IMAGES IN SARCOIDOSIS

Lofgren's syndrome: A clinical puzzle in a case of monoarthritis

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Case presentation

A 34-year-old woman presented to our outpatient clinic with complaints of pain and swelling of the left ankle, multiple painful reddened swellings on the skin of both legs and high fever. The symptoms had an acute onset one week prior. Initially, ankle pain developed, followed by the appearance of skin lesions and fever up to 38.5 °C, which subsequently decreased spontaneously. Physical examination revealed bilateral skin lesions compatible with erythema nodosum (Figure 1A), and monoarthritis of the left ankle (Figure 1B). Acute phase reactants were high (ESR: 76 mm/h and CRP: 1.9 mg/dL). RF, anti-CCP and ANA tests ordered for differential diagnosis were negative. Calcium and serum ACE levels were within the normal range, but vitamin D was low. The ultrasound showed left tibiotalar joint effusion. Chest radiograph showed bilateral hilar lymphadenopathy (Figure 2). A chest computed tomography scan revealed bilateral hilar lymphadenopathy with patchy ground-glass opacities and nodular infiltrates in the medial parts of the bilateral lower lobes. The combination of pulmonary infiltration and hilar lymphadenopathy was considered compatible with stage 2 sarcoidosis according to Scadding scoring (1). The patient was diagnosed with Lofgren's syndrome and started on ibuprofen treatment. However, low-dose corticosteroid was added due to insufficient regression of arthritis. A complete clinical response was achieved.

Discussion

Lofgren's syndrome is an acute-onset variant of sarcoidosis characterized by fever, hilar lymphadenopathy, erythema nodosum and arthritis. This syndrome, which accounts for approximately 5-10% of sarcoidosis cases, is more common in the 3-4th decade of life and in females (1, 2). Fever and erythema nodosum are also more common in women. Lung imaging shows bilateral hilar lymphadenopathy in almost all cases. Laboratory tests show an elevated ESR in most patients, and hypercalcemia in only 2% of patients (2). Serum ACE levels may be elevated in 15% of patients and arthritis is more persistent in these patients (3). Bilateral hilar lymphadenopathy, erythema nodosum and bilateral ankle arthritis can make the diagnosis with 93% sensitivity and 95% specificity (4). Biopsy may be necessary in the presence of atypical clinical and radiological findings, or when there is doubt about the diagnosis. Among

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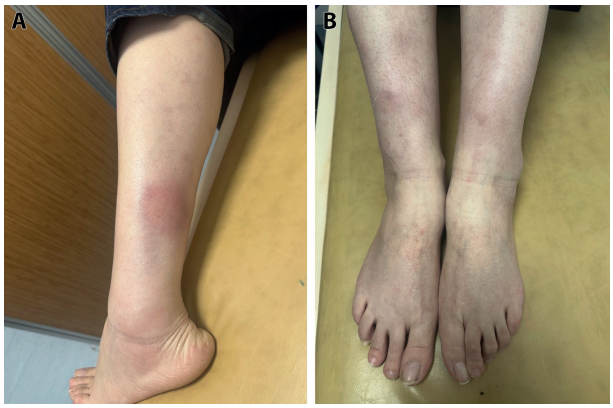

Figure 1. (A) Erythema nodosum on the left leg. (B) Left ankle arthritis.

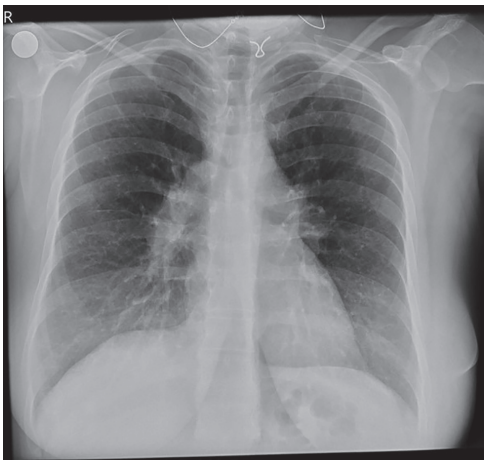

Figure 2. Bilateral hilar lymphadenopathy on chest radiograph.

the rheumatic diseases, reactive arthritis, rheumatoid arthritis, and crystal arthritis should be considered in the differential diagnosis of Lofgren's syndrome. Lofgren's syndrome is a self-limiting disease and does not require specific treatment. NSAIDs may be given in symptomatic cases. Hydroxychloroquine or colchicine are other treatment options in resistant erythema nodosum lesions. Short-term low-medium dose corticosteroids can be used in symptomatic arthritis that does not respond to NSAIDs (5). Although serum ACE levels may be elevated in a subset of patients, there is currently no strong evidence to support their use for diagnosis, prognostication, or monitoring of sarcoidosis (1). Genetic factors play a pivotal role in disease susceptibility and outcome. HLA-DRB1*03, *0301, and *1501 have been linked to Lofgren's syndrome, whereas HLA-DRB1*07, *14, *15, *01, *03, and DQB1*0602 are associated with progressive pulmonary sarcoidosis (1, 6, 7). In a Turkish cohort, HLA-DRB1*10 and HLA-DRB1*03 were correlated with favorable outcomes, while HLA-DRB1*13 and HLA-DQB1*06 conferred increased susceptibility (8). Similarly, a Scandinavian study confirmed the association between HLA-DRB1*03 and acute-onset sarcoidosis with spontaneous remission (7). At the immunopathogenic level, Lofgren's syndrome represents an acute and self-limiting immunogenetic subtype of sarcoidosis, characterized by a transient yet exaggerated Th1/Th17-mediated immune response. In genetically predisposed individuals particularly those carrying HLA-DRB1*03 or HLA-DQB1*02 alleles, exposure to self or environmental antigens triggers activation of macrophages and dendritic cells, leading to CD4□ T-cell recruitment and the release of pro-inflammatory cytokines such as TNF-α, IFN-γ, and IL-17. The mTORC1 and Rac1 signaling pathways further amplify macrophage proliferation and granuloma formation; however, immune regulation is typically restored, preventing chronic progression (9). Consequently, this transient immunologic activation likely accounts for the favorable prognosis and spontaneous remission commonly observed in this acute sarcoidosis phenotype. Large multicenter data indicate that Lofgren's syndrome predominantly affects younger women, presents with stage I radiologic findings, and carries a markedly lower risk of chronic evolution, whereas older age and stage II disease predict a more persistent course (10). Taken together, these findings suggest that our patient's presentation with arthritis, erythema nodosum, and bilateral hilar lymphadenopathy along with a rapid response to low-dose corticosteroid therapy reflects a transient, genetically mediated inflammatory process consistent with the benign course of Lofgren's syndrome.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Ethical Approval: This was a purely observational case study which did not alter the patient's management and clinical outcomes. Thus, ethics approval was not required for this case report.

Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: No datasets were generated or analyzed in this case report.

Declaration on the Use of AI: The authors declare that no AI tools were used in the preparation of this manuscript.

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