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All Red is Not Always Bacterial Cellulitis: A Case of Löfgren's Syndrome

Gagan Kumar, MD; Nilay Kumar, MD, MPH

ABSTRACT

Löfgren's syndrome is a rare variant of sarcoidosis characterized by the triad of hilar adenopathy, acute polyarthritis, and erythema nodosum. It can be the first presentation of underlying sarcoidosis. Also, the initial presentation of Löfgren's syndrome may be confused with cellulitis. This is a self-limiting disease with a very good prognosis. Non steroidal anti-inflammatory drugs (NSAIDs), along with supportive care and close monitoring, are the mainstay for treatment.

CASE

A 53-year-old man presented with progressively worsening pain and erythema in the right foot for 2 weeks. He was seen by his primary care physician for this condition and was empirically started on antibiotics (500mg of oral cephalexin 2 times daily) for 10 days to treat presumed cellulitis. He did not have any significant contributory past medical history. Despite the antibiotic treatment, the erythema worsened over the next week and spread toward the leg. He then developed episodic fever spikes to 101°F and a painful effusion in the right ankle joint. He revisited his primary care physician after completing the antibiotic course and his antibiotic was changed to trimethoprim-sulfamethoxazole to cover for community-acquired, methicillin-resistant *Staphylococcus aureus* cellulitis. The erythema continued to worsen and progressed to his shins. He then developed new tender nodular erythematous lesions in his bilateral lower extremities. Despite continued antibiotic therapy, the patient continued to have low-grade fevers and was admitted to inpatient medical service for further evaluation. He did not recall any trauma or significant travel history prior to his symptoms.

On admission, the patient had a temperature of 101°F, but was otherwise hemodynamically stable. On examination he appeared comfortable. He had a confluent erythematous macular lesion on the dorsal aspect of right foot and right shin and 2-3 cm circular erythemaous macular lesions on his left shin (consistent with erythema nodosum [EN]). Also noted was an effusion involving the right ankle joint that was tender to palpation, with somewhat limited range of motion without any distal neurovascular compromise. The rest of his systemic examination was unremarkable. He was noted to have leucocytosis of 13.2×10^9 cells/L with 91% neutrophils. His inflammatory markers were elevated with an erythrocyte sedimentation rate (ESR) of 48 and C-reactive peptide of 17.2. Complement levels were normal. His chest X-ray and urine analysis were normal. Blood cultures were drawn on admission and continued to test negative.

He was started on the broad spectrum antibiotics vancomycin and piperacillin/tazobactam. As the lesions continued to worsen, a skin biopsy was performed that revealed features suggestive of panniculitis. Special stains were performed and tested negative for microorganisms. The diagnosis of EN was also suggested but could not be made definitively due to insufficient subcutaneous tissue in the specimen.

An infectious disease consultation was obtained. An array of further testing was done that included antistreptolysin-O (ASO) titres for streptococcus, serum quantiferron for mycobacterium, polymerase chain reaction (PCR) for mycoplasma, enzyme linked immunosorbent assay (ELISA) for HIV 1 and 2, and fungal antigen. These all came back negative. Blood cultures and wound cultures did not show any bacterial or fungal growth. The antibiotics were discontinued on the second day.

For further evaluation of systemic causes for EN noted on the patient's legs, a computed tomography

Author Affiliations: Hospital Medicine, Froedtert & The Medical College of Wisconsin, Milwaukee, Wis.
Corresponding Author: Gagan Kumar, MD, Assistant Professor, Section of Hospital Medicine, Froedtert & The Medical College of Wisconsin, Clinical Cancer Center, 5th Fl, 9200 W Wisconsin Ave, Milwaukee, WI 53226; phone 414.805.0820; fax 414.805.0855; e-mail gkumar@mcw.edu.

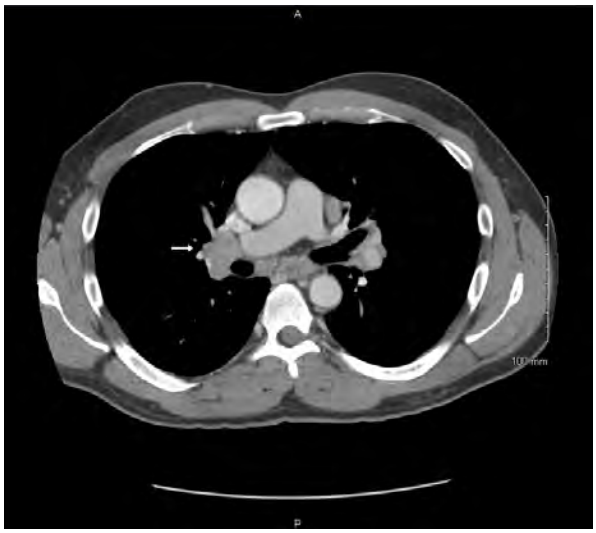

Figure 1. Contrast-enhanced computed tomography (CT) of chest showing hilar lymphadenopathy.

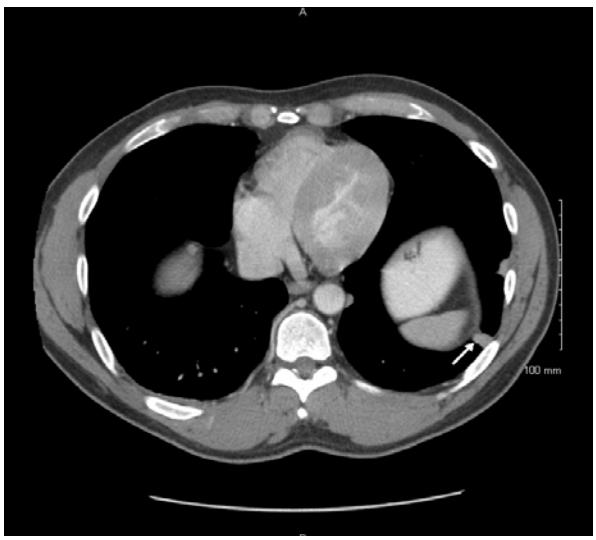

Figure 2. Contrast-enhanced computed tomography (CT) of chest showing sarcoid nodules.

(CT) scan of his chest and abdomen were done to exclude lymphoma and sarcoidosis. The CT scan revealed multiple mediastinal and hilar lymph nodes and pulmonary nodules suggestive of sarcoidosis. For definitive diagnosis, a mediastinoscopy and biopsy, along with video-assisted thoracic lung surgery (VATS) and wedge biopsy, was performed (Figures 1 and 2). The histopathology on the tissue sample showed non-necrotizing granulomas consistent with sarcoidosis. In light of the new findings, the patient was diagnosed with Löfgren's syndrome and started on ibuprofen 400mg by mouth twice daily. The patient showed significant improvement with this therapy and was discharged home with instructions to follow up with his primary care physician in 1 month. His lesions continued to respond very well to the treatment, and his fevers and the effusion in the right ankle also resolved.

DISCUSSION

Löfgren's syndrome was first described by Sven Löfgren in 1953. The syndrome consists of triad of EN with bilateral hilar lymphadenopathy and arthralgia or arthritis. It is currently considered a variant of sarcoidosis. The periarticular ankle inflammation associated with bilateral hilar lymphadenopathy is considered a variant of Löfgren's syndrome.[1] Other symptoms include fever (38%), cough (13%), hepatomegaly (6%), hypercalcemia (2%), and salivary gland hypertrophy (1%).[2]

A biopsy is needed for definitive diagnosis for sarcoidosis and Löfgren's syndrome and to rule out other conditions such as fungal infection, tuberculosis, lymphomas, and bronchogenic carcinoma, among others that can cause hilar lymphadenopathy with EN. The histopathology of the lymph nodes reveals non-caseating granulomas. Angiotensin converting enzyme (ACE) level is elevated in 50% of patients[2] with EN but is nonspecific and can be elevated in hepatitis, lymphomas, and other conditions. The ACE levels can be useful as a follow-up marker for resolution of disease. Other tests, such as Ga^{67} scan, are not specific for sarcoidosis and are not clinically useful.[2] The workup should include a CT scan of the chest to evaluate hilar lymphadenopathy.

Although rare and a diagnosis of exclusion, Löfgren's syndrome should always be considered in patients with EN. In a study of 106 patients with biopsy proven EN, 22% of the patients were found to have Löfgren's syndrome or sarcoidosis.[3] Other etiologies to consider while evaluating a case of EN are viral upper respiratory tract infection (20%), Group A beta hemolytic streptococci (7%), tuberculosis (5%), drugs like penicillin and sulpha drugs (3%), inflammatory bowel disease, and malignancy.[3] Idiopathic cause constitutes one-third of the causes.[3]

NSAIDs are the mainstay of treatment along with bed rest. Steroids can be used in serious arthritis, hypercalcemia, and granulomatous skin lesions.[4] The prognosis of Löfgren's syndrome is excellent; in 1 of the largest studies of 186 patients, only 8% of patients had significant disease at the end of a 2-year follow-up.[1]

CONCLUSION

Löfgren's syndrome can present as erythematous lesion in lower extremities with fever and mild leucocytosis

and can be difficult to differentiate from cellulitis in early stages. Poor response to antibiotics, typical skin lesions, and presence of arthritis or arthralgia should raise the suspicion of this entity and skin biopsy should be performed to confirm it. Workup for infectious etiologies like group A streptococcus, mycobacterium, fungal, and viral causes should be performed. Prognosis is good and relapse is uncommon. The treatment of choice is NSAIDs.

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