CASE REPORT

Sarcoidosis with bilateral leg lymphedema as the initial presentation: a review of the literature

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ABSTRACT

Sarcoidosis is a granulomatous disease, characterized microscopically by noncaseating granulomas, which may involve multiple organs; however, the lung, skin, and lymph nodes are commonly affected. Sarcoidosis is a great imitator; in the skin, it presents with different cutaneous manifestations including lupus pernio, infiltrated plaques, maculopapular eruptions, infiltration of old scars, and subcutaneous sarcoidosis. Lymphedema as an initial presentation is extremely rare; cases are reported in African-American but not Asian patients. Lymphedema associated with sarcoidosis may result from lymphatic obstruction by infiltrating sarcoidosis. We present a case where the symptoms and signs of sarcoidosis were improved after treatment with systemic steroids.

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. The skin and lungs are the organs most commonly affected by sarcoidosis. In the skin, typical manifestations are infiltrated plaques, maculopapular eruptions, or subcutaneous involvements. Sarcoidosis with initial presentation of edema in bilateral lower extremities is extremely rare. This report presents the first case of sarcoidosis with initial presentation of leg edema in an Asian woman.

Case report

The patient was a 48-year-old housewife with no prior systemic diseases. She visited our outpatient department due to bilateral leg edema (Figure 1A). The edema was noted to gradually progress from both feet to both legs, and was accompanied by joint pain over the shoulders, ankles, and knees. The leg edema was mild pitting without significant surface change. An indurated noduloplaque lesion approximately 2 cm × 4 cm and associated with itching and tenderness was present on her right forearm (Figure 1B). There was no fever, dyspnea, blurred vision, or mucosal involvement. Physical examination showed bilateral clear breathing sounds and a regular heartbeat. No lymphadenopathy was palpable. However, multiple subcutaneous asymptomatic nodules developed over both legs in the subsequent examination (Figure 1C). Biopsy of the right forearm plaque revealed multiple noncaseating granulomas with fibrosis and cell infiltration in the subcutaneous fat. The granulomas were composed of multinucleated giant cells and a few histiocytes with chronic inflammatory cells (Figure 2). Special stains for foreign body, acid-fast bacilli, and fungi were all negative, rendering the pathologic diagnosis of sarcoidosis. Skin biopsy of another nodule on the leg also revealed multiple similar, dense, uniform, circumscribed nests of noncaseating granulomas infiltrating the dermis.

Blood examinations showed a twofold increase in the level of angiotensin-converting enzyme (45.85 IU/L, normal range < 22.5 IU/L). The tests for antinuclear antibody and rheumatoid factor were negative. The levels of complement components C3 (126.00 mg/dL) and C4 (29.80 mg/dL) were within the normal ranges. Complete blood cell counts and blood levels of urea nitrogen, creatinine, liver enzymes, and electrolytes were all within the normal ranges. Chest radiography revealed a left hilar nodule of approximately 0.8 cm. Additional chest computed tomography showed mildly enlarged lymph nodes (all < 1.3 cm) in the mediastinal and bilateral hilar regions, confirming the diagnosis of
sarcoidosis (Figure 3). The patient was treated with methylprednisolone at 0.5 mg/kg/d. The bilateral leg edema was significantly improved within 10 days and the subcutaneous nodules over the legs and right forearm were also resolved.

Discussion

Sarcoidosis is a common systemic, noncaseating granulomatous disease of unknown etiology. There is a higher incidence rate among African Americans and in women compared to men. Cutaneous sarcoidosis manifests itself in approximately 20–35% of patients with sarcoidosis; however, lymphedema is a rare initial manifestation of sarcoidosis.

Currently, few cases of sarcoidosis with initial presentation of leg edema have been reported in African Americans; however, no cases have been reported in Asians. The mechanisms of sarcoidosis-related leg edema are unknown; suggested etiologies include sarcoidosis-related lymphadenopathy (direct sarcoidosis infiltration or lymph duct obstruction by soft tissue sarcoidosis) and tenosynovitis. In the case presented here, the leg edema may be related to multiple soft-tissue sarcoidosis that led to upstream lymphatic duct obstruction.

Furthermore, elevated serum angiotensin-converting enzyme (ACE) levels were observed in our case. ACE converts angiotensin I into angiotensin II and inactivates bradykinin via the kallikrein-kininogen system. Elevated serum ACE levels are present in sarcoidosis; elevated levels may result from the production of ACE.
from the granuloma cells of sarcoidosis, or from the activation of the monocyte–macrophage–epithelioid cell system. ACE level is considered an activity marker of sarcoidosis.4

Corticosteroids remain the first-line treatment for localized or cutaneous sarcoidosis.5 Topical and intralesional corticosteroids are often prescribed for limited and discrete papules and plaques. For chronic and widespread lesions of sarcoidosis, systemic steroids may be considered at an initial dose of 0.5–1 mg/kg/d and gradually adjusted to the lowest effective dose.6 Alternatively, anti-inflammatory and immunosuppressive agents such as tetracycline and methotrexate are administered as monotherapy or as adjuvants to avoid corticosteroid use. For recalcitrant skin lesions of sarcoidosis, tumor necrosis factor-α inhibitors (infliximab and adalimumab) may be important treatments.

Only eight cases of sarcoidosis presenting with lymphedema are reported in the literature. Of these, six cases were women all of whom were aged 40–49 years, almost all cases were black patients, and two cases were African Americans. Our case is the first case reported in an Asian patient. Three of the reported cases had other skin manifestations, such as maculopapular eruptions, extensive ulcerations, and subcutaneous nodules. All patients were determined to have lymphadenopathy in further imaging studies; 50% were in bilateral hilar and inguinal lymph nodes. However, cervical, paratracheal, mediastinal, and retroperitoneal lymph node involvement was also reported. Although sarcoidosis can have diverse manifestations, the first-line treatment is systemic corticosteroids. In the previously reported cases, administration of prednisolone 30–60 mg/d for 1 month resulted in significant improvement of lymphedema in an average of 3.7 months. In one case, progressive pelvic and inguinal lymphadenopathy was reported, and the patient died after 6 months. The cause of death was

Table 1 Comparison between cases of sarcoidosis associated with lymphedema.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Age (y)/Sex/Race</th>
<th>Initial presentation</th>
<th>Lymphedema</th>
<th>Other clinical presentation</th>
<th>Lymphadenopathy in image findings</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver et al5 (1966)</td>
<td>30/F/Black</td>
<td>Both legs lymphedema</td>
<td>Pitting</td>
<td>Nil</td>
<td>Cervical Retropertoneal Inguinal</td>
<td>Prednisolone 30 mg/d for 4 mo</td>
<td>Leg edema improved in 1 y</td>
</tr>
<tr>
<td>Nathan et al7 (1974)</td>
<td>32/F/Black</td>
<td>Skin eruption and both legs lymphedema</td>
<td>Nonpitting</td>
<td>Maculopapular eruptions Ucerated nodule</td>
<td>Bilateral hilar</td>
<td>Prednisolone 45 mg/d for 1 mo</td>
<td>Skin lesions and leg edema improved in 2 mo</td>
</tr>
<tr>
<td>Sweeney et al6 (1980)</td>
<td>30/M/Black</td>
<td>Nontender calf mass</td>
<td>Nonpitting</td>
<td>Non tender subcutaneous Nodules Legs ulceration</td>
<td>Bilateral hilar Paratracheal</td>
<td>Prednisolone 40 mg/d for 1 mo</td>
<td>Leg edema improved in 1 mo</td>
</tr>
<tr>
<td>Mühlemann et al9 (1985)</td>
<td>59/F/Black</td>
<td>Right leg lymphedema</td>
<td>Nonpitting</td>
<td>Abdominal</td>
<td>Prednisolone 40 mg/day for 1 mo</td>
<td>Leg edema and ulceration improved in 6 mo</td>
<td></td>
</tr>
<tr>
<td>Hoover et al10 (1994)</td>
<td>39/F/Black</td>
<td>Periorbital nodule</td>
<td>Pitting</td>
<td>Bilateral hilar</td>
<td>Prednisolone 60 mg/d for 1 mo</td>
<td>Leg edema improved in 1 mo</td>
<td></td>
</tr>
<tr>
<td>Tomoda et al2 (1999)</td>
<td>55/F/Unknown</td>
<td>Both leg lymphedema</td>
<td>Nonpitting</td>
<td>Thoracic, Abdominal Inguinal Right inguinal</td>
<td>Prednisolone 60 mg/day for 2 wk</td>
<td>Leg edema improved in 1 wk</td>
<td></td>
</tr>
<tr>
<td>George et al1 (2013)</td>
<td>50/F/African American</td>
<td>Right groin lymphedema</td>
<td>Nonpitting</td>
<td>Nil</td>
<td>Prednisolone 40 mg/d</td>
<td>Died after 6 mo</td>
<td></td>
</tr>
<tr>
<td>Patel et al11 (2014)</td>
<td>28/M/African American</td>
<td>Both legs lymphedema</td>
<td>Nonpitting</td>
<td>Bilateral hilar Mediastinal Inguinal</td>
<td>Prednisolone 40 mg/d for 1 mo</td>
<td>Leg edema improved</td>
<td></td>
</tr>
<tr>
<td>Our case</td>
<td>48/F/Taiwanese</td>
<td>Both legs lymphedema</td>
<td>Nonpitting</td>
<td>Indurated noduloplaque on legs</td>
<td>Bilateral hilar Mediastinal</td>
<td>Methylprednisolone 35 mg/d for 14 d</td>
<td>Skin lesions and leg edema improved in 10 d</td>
</tr>
</tbody>
</table>
unknown.\textsuperscript{3} ACE level was only referred to in one case (Case 2). We suggest that the ACE level may be a good candidate for monitoring disease activity, especially in severe cases.

Here, we present the first case in Asia of sarcoidosis with bilateral leg lymphedema as the initial presentation. Notably, cutaneous manifestation is common in sarcoidosis.\textsuperscript{1,2} This case reminds us to consider sarcoidosis in the differential diagnosis of leg lymphedema, thereby prompting early diagnosis and treatment.

References