

Tender pretibial nodules with polyarthralgia and cough

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SELF-ASSESSMENT QUIZ

A 31 year old female presented to the emergency department complaining of a sudden onset of fever, malaise, and joint pain of her ankles, wrists, the proximal interphalangeal joints, and the elbows, with painful bruises on her legs below the knees of about one week's duration.



Figure 1. Bilateral extremely tender, subcutaneous erythematous warm nodules on the anterior tibia

On examination, bilateral, extremely tender, subcutaneous, erythematous, warm nodules were seen on the anterior tibia (Fig. 1). The patient was complaining also of non productive cough. Therefore, a chest X-ray was done, which revealed bilateral hilar lymphadenopathy (Fig. 2).



Figure 2. X-ray chest showing bilateral hilar lymphadenopathy

Laboratory studies disclosed an elevated angiotensin converting enzyme (159 U/L), and erythrocyte sedimentation rate (105 mm/hr). The biopsy specimen showed granulomas at the dermal-subcutaneous junction characterized by multinucleated giant cells and epithelioid histiocytes with a sprinkling of surrounding and intermixed lymphocytes.

Questions

1. What is the diagnosis?
2. How is the diagnosis made in such a patient?
3. Describe the etiology and pathogenesis of this condition.
4. What is the treatment and prognosis of this condition?

(Please turn to next page for answers.)

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Answers

1. What is the diagnosis?

The diagnosis is Lofgren's syndrome.

Lofgren's syndrome refers to the triad of erythema nodosum, bilateral hilar lymphadenopathy, and polyarthralgias, which represents an acute form of systemic sarcoidosis. It is common in European countries, but very rare in Japan. Most of the patients are white women, with a mean age of 37 (± 11) years. The onset of symptoms in nearly one half of the patients is between April and June.¹ Erythema nodosum (EN) is the most common nonspecific cutaneous lesion of sarcoidosis.² Erythema nodosum is usually the earliest manifestation of sarcoidosis, and a search for an etiologic agent is likely to be more fruitful in these patients.¹ Therefore the diagnosis of Lofgren's syndrome should be considered in any patient who presents with erythema nodosum.³

According to a worldwide review of 3676 sarcoidosis patients, erythema nodosum was found in 17% of cases [range 4% (Tokyo) to 33% (Edinburgh)].⁴ In a series of 106 patients with biopsy-proven erythema nodosum in Spain, 21 (20%) of them had Lofgren's syndrome ($n = 17$) or sarcoidosis ($n = 4$).⁵

The other etiologic factors leading to EN can be divided into:⁶

PHARMACOLOGIC CAUSES: Several drugs including sulfonamides, bromides, iodides, omeprazole and oral contraceptives.

INFECTIONS: tuberculosis, streptococcal infection, leprosy, yersinia infections, campylobacter infections, hepatitis C, Epstein-Barr virus, and syphilis.

FUNGAL CAUSES: histoplasmosis, coccidioidomycosis, blastomycosis, and tinea capitis.

CHRONIC MEDICAL CONDITIONS:

Sarcoidosis, inflammatory bowel disease, ulcerative colitis, and Crohn's disease.

Erythema nodosum also may signal the later onset of Behçet's syndrome, appearing up to 27 months before the disease.⁷

2. How is the diagnosis made in such a patient?

Preliminary diagnosis of sarcoidosis is based on the patient's medical history, routine tests, a physical examination, and a chest X-

ray. The diagnosis of sarcoidosis is confirmed by eliminating other diseases with similar features. These include such granulomatous diseases as berylliosis (a disease resulting from exposure to beryllium metal), tuberculosis, farmer's lung disease (hypersensitivity pneumonitis), fungal infections, rheumatoid arthritis, rheumatic fever, and cancer of the lymph nodes (lymphoma).

In the absence of a known causative agent, the diagnosis of sarcoidosis remains mainly a diagnosis of exclusion. Since there are no definitive diagnostic serological or radiological tests, the presence of non-caseating granulomas on tissue biopsy together with compatible clinical features is usually considered as proof of the diagnosis of sarcoidosis. However, even in cases with tissue biopsy consistent with the presence of sarcoidosis, other possible causes of granulomatous diseases should be evaluated. Although biopsy is not pathognomonic, tissue examination is essential to differentiate sarcoidosis from infections or malignancies.

Chest radiograph usually shows hilar adenopathy in combination with interstitial lung disorder. Chest computed tomography has been reported to be more sensitive than radiography.⁸

Measurements of serum angiotensin converting enzyme (ACE) level reflect the disease activity; ACE levels fluctuate with corticosteroid use, but are not specific enough for diagnostic purposes.⁹ High levels of serum ACE have also been reported for other diseases (for example, tuberculosis, leprosy, and diabetes mellitus). Moreover, as serum ACE levels reflect the systemic burden of inflammation, normal serum ACE levels do not exclude the diagnosis of sarcoidosis, especially not in those with isolated ocular disease.

The combination of raised serum ACE levels with abnormal gallium scanning was a specific and sensitive tool for diagnosing patients suspected of having sarcoidosis who had normal chest radiographs.¹⁰ Gallium scan uptake, serum lysozyme levels, hypergammaglobulinemia, and decreased delayed type hypersensitivity are not specific for sarcoidosis. In patients with active systemic sarcoidosis, gallium-67 scanning had a sensitivity of 95%, but a low specificity (68%), while the sensitivity of chest radiography was 80%, and of serum ACE 77%.¹¹

The Kveim-Siltzbach skin test in which spleen or lymph node homogenate from a patient with sarcoidosis is injected intradermally and later subjected to biopsy, is not widely available, not well standardized, and not approved for general use by the US Food and Drug Administration.¹²

3. Describe the etiology and pathogenesis of this condition.

The etiology of sarcoidosis remains unknown. A genetic predisposition to the disease has been described: patients with sarcoid acute arthritis (Lofgren's syndrome) have a higher prevalence of HLA-B8, HLA-DR17 and HLA-DR3 alleles.¹³

Sarcoidosis has been associated with increased T-cell responses and decreased cellular immunity due to the intense granulomatous formation along with frequent anergy to cutaneous antigens such as tuberculin, trichophyton, and mumps.¹⁴ The earliest immunologic event is often a CD4 T-cell alveolitis. Immunologic studies of biopsy material, infiltrates, and broncho-alveolar lavage have shown a predominance of T-helper cells and macrophages. Cytokine release from these T-cells may attract macrophages that in turn secrete IL-15 and stimulate T-cell growth perpetuating the response. Leukotriene B4 is also secreted by macrophages and amplifies the granulomatous reaction by recruiting mononuclear phagocytes from the peripheral blood.¹⁵

4. What is the treatment and prognosis of this condition?

Patients with Lofgren's syndrome have a good prognosis. Neville, et al.¹⁶ studied 251 cases of sarcoidosis presenting with EN; 83% of patients had remission of their sarcoidosis in 2 years, whereas 16% had active disease 2 years after presenting with EN. Mana, et al.¹⁷ noted in a multivariate analysis of 209 patients over a 14-year period that the absence of EN was a risk for persistent disease activity in sarcoidosis.

Although the overall prognosis for sarcoidosis is good, approximately 50 percent of patients have at least a mild degree of permanent organ dysfunction. Clinical variables associated with poorer prognosis include black race, onset of disease after the age of

40, symptoms that last for more than six months, the absence of erythema nodosum, splenomegaly, and the involvement of more than three organ systems.¹⁸

The optimal therapy for sarcoidosis is not well defined; therapeutic decisions are dictated by the localization of the disease and severity of organ involvement. The mainstay of treatment is corticosteroid therapy, which exhibits especially short term beneficial effects.¹⁹ The controversy remains, however, concerning the efficacy of corticosteroids to alter the natural course of the disease.

Of the alternatives, in refractory cases or when steroid sparing is desirable, the anti-malarial agent chloroquine (or hydroxychloroquine), methotrexate, and azathioprine are currently the 'best buys'. Azathioprine, methotrexate, and chloroquine remain as viable alternatives or adjuncts to steroid treatment, most commonly as steroid sparing agents. Azathioprine is usually reserved for severe refractory cases, and has occasionally been reported to be effective in sarcoidosis apparently resistant to steroid treatment. In a recent study azathioprine combined with prednisolone was reported to induce remissions in a small number of patients with chronic relapsing pulmonary disease. Rather more experience has been reported with the use of the folate antagonist methotrexate, though largely from one group of investigators.²⁰ Their observational data on prolonged treatment in more than 100 patients suggest functional improvement and the ability to reduce or withdraw chronic steroid treatment in a significant proportion. The drug is given orally once a week in a usual dose of 10 mg.

Other than corticosteroids, the drug with the best controlled evidence in sarcoidosis is chloroquine. It has been widely used by dermatologists treating cutaneous sarcoidosis.²⁰ Unfortunately, the long-term administration of chloroquine can lead to irreversible retinopathy and blindness. Therefore, careful eye examinations are required every three to six months. Because of the risk of retinopathy, chloroquine treatment is best limited to a six-month period of time.²¹ Hydroxychloroquine has been used for prolonged periods without retinal damage. Hydroxychloroquine is preferred to chloroquine, because of the lower risk of ocular toxicity.²¹

New agents, including pentoxifylline, thalidomide, and infliximab have proved useful in selected cases. The effectiveness of these agents seems to lie in their ability to block Tumor Necrosis Factor (TNF), especially in the treatment of chronic disease.²² TNF-alpha appears to be an important cytokine in the inflammation in sarcoidosis.²³ Infliximab is a chimeric IgG monoclonal human-murine antibody against human TNF—in clinical use primarily for rheumatoid arthritis and Crohn's disease. However, recent case reports suggest that infliximab therapy may be effective in patients with refractory pulmonary and systemic sarcoidosis.²⁴

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