CASE REPORT

Löfgren's Syndrome: An Acute Variant of Sarcoidosis Diagnosed by Mediastinoscopy

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ABSTRACT

Löfgren's syndrome is an acute clinical form of sarcoidosis that is first described by Sven Löfgren as bilateral hilar lymphadenopathy together with Erythema Nodosum (EN) and accompanying arthritis/arthralgia. This syndrome has some differences in terms of treatment, prognosis and recurrence compared to sarcoidosis. In this report, we describe a 70 years old lady who admitted with multiple erythematous lesions and arthralgia of both lower extremities and she was diagnosed as Löfgren's syndrome via mediastinoscopy.

Key Words: *Löfgren's syndrome. Sarcoidosis. Mediastinoscopy. Erythema nodosum.*

INTRODUCTION

Sarcoidosis is a multisystemic disorder of unknown cause characterized by non-caseating granulomatous lesions in different tissues. It is seen more frequently in women than men. The global incidence of sarcoidosis is 16.5 - 19/100,000.[1] The clinical presentation of sarcoidosis depends on which organ involved. Also it causes cutaneous lesions classified as specific and non-specific. The acute form of sarcoidosis that includes Erythema Nodosum (EN), which is a non-specific cutaneous lesion caused by sarcoidosis, bilateral hilar Lymphadenopathy (LAP) and arthritis or arthralgia is called the Löfgren's syndrome.[2,3]

In this report, the authors present the case of a patient with bilateral multiple EN on the pretibial location and was diagnosed as Löfgren's syndrome with mediastinoscopy.

CASE REPORT

A 70 years old female patient was presented to the internal medicine outpatient clinic with the complaint of multiple swollen, painful and erythematous lesions that are located bilaterally on anterior surfaces of both legs. According to patient's anamnesis, these lesions were developed 4 - 6 months ago and were resolving without scarring over a 3 - 4 weeks period. Malaise, weight loss, arthralgia and fever (38.2°C) were accompanying to these lesions for 8 weeks. She also had a history of vertigo and hypertension. Physical examination finding were blood pressure = 140/80 mmHg, heart rate = 88/minute and regular, body temperature = 36.5°C, and respiratory rate = 15/minute and regular. Multiple erythematous, solid and painful subcutaneous nodules were found on bilateral pretibial region, the biggest of which were 6 x 6 cm and 3 x 3 cm (Figure 1). The remaining systems examination revealed no abnormalities. The lesions found on the physical examination were initially pre-diagnosed as EN.

Further diagnostic workup was started for etiology of these lesions. For the differential diagnosis detailed physical examination and bilateral lower extremity Doppler Ultrasonography (US) was performed. There were no petechia, purpura, hemorrhagic bulla, ulceration and *livedo reticularis* on physical examination. Doppler US revealed no abnormalities in veins and arteries of lower extremities. So cutaneous vasculitides and superficial thrombophlebitis were eliminated. Cultures of throat, oropharynx, urine and blood were obtained and no pathologic bacteria were found. There was no lymphadenopathy on physical examination. Additional bacterial, viral and parasital tests were performed to rule out other causes of fever but revealed no abnormalities. Common infectious etiology of these nodular lesions was ruled out with these results. According to history, detailed examination, and typical location with typical behavior of lesions, the lesions of patient were diagnosed as EN. Complete blood count, posterior-anterior chest X-ray, liver function tests, Erythrocyte Sedimentation Rate (ESR), Anti-Streptolysin O (ASO) and renal function tests (Table I) were then performed. Her ESR was found 103 mm after 1st hour (normal range: 0 - 20 mm after first hour). Patient's chest X-ray revealed bilateral hilar widening. Thorax Computed Tomography (CT) was performed and revealed mediastinal Lymphadenopathy (LAP) in the stations 4R, 10R and 10L. Purified Protein Derivative (PPD) skin test

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Table I: Patient's laboratory values.

Parameter	Normal range	Result	Parameter	Result
Glucose (mg/dL)	60 - 100	84 mg/dL	Anti Toxoplasma IgG	Negative
AST (U/L)	5 - 32	11 U/L	Anti Toxoplasma IgM	Negative
ALT (U/L)	5 - 33	18 U/L	Anti EBV EA IgM	Negative
D.Bilirubin (mg/dL)	0 - 0,3	0,18 mg/dL	Anti EBV EBNA IgM	Negative
T.Bilirubin (mg/dL)	0 - 1,2	0,27 mg/dL	Anti VCA IgM	Negative
Potassium (mmol/L)	3,5 - 5,1	4,9 mmol/L	Anti HBs	Negative
Creatinin (mg/dL)	0,7 - 1,2	0,77 mg/dL	Anti HCV	Negative
BUN (mg/dL)	0 - 50	41 mg/dL	Anti HIV	Negative
Total protein (gr/dL)	6,4 - 8,3	6,48 gr/dL	HBs Ag	Negative
Albumin (gr/dL)	3.9 - 4.9	3,4 gr/dL	PPD	Negative
B12 (pg/mL)	191 - 663	396 pg/mL	HLA B5	Negative
Phosphorus (mg/dL)	2,5 - 4,5	3,44 mg/dL	ANA	Negative
Calcium (mmol/L)	8,6 - 10,2	9 mmol/L	A-CCP	Negative
Hemoglobin (gr/L)	13 - 16	12,6 gr/L		
WBC (10^3/uL)	4000 - 10000	13500 10^3/uL		
Platelet (10^3/uL)	400 - 1000	496000 10^3/uL		
MCV (fL)	80 - 100	92 fL		
ESR (mm/h)	0 - 20	103 mm/h		
CRP (mg/dL)	0 - 08	21 mg/dL		

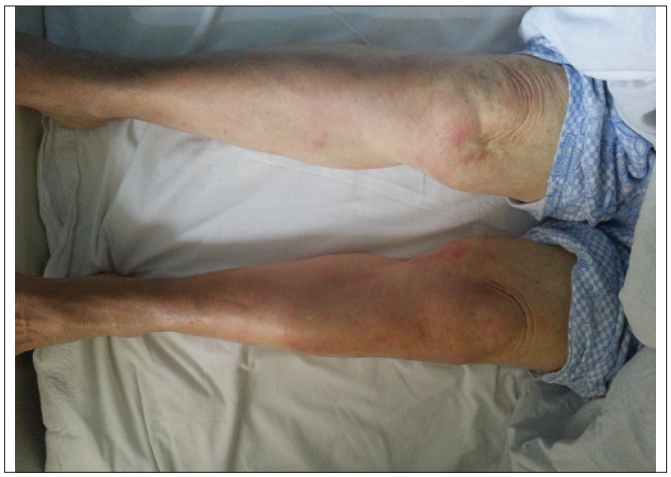

Figure 1: Erythematous lesions of the patient.

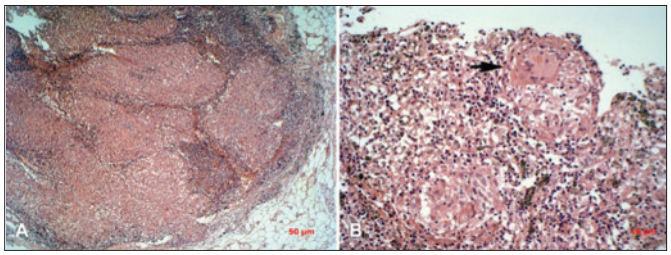

Figure 2: A. Granuloma formations that destroy the lymph node architecture and tend to coalesce (Hematoxylin Eosin x 50) **B.** Giant cells that are seen in non-caseating granulomas (arrow, Hematoxylin Eosin x 200).

and Acid Resistant Bacilli (ARB) stain of sputum specimen was performed to rule out tuberculosis and was found negative.

At this point, the thoracic surgery department was consulted to perform mediastinoscopic lymph node biopsy. Multiple biopsies from the lymph node at the mediastinal 4R station via standard cervical mediastinoscopy were taken and sent to the pathology laboratory for investigation. The result of the histopathological analysis of the biopsy material was reported as non-caseating granulomatous lymphadenitis (Figure 2). Etiology of the EN was established as sarcoidosis with this histopathological finding. The patient was clinically diagnosed as Löfgren's syndrome with the findings of EN, bilateral hilar LAP and polyarthralgia. She was referred to the internal medicine clinics for the treatment and follow-up of the acute variant of sarcoidosis, the Löfgren's syndrome. She responded well to anti-inflammatory treatment and bed rest and is still under follow-up without any recurrence with the interval of 3 months.

DISCUSSION

EN is usually seen in the lower extremities with painful, tender, erythematous subcutaneous inflammatory nodules. It is a self-limiting disease related to several systemic disorders (sarcoidosis, Behçet's disease, connective tissue disorders), infectious diseases (*Streptococcus* infections, toxoplasmosis, blastomycosis, histoplasmosis, mycoplasma infections) and drug use (penicillin, oral contraceptives).[4] This patient has presented with painful and erythematous lesions on her lower extremities, and was pre-diagnosed as one of the granulomatous diseases as a result of laboratory tests and cultures. Diagnostic biopsies were taken from the mediastinal lymph nodes via mediastinoscopy and the patient was histopathologically diagnosed as sarcoidosis.

In order to certify the diagnosis of sarcoidosis histopathological proof is necessary in addition to clinical findings.[1,5] In sarcoidosis, biopsies should be taken from the tissues that non-caseating granulomas could be

found. As in this case, in the patients who have bilateral hilar and mediastinal lymphadenopathy, biopsies should be taken from the lymph nodes that are found can be diagnostic. Mediastinoscopy, which is a method of biopsy, is an effective and trustworthy method for lymph node biopsy in experienced hands.[6]

EN is the most common among the cutaneous lesions seen in sarcoidosis with the rate between 20 - 35%.[7] Besides, sarcoidosis and its acute variant, the Löfgren's syndrome is the second most common cause of EN after idiopathic ones.[4] This patient also presented with complaints of EN and arthralgia. Polyarthralgia and EN may be present in many collagen tissue disorders. In this patient, these diseases were eliminated with laboratory and biopsy results as mentioned in case section.

Löfgren's syndrome was first described by Sven Löfgren in 1953 as bilateral hilar lymphadenopathy together with EN and accompanying arthritis/arthralgia, is an acute form of sarcoidosis.[2,3] Sarcoidosis is usually a disease of adults under 40 years of age.[5] The incidence of sarcoidosis is higher in women than men and it is also increased in women aged more than 50 years. Despite a contradictory evidence in another report about late onset sarcoidosis that no women were diagnosed as late onset sarcoidosis, this patient with the age of 70 is the oldest patient to be diagnosed as Löfgren's syndrome in the academic literature.[8]

Löfgren's syndrome has some differences in terms of treatment, prognosis and recurrence compared to sarcoidosis. In contrast to sarcoidosis, Löfgren's syndrome is a self-limiting disease that usually lasts for 3 months. Short-term bed rest and non-steroidal anti-inflammatory treatment is usually enough. Usage of corticosteroids may be warranted for more severe cases with pulmonary parenchymal involvement, hyper-calcemia and severe arthritis.[9] Corticosteroid therapy in sarcoidosis can cause many complications in elderly patients such as this patient who was 70 years old. In this patient short-term bed rest and non-steroidal anti-inflammatory treatment was enough for symptomatic relief. This proved that the diagnosis was accurate and the treatment protocol was correct. The prognosis of the Löfgren's syndrome is better than sarcoidosis and its recurrence rates are considerably lower. It has been reported that remission with conservative treatment in patients with Löfgren's syndrome can be achieved in 3 - 12 months and have a very low relapsing rate of 6%.[10]

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