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ENDGAMES

CASE REVIEW

Just a painful swelling of the ankles?

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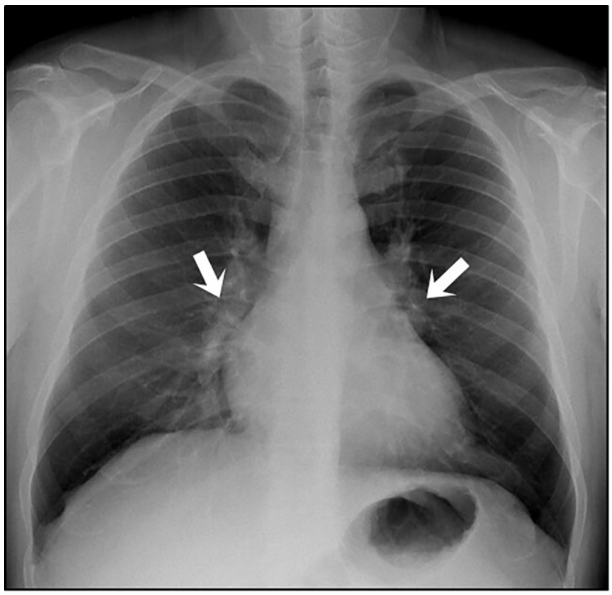
A 41 year old man presented with a three week history of acute painful swelling of both ankles accompanied by local erythema and heat, morning stiffness of short duration, and fever. During the fourth week, a tender nodular erythematous eruption developed in both legs, suggestive of erythema nodosum. The man had no personal, family, or epidemiological medical history. He reported no previous infections, trauma, or new medications. On physical examination, his temperature was 38.2°C. There was erythema, oedema, pain, and heat in both ankles, with a normal range of movement in the ankle joints, and lesions compatible with erythema nodosum on the anterior aspect of both legs.

Laboratory results showed

- Leucocytosis of 14.5×10^9/L (reference range 4-10) with neutrophilia
- Erythrocyte sedimentation rate of 56 mm in first hour (1-20)
- C reactive protein 9.53 mg/dl (<0.5)
- Normal results on tests of renal, liver, and thyroid function
- Normal levels of calcium (serum and urinary); 1,25-dihydroxyvitamin-D, and angiotensin converting enzyme
- Negative blood and urine cultures, viral serology (Epstein-Barr, cytomegalovirus, HIV, hepatitis, parvovirus-B19), interferon-gamma-release-assay, and negative autoantibody test results
- Chest radiography showed mild bilateral hilar lymphadenopathy (fig 1). A chest computed tomography scan and 18F-FDG-PET/computed tomography scan confirmed symmetrical bilateral hilar lymphadenopathy, with no other findings. Ankle ultrasound showed bilateral peri-articular soft tissue oedema, without synovitis or tenosynovitis.
- Bronchoalveolar lavage fluid contained 45% lymphocytes, 11.1 CD4/CD8 cell ratio, and negative bacteriological examination. Bronchial aspiration showed polymorphonuclear cells. Pulmonary function tests were normal.



Radiograph of the chest showing bilateral hilar lymphadenopathies (arrows)

Questions

1. What is the most likely diagnosis?
2. Are further tests needed to confirm the diagnosis?
3. How is this condition managed and what is the prognosis?

Answers

1.

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What is the most likely diagnosis?

Short answer

The combination of arthralgia (with ankle involvement), erythema nodosum, and bilateral hilar lymphadenopathy make Löfgren syndrome,[1] an acute form of sarcoidosis, the most likely diagnosis.

Discussion

Löfgren syndrome occurs in 2% to 50% of patients with sarcoidosis.[2 3] The lowest rate is reported in Japan and the highest in Spain and northern European countries.[4] The condition involves erythema nodosum, bilateral hilar lymphadenopathy, and arthritis or arthralgia (the ankle being the most frequently involved joint). It can also present with non-specific signs, such as fever. Löfgren syndrome is generally a self limiting disease, resolving within a few months, although articular manifestations might persist for more than two years in some cases.[5]

Differential diagnoses for bilateral hilar lymphadenopathy include lymphoma, infection, and autoimmune disease.

Negative serology and cultures make infectious disease unlikely.

Lymphoma is considered unlikely because of the absence of asymmetric hilar lymphadenopathy,[6] weight loss, or coexisting extrathoracic lymphadenopathy.

Some autoimmune conditions can present with all the features observed in Löfgren syndrome; however, the absence of oral and genital ulcers (as, for example, in Behçet syndrome), arthritis, or internal organ involvement (eg, connective tissue diseases), abdominal pain, diarrhoea, and weight loss (eg, inflammatory bowel diseases) make these diagnoses less likely.

2. Are further tests needed to confirm the diagnosis?

Short answer

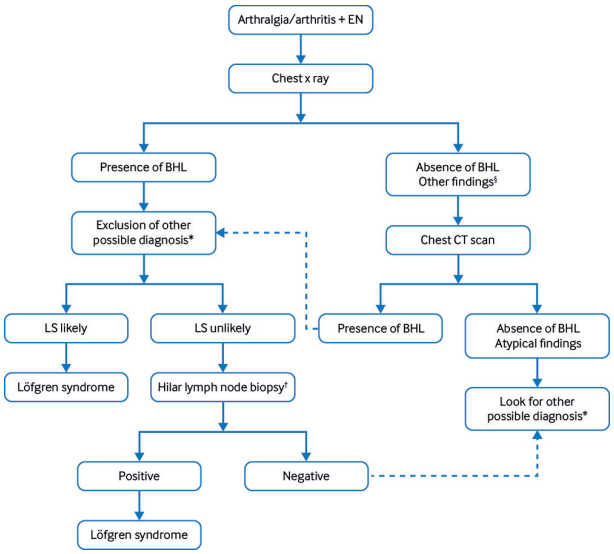
The diagnosis of Löfgren syndrome relies on clinical history, examination findings, and exclusion of other diagnoses. A hilar lymph node biopsy is often needed to verify a diagnosis of sarcoidosis; however, the presence of typical features of Löfgren syndrome (bilateral hilar lymphadenopathy, erythema nodosum, and arthritis/arthralgia) confers a high diagnostic specificity, and hence invasive diagnostic tests are usually not needed.

Discussion

The diagnosis of sarcoidosis is based on clinical and radiological findings[7] after similar conditions have been excluded. If necessary, a biopsy with evidence of non-caseating granulomas verifies the diagnosis, but this is seldom needed in the presence of specific clinical and radiological findings.

Angiotensin converting enzyme levels reflect the total body granuloma burden in sarcoidosis. However, testing of these levels as a diagnostic tool is questionable, because of poor sensitivity and specificity.[3 8] Elevated levels of angiotensin converting enzyme are often absent in Löfgren syndrome.[5] Studies show that an elevated level of soluble IL-2 receptor is a more sensitive marker for diagnosis of sarcoidosis, and is an indicator of disease activity,[9] but testing is not widely available. Chest radiography is often requested to look for hilar lymphadenopathy.

A proposed diagnostic algorithm for Löfgren syndrome is shown in figure 2.



Diagnostic approach to Löfgren syndrome. EN: erythema nodosum; CT: computed tomography; LS: Löfgren syndrome; BHL: bilateral hilar lymphadenopathy. §Doubtful or atypical hilar lymph node enlargement and/or pulmonary involvement; *See discussion of differential diagnosis. †Characteristic findings of sarcoidosis: non-caseating epithelioid cell granulomas with lack of acid fast bacilli. #Common differentials: infections, drugs, malignancy, autoimmune/inflammatory conditions

3.

How is this condition managed and what is the prognosis?

Short answer

The main treatment for musculoskeletal symptoms and erythema nodosum (both cardinal manifestations of Löfgren syndrome) is non-steroidal anti-inflammatory drugs (NSAIDs) and bed rest. In refractory cases, a short period of oral corticosteroids might be given.

Löfgren syndrome generally has a good prognosis, with >80% of patients achieving complete remission in 3-24 months.[5]

Discussion

Erythema nodosum treatment is detailed in box 1.[10 11]

Box 1: Management of erythema nodosum

General measures

- Treatment of the underlying cause
- Leg elevation
- Rest
- Compression stockings (if tolerated)

Pharmacological treatment

First line treatment
- NSAIDs
  Ibuprofen 400-800 mg, 3-4 times daily
  Naproxen 250-500 mg, twice daily
  Indomethacin 25-50 mg, 2-3 times daily
- Potassium iodide* 300 mg, 3 times daily

Second line treatment†
- Systemic glucocorticoids (second line)
- Prednisolone 20-40 mg/day

Alternative treatment for chronic/recurrent erythema nodosum**
- Dapsone 50-100 mg/day
- Colchicine 0.6-1.2 mg, twice daily
- Hydroxychloroquine 200 mg, twice daily
- Intralesional corticosteroid injection (eg, single dose of 10-20 mg/ml of triamcinolone acetonide)
- Other immunosuppressant therapy (eg, tumour necrosis factor-α inhibitors, ciclosporin, thalidomide, methotrexate)

*Avoid if tuberculosis suspected
†Infectious causes should be ruled out

In cases of progressive pulmonary involvement or severe extrapulmonary disease, the British Thoracic Society recommends oral corticosteroids (prednisolone or equivalent, 0.5 mg/kg/day for four weeks, reducing to a maintenance dose to control symptoms and disease progression) for 6 to 24 months.[12] In most cases of Löfgren syndrome this will not apply, as 97% of patients have asymptomatic stage 1-2 chest radiograph changes, as defined by the Scadding Staging System of sarcoidosis. These changes correspond mostly to nodal enlargement.[5]

Around 8% of patients have persistent symptoms two years after the diagnosis, and 6% have recurrent episodes.[5] There are no standardised follow-up recommendations for these patients, and they should be considered on a case by case basis. We suggest the following approach:

1. Pulmonary function test, chest radiograph, blood tests at least every six months.

2. If asymptomatic, clinical assessment can be performed at least every three to six months initially, and if stable, these intervals can subsequently be increased.

3. If the patient is symptomatic, treat with NSAIDs or steroids and review every one to three months, depending on disease severity and response to treatment.

4. Refer the patient to specialised care if the condition is refractory to usual treatment or there is evidence of disease progression (eg, onset of new manifestations, or worsening of previous symptoms/physical findings, laboratory/imaging abnormalities, or indication of major organ involvement).

Patient outcome

The patient's symptoms (fever, erythema nodosum, arthralgia) persisted, and elevated inflammatory markers were unresponsive to bed rest and treatment with NSAIDs for Löfgren syndrome. A positron emission tomography/computed tomography scan was performed to better assess inflammatory activity, identify occult extrathoracic disease, and help exclude underlying disease other than sarcoidosis (eg, malignancy or infectious conditions).[3 13]

Treatment with oral prednisolone was required (0.5 mg/kg/day), and the dose was reduced over three weeks. During this period, the skin and joint manifestations resolved, acute phase reactants returned to the normal range, and hilar lymphadenopathy regressed. No recurrence has been observed since.

We have read and understood the BMJ policy on declaration of interests and declare no competing interests.

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Patient consent obtained.

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