

When nuisance is nice: ignored erythema nodosa heralding the Löfgren's syndrome in a Nigerian woman

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Abstract

Löfgren's syndrome (LS) is a variant of sarcoidosis characterised by the triad of erythema nodosum (EN), radiographic bilateral hilar adenopathy, and arthralgia/arthritis. Like all cases of sarcoidosis, it is of unknown aetiology and may constitute a diagnostic difficulty in the ambiguous phenotype. Löfgren's syndrome is associated with a good prognosis and commonly undergoes spontaneous remission within four months. However, the co-existence of multiple good and adverse prognostic factors in a patient may call for guarded expectation. Sarcoidosis is generally more prevalent among people of African descent, but the vast majority of the literature on sarcoidosis are from the western hemisphere. Löfgren's syndrome has been rarely documented in West Africans despite the availability of some reports of sarcoidosis in the region. We present a case of a Nigerian woman with LS that started out as isolated EN, which was ignored for months until the onset of florid pulmonary and systemic symptoms.

Key words: sarcoidosis, erythema nodosum, Löfgren's syndrome.

Introduction

Sarcoidosis is an infiltrative granulomatous disorder of unknown origin. It is characterised by variable presentations and courses and often constitutes a diagnostic confusion in the ambiguous phenotype. Löfgren's syndrome (LS) is an acute benign form of sarcoidosis characterised by the triad of erythema nodosum (EN), radiologic evidence of bilateral hilar lymphadenopathy, and arthralgia/arthritis. While the pathogenesis of sarcoidosis has remained elusive, well-documented dysfunction of cellular immunity and inflammatory response are associated with the disease [1]. Sarcoidosis has a worldwide distribution, although rarely reported in Africans; the highest prevalence is in northern Europe. With a reported peak age of incidence between 20 and 40 years, epidemiological information of sarcoidosis from Africa is scarce [2]. Surveys from the United States, however, reveal an incidence rate of 35.5/100,000 and 10.9/100,000 cases among black and white Americans, respectively [3].

Löfgren's syndrome was first described in 1953 by Swedish clinician Sven Löfgren, and it has been mostly

reported among northern Europeans. It is, however, rare in Africans and Japanese [4, 5]. LS is considered to be associated with a good prognosis and is often a self-limiting disease. However, chronic inflammatory arthritis may be found especially in patients with the HLA-DR3 and DQ2 alleles [6]. Immunogenic peculiarities may underlie the disparities in the manifestations and the natural histories of this syndrome in different individuals [7]. Despite the few reports of sarcoidosis and associated extrapulmonary disease, LS is considered to be alien to West Africans. Herein we present the first case report of Löfgren's syndrome in a Nigerian woman.

Case presentation

A 39-year-old Nigerian woman presented to the rheumatology clinic with two-month history of cough, easy fatigability, and painful swelling of the ankles. The cough was dry, persistent, without any known aggravating or relieving factors. There was no history of orthopnoea or paroxysmal nocturnal dyspnoea. Fatigue had been persistent since onset of cough. It was worsened

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Fig. 1. Palpable nodules within inch long scar.



Fig. 2. Tender spots of Erythema nodosum.



Fig. 3. Early lupus pernio.



Fig. 4. Plain chest radiograph showing bilateral hilar adenopathy and reticulonodular infiltrates.

by moderate exertion but was not associated with respiratory distress. There was no fever or symptoms suggestive of any focus of sepsis. Both ankles were painful and swollen causing distress with mobility. She also had arthralgia in both knees and occasionally in the small joints of the hands. For several months prior to the onset of these symptoms, she noticed multiple recurrences of one or two painful spots on one or both legs or feet. These spots were not very distressing and there were several periods during which she forgot she had them. They seemed to disappear and re-appear at intervals and the patient never had to take any medication or see a doctor for that reason.

The described patient had sustained a slight injury to the dorsum of her right foot from a minimal domestic accident about a year earlier. This was treated with a few

stitches with resulting good healing within a short period. However, a month prior to presentation, she started experiencing new onset of pain and palpable nodules within the inch-long scar (Fig. 1) of the long-healed wound. On examination, two tender spots of EN (Fig. 2) were identified on her feet. Faint but distinctive hyper-pigmented patches of early lupus pernio (Fig. 3) were identified on her nasal alae. She was otherwise clinically stable.

The patient had presented at the pulmonology clinic where she was initially evaluated. Tuberculosis was ruled out by negative GeneXpert and sputum Acid and Alkaline Fast Bacilli tests. Chest radiograph showed bilateral hilar adenopathy and widespread reticulonodular infiltrates (Fig. 4).

Viral screening was negative for HIV, and hepatitis B and C. Serum electrolytes, urea, and creatinine were

within normal ranges. Full blood count and urinalysis were also normal. The erythrocyte sedimentation rate was 32 mm/hr and reference range of C-reactive protein (CRP) – 0–16 mg/dl. Antinuclear antibody was positive at a low titre of 1 : 80 with a speckled immunofluorescent pattern. A diagnosis of LS was made and an assay of serum angiotensin converting enzyme (ACE) was ordered. Treatment with prednisolone, azathioprine, and naproxen was started. The ACE level came out to be 104 U/l (reference: 8–50 U/l). The cough subsided within a week on immunosuppressants but the arthritis persisted. The patient had intra-articular triamcinolone injection into both ankles and was also placed on hydroxychloroquine. This treatment led to resolution of the arthritis but only a slight reduction in fatigue was observed. After four months on treatment, the EN and lupus pernio healed; the serum ACE concentration reduced to 54 U/l, and ESR and CRP reduced to 15 mm/hr and 7 mg/dl, respectively.

Discussion

Erythema nodosum is quite rare among previously reported cases of sarcoidosis in Nigeria, and the long history of recurrent EN before acute onset of LS is highly unusual for the known patterns of West African sarcoidosis [8, 9]. Typically, EN, which is an indicator of acute-onset disease, is more frequent among Caucasians with sarcoidosis while lupus pernio is common among people of African descent [1]. Although LS as an entity has been associated with a benign course of disease, the mixed picture of good and adverse prognostic features in our patient called for guarded expectations. The presence of the full triad of LS symptoms is sufficient for the diagnosis of sarcoidosis and the typical case of Löfgren's syndrome often undergoes spontaneous remission within four months [10, 11]. Our patient, however, also had lupus pernio, which has been linked with aggressive and persistent disease. Lupus pernio is frequently disfiguring as it can progress to destruction of the nasal cartilage, bone, and soft tissue. It is more often seen in female patients and tends to be associated with pulmonary parenchymal disease [12].

The aetiology of LS, just like other forms of sarcoidosis, is unknown but winter seasonality has been observed prompting the suspicion of a possible infective association. Postulations have been made to the effects of different polymorphisms in the CR2 gene on chromosome 3, one particular haplotype of which appears to be associated with an increased risk of LS [13, 14]. There is a strong association with human leukocyte antigen (HLA)-DRB1 allele, and the association with HLA-DRB1*03 is a very strong marker for a good prognosis [15]. Löfgren's syndrome with persistent arthritis has

also been associated with the black race, lupus pernio, and diffuse organ involvement [1, 11].

Sarcoid arthritis is seen in fewer than one quarter of patients and it is more prevalent in blacks [16]. Symmetrical ankle arthritis seems to be more typical and it may progress to joint destruction or the non-erosive Jaccoud's arthropathy [11]. Exceptionally high diagnostic utility has been found for the presence of any of the following three: symmetrical ankle arthritis, age below 40 years, and EN and symptom duration of less than two months [11]. Serum ACE tends to be elevated in 41% of all patients with sarcoidosis and 15% of those with LS, and the test has found application in the monitoring of the disease activity [11, 17]. Patients with elevated ACE levels tend to have a more persistent arthritis [11].

Infiltration of scar tissues has been well recognised in West African patients [18]. This is one of the more frequent cutaneous manifestations of sarcoidosis in the region. Commonly, long-standing tribal marks found on the face are invaded by the sarcoid granuloma and this may characterise an early manifestation of sarcoidosis. This is similar in mechanism to the frequent occurrence of scar sarcoidosis in tattoos and other skin traumas, and the finding of a presentation in this appearance should prompt an investigation for possible systemic sarcoidosis [19].

For most patients, fatigue is one of the most debilitating aspects of sarcoidosis and it has had a drastic impact on the health-related quality of life of our patient. The fatigue in sarcoidosis is more frequent in the younger patients than in the elderly and may not show much correlation with the overall disease activity. Although various factors including prednisolone use, obstructive sleep apnoea, and pulmonary hypertension have been associated with fatigue in sarcoidosis, multiorgan disease and multiple comorbidities seem to be the most important predictors of fatigue [20].

Sarcoidosis, a potentially difficult diagnosis to make, may mimic or co-exist with several rheumatic diseases and it is not strange to find positive antinuclear antibody in the sarcoid patient as it was in our patient [1]. Where locomotor symptoms are present, and especially in the absence of LS or failure to recognise it, the risk of erroneously diagnosing a primary rheumatic disease is higher and the need for demonstrating non-caseating granuloma by histology becomes more important.

Conclusions

Löfgren's syndrome has been rarely reported in West Africans but may have been frequently missed for reasons including the failure of all the components to emerge at the same time and paying inadequate atten-

tion to other attributes of the systemic disease like scar invasion and indolent lupus pernio.

The authors declare no conflict of interest.

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