uveitis. She was treated with multiple immunosuppressive medications and an implantable defibrillator with moderate improvement. This large, nodular sarcoidal lesion was felt to be cellulitis or an abscess. Drainage was attempted and pathology showed noncaseating granulomas. Lid reconstruction was necessary. With escalation of therapy and use of third line agents, significant control of inflammation was finally attained.

Photos: Richard Burgett, MD (top) John Murphy (bottom)

Subtle changes on a detailed ophthalmologic exam can provide supportive evidence in difficult cases of sarcoidosis.

Neurologic symptoms. A patient with central nervous system involvement may have headaches, visual disturbances, paresis of the lower extremities and cranial nerve palsies. "I would take a history, then begin by performing a neurologic exam consisting of mental status testing, cranial nerve evaluation, motor and sensory examination, cerebellar testing, and station and gait evaluation," says Holli Horak, MD, assistant professor of clinical neurology. "Subsequent testing would depend on whether the problem is central or peripheral; further, many other disease processes including infectious, demyelinating and autoimmune can mimic or overlap with sarcoid. It's important to take all that into consideration during an examination."

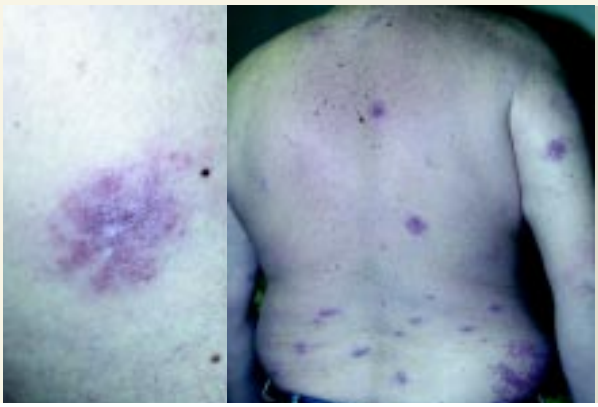
Testing alternatives. A patient suspected of having sarcoid will routinely undergo pulmonary function testing and a chest X-ray – sometimes leading to a CT scan, depending on how much the lung is involved. An ophthalmology consult is common, as well as an EKG to seek out abnormalities in the conduction system.

Other manifestations of sarcoidosis include diabetes insipidus, hypercalcemia and hypercalciuria. The latter two may result in renal calculi or nephrocalcinosis and renal failure. Sometimes the exact cause of these maladies is difficult to pinpoint. "It needs to be stressed sarcoidosis is a diagnosis of exclusion," says Dr. Wilkes.

In the proper clinical setting, a serum angiotensin coverting enzyme (ACE) level test may provide useful information. It is not specific to sarcoidosis, but if someone with a cough, shortness of breath and eye soreness also has an elevated ACE level, it could indicate the presence of sarcoidosis.

Other blood work might include a white cell count, since patients with sarcoidosis have low white cells and sometimes low red cell counts as well.

Often these tests are taken routinely for baseline studies. "Sarcoidosis can get better in the eye, then manifest in the lung," says Dr. Knox. "Sometimes it can be a lifelong disease, sometimes it improves on its own, and sometimes it degenerates and stays exactly the same. We have to tailor our treatment plans according to how the patients are doing."



Lupus pernio is a disease-specific cutaneous manifestation of sarcoidosis which is shown here on the trunk but typically found on the face. Biopsies of this lesion will yield noncaseating granulomas, supporting the diagnosis of sarcoidosis.

Photos: John Murphy

SYMPTOMS IN PATIENTS WITH SARCOIDOSIS

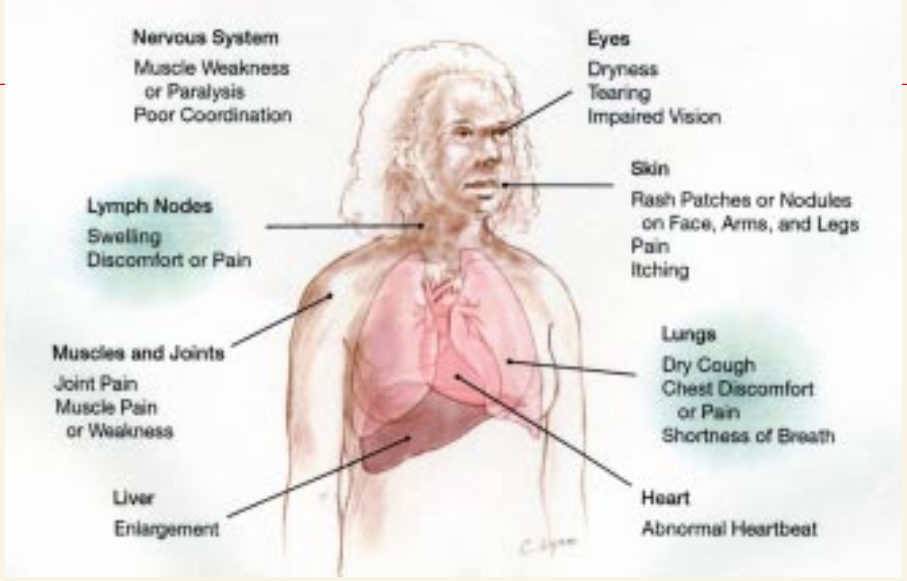


Illustration: Cassio Lynm; courtesy of the American Medical Association.

CAREFUL PATIENT MANAGEMENT IS KEY TO TREATMENT OPTIONS

First line treatments are corticosteroids like prednisone. This has proven extremely effective in most patients, but because of the side effects, it is not desirable for long-term treatment. "Again, you don't know who's going to decline, improve or stay the same, so you have to monitor this carefully," says Dr. Knox.

Certain manifestations must be treated immediately and aggressively. For example with cardiac or neurologic involvement, patients need high doses of steroids and sometimes a second or third agent.

Pulmonary sarcoidosis will often improve without treatment. Physicians typically wait three to six months to see if patients get better on their own if they have mild disease – and this occurs 50 percent of the time. Low oxygen levels, however, would preempt a "wait-and-see" trial period.

The observation period is important for another reason. "There are other diseases which can cause this type of granulomatory inflammation, and if exposed to steroids, can worsen," says Dr. Wilkes. "Therefore, it's important to exclude other diseases such as histoplasmosis or tuberculosis."

When sarcoidosis with lung involvement is clearly indicated, prednisone works well in 70 to 80 percent of patients. With isolated liver disease, the response to prednisone is unpredictable, so it much be watched closely and switched to other agents when necessary. Although pulmonary sarcoid seems to respond well to prednisone, according to Dr. Wilkes, there are no adequately controlled trials of what works well for the central nervous system.

Despite the general effectiveness of prednisone, complications such as cataracts, bone loss, weight gain, glucose intolerance, irritability and mood swings become worrisome after a year of therapy. In patients with these side effects, the dose is sometimes lowered and used in conjunction with a second agent. Hydroxychloroquine is a second line agent used initially for certain lines of cutaneous disease including sarcoid.

With a number of diabetic patients who contract sarcoidosis, therapy must be carefully managed because of the negative response to corticosteroids. Often they have to go sooner to a secondary agent. These work more like chemotherapy and include drugs like azathioprine and methotrexate.

In patients with refractory sarcoidosis, treatment might include a high dose steroid burst or escalation with a second agent. "You tend to fold in more therapies as you go," says Dr. Knox. "People may have life threatening lung disease, but it's usually slow to progress. Over years, continued inflammation and destruction of the lung may require a lung transplant."

Sarcoidosis often is a chronic disease. With granulomatous uveitis, aggressive initial treatment may be followed with symptom-controlling eye drops. With cutaneous sarcoid, the patient may be able to control it with local steroid injections or crèmes and ointments as opposed to systemic steroids. Less intensive therapy may work once the disease is under control.

INVESTIGATIONAL PROTOCOLS FOCUS ON IMMUNE SYSTEM AND GENETICS

These therapies have been available for quite some time, although newer, investigational agents manipulate the immune system more specifically, inhibiting cytokine cascades.

Third line treatments are less traditional and include the use of inflixamab, which is often used to treat other inflammatory diseases such as rheumatoid arthritis and Crohn disease. "When all else fails, we need to consider this," says Dr. Wilkes.

The results look promising but problems may arise with opportunistic infections which appear in patients who are treated with this drug – not for sarcoidosis per se, but in general. These are the very infections that have caused the granulomous inflammation in the first place. "But maybe we'll unmask a common denominator," says Dr. Wilkes. "It's very investigational at this point."

There are several research protocols currently underway at the IU School of Medicine, one of a dozen centers around the country which treats sarcoidosis and one in eight utilizing a multi-disciplinary approach. "Right now we're trying to gather as much information as we can. We currently are seeking patients who are naive to therapy and testing their blood cells in vitro" says Dr. Knox. "In the future, we anticipate having more of an interventional treatment protocol."

There are really no surgeries for sarcoidosis – certainly none that cure the disease. In cases where there has been lung transplantation, there may be a recurrence of the disease, although it's usually mild. Treatments under investigation at the NIH are aimed at manipulating the cytokine cascade, such as pentoxifylline, which is delivered in pill form.

Another area of intense investigation is in the area of genetics. There is some evidence the genes for the ACE enzyme may be different in certain populations, suggesting a more genetic than environmental trigger. "There might be a revealing familial association," says Dr. Knox. "There might be certain genes involved that need to be 'turned off' to stop this inflammation. Much current research is directed toward the genetic basis of sarcoidosis – and I think that's where the future of treatment lies." ■

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