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Subcutaneous Sarcoidosis Associated with Arthritis: Outcomes of Different Therapeutic Agents

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Abstract

Observations: We report a very rare case of arthritis associated with subcutaneous sarcoidosis. A 52-year-old female patient presented with multiple slightly tender, firm, and skin coloured subcutaneous nodules over her upper and lower extremities and concurrently occurring severe arthralgia, swelling, erythema, and local tenderness over left knee and wrist. Transverse sonograms of the nodules demonstrated several well-demarcated subcutaneous hyperechoic lobular lesions with irregular contours. Histopathological examination of a nodule revealed multiple non-caseating epitheloid granulomas and multinuclear giant cells with *Schaumann* bodies in panniculus. Based on the clinical and histopathological findings, the patient was diagnosed as having subcutaneous sarcoidosis associated with arthritis, which was the sole extracutaneous involvement. Systemic steroids resulted in total resolution of arthritis and softening of nodules in a few days. Since glucose dysregulation was emerged, the patient was put on steroid sparing agents including methotrexate, doxycycline, and then antimalarial subsequently. Although the drugs caused some considerable adverse effects, both subcutaneous nodules and arthritis regressed successfully under appropriate treatment.

Introduction

Sarcoidosis is a multisystem disorder with an unknown aetiology. Cutaneous involvement is seen in 9-37 % of patients with systemic disease [1, 2]. Subcutaneous sarcoidosis is the least form of specific cutaneous lesions, characterized by multiple asymptomatic or slightly tender nodules with variable sizes, mainly located over extremities [1, 3]. It mostly affects white race, females, and forty ages [3]. The diagnosis is mainly based on typical histopathological findings including non-infectious sarcoidal granulomas with minimal lymphocytic inflammation within the panniculus [4]. To date, about 85 cases of subcutaneous sarcoidosis have been reported in the literature [5]. The most common systemic disease associated with subcutaneous sarcoidosis is pulmonary disease [4]. However,

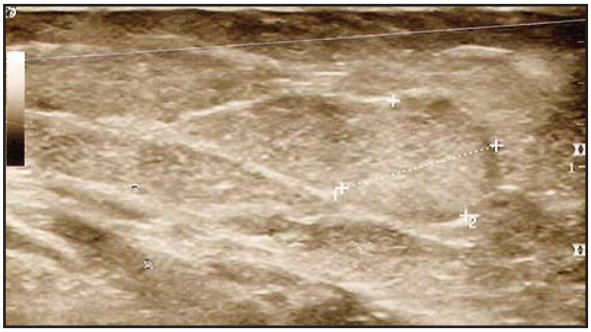

Figure 1. Gray scale image of well-demarcated hyperechoic lobular lesion about 9 x 8 mm size in subcutaneous tissue in transverse sonogram of the nodule over the left olecranon

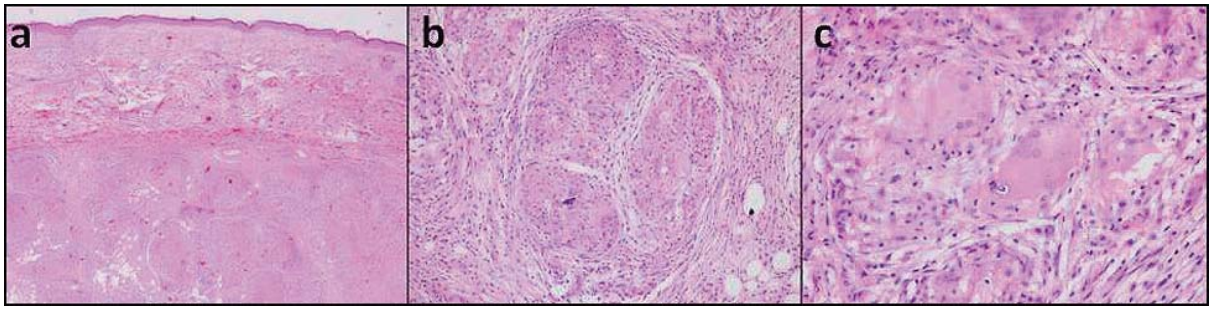

Figure 2. (a) Multiple granulomatous lesions involving panniculus (H&E, x 40); **(b)** naked granuloma formation with multinuclear giant cells and epitheloid histiocytes surrounded with minimal lymphocytic inflammation (H&E, x 200); **(c)** concentric calcium deposits in the multinuclear giant cell (H&E, x 400)

association of arthritis and subcutaneous sarcoidosis is a very rare presentation and was only reported in 4 cases in the literature [**4, 6**]. In this report, we describe a patient with subcutaneous sarcoidosis and arthritis, which was the sole extracutaneous involvement.

Case Report

A 52-year-old female patient presented to our outpatient clinic with multiple slightly tender firm subcutaneous swellings over her upper and lower extremities and severe arthralgia over left knee and wrist, lasting for 2 months. Arthralgia and cutaneous lesions had emerged concurrently. She denied trauma to joints or drug injections sites of cutaneous lesions. She did not have fever. Family history was unremarkable. She was on medication with oral antidiabetic and antihypertensive drugs for years. Dermatological examination revealed bilaterally and asymmetrically located multiple skin coloured firm subcutaneous nodules sized about 2x1 – 2x3 cm in diameter over upper and lower limbs, which could be noticed by palpation, not by inspection. The left knee and wrist had moderate oedema, localized erythema and inflammation. Transverse sonograms of the nodules demonstrated several well-demarcated subcutaneous hyperechoic lobular lesions measuring up to 3x1 cm in diameter with irregular contours (**Figure 1**). Histopathological examination of a nodule revealed multiple non-caseating epitheloid granulomas surrounded with minimal lymphocytic inflammation in panniculus. Concentric calcium deposits (Schaumann bodies) were seen in the multinuclear giant cells (**Figures 2a-c**). Stains for acid fast bacilli, fungus, and bacterial microorganisms were all negative.

Total blood count, liver, kidney, and thyroid function tests, urine analysis, serum angiotensin converting enzyme (ACE) and calcium levels and 24-hour urine calcium excretion were all within normal limits, except high fasting glucose (206 mg/dl). C-reactive protein was 11.3 mg/l (normal range: 0-4.99). Anti SSA, SSB, scl-70, Jo-1, SM, SM/RNP, antidsDNA, rheumatoid factor, antinuclear antibody, antithyroglobulin, and antithyroid peroxidase antibodies were negative. No pulmonary, cardiological, or ophthalmological involvement was detected. Based on the clinical and histopathological findings, the patient was diagnosed as having subcutaneous sarcoidosis associated with arthritis. The patient was put on 16 mg/d (approximately 0.25 mg/kg) oral methyprednisolone therapy. The nodules became rapidly softer and arthritis completely resolved in a few days; however, therapy was stopped because of uncontrolled blood glucose alterations. Then, 200 mg/day doxycycline was initiated. However, the nodules did not regress and even rose in number within 2 months. Treatment was switched to weekly sc injections of 15 mg methotrexate (MTX) which provided regression of almost all lesions within 2 weeks. After 4 months of therapy, the patient ceased MTX by herself and came to her control visit in which leukopenia due to MTX was detected. The white blood cell count rose to normal range 2 weeks after MTX was stopped; however, multiple new lesions emerged rapidly within this period. Therefore, 400 mg/d of hydroxychloroquine (approximately 6.5 mg/kg/d) was initiated. Total regression was observed after 1 month of therapy. Since no new lesions or systemic progression of the disease was detected for about 6 months, the dosage was reduced to 300 mg/d. After 2 months, development of loss of peripheral visual fields obstructed the therapy. The patient is in remission for 4 months without any treatment and coming for her regular follow-ups.

Discussion

In this case, we described a patient with subcutaneous sarcoidosis with arthritis in detail. The evaluation of these nodules was the important key point for diagnosis. The differential diagnosis of subcutaneous sarcoidosis includes various nodular lesions [**5, 7**].

Ultrasonographic examination of a subcutaneous nodule is a helpful and non-invasive method which demonstrates the size, nature, depth of the nodule and also the relationship between the surrounding structures and vessels. Ultrasonography may easily detect isoechoic lipomas and epidermal cysts with dorsal acoustic amplification. Subcutaneous sarcoidal nodules have hypoechoic and hyperechoic parts, representing noncaseating granulomas and surrounding inflammatory infiltrate, respectively [**7**]. Consistent with these, sonograms of our case showed multiple hyperechoic lobular lesions in the subcutaneous tissue. Although these features were not specific, sonograms were informative for an initial evaluation before biopsy. The diagnosis of subcutaneous sarcoidosis was made based on the typical diagnostic criteria including sarcoidal granulomas in the panniculus. Histopathological findings and special stains for microorganisms differentiated other nodular lesions such as rheumatoid nodules, erythema induratum, deep fungal infections, foreign body reactions, leprosy, lymphoma, and cutaneous metastases of internal malignancies [**5, 7, 8**].

Subcutaneous sarcoidosis is reported to occur in 1.4-16.3 % of patients with systemic disease [**4, 9**]. Although this form is rare, subcutaneous sarcoidosis is strongly associated with systemic disease with a range of 80-93 % [**2, 3**]. Subcutaneous sarcoidosis was mostly reported in patients with radiologically stage 1 and active disease not more than 2 years although there is small number of patients [**9**]. In the largest case series of subcutaneous sarcoidosis, the most common systemic disease associated with subcutaneous sarcoidosis was pulmonary disease, especially bilateral hilar lymphadenopathy [**4**]. The others were uveitis, parotitis, uveitis, arthritis, mucositis, dactilitis, peripheral neuropathy, and renal disease. Tenosynovial involvement is also very rarely reported in patients with disseminated sarcoidosis presenting with subcutaneous nodules [**10**]. Serum ACE level is usually within normal limits at the onset and during follow ups of patients with subcutaneous sarcoidosis. The elevated levels are associated with abnormal radiological findings. In our case, the medical history, typical clinical and laboratory examinations in addition to the histopathological findings of the nodules also differentiated rheumatoid, psoriatic, reactive, infectious or gouty arthritis. The patient had normal ACE levels and associated arthritis.

The association of arthritis and subcutaneous sarcoidosis is a very rare presentation and was only detected in 4 cases of 85 reported cases (4.7%) in the literature [**4, 6**]. *Cacoub* et al [**6**] described a 62-year-old female patient with subcutaneous sarcoidosis associated with arthritis, uveitis, pneumonitis, and heart involvement emerging 2 months after interferon alpha treatment for chronic hepatitis C infection. The symptoms resolved after stopping the drug and beginning systemic corticosteroid therapy. *Ahmed* and *Harshad* [**4**] reported only 3 cases with arthritis in their large case series; however, the details of these patients were not available for comparing with our patient. Best to our knowledge, the present case is the unique one describing subcutaneous sarcoidosis associated with only arthritis as the extracutaneous involvement.

Articular involvement in sarcoidosis may be up to 25% of patients. However, sarcoid arthritis is a very rare presentation with only 1,6% of patients with arthralgia. The majority of cases with arthritis are oligoarthritic or polyarthritic. Sarcoidosis arthritis may be classified into acute (transient) and chronic (persistent) types. Acute sarcoid arthritis often occurs as a component of Löfgren syndrome, which is characterized by the triad of erythema nodosum, bilateral hilar lymphadenopathy, and arthritis or arthralgia. Chronic type classically occurs in the setting of systemic sarcoidosis and persistent inflammation may cause destruction [**11**]. Acute sarcoid arthritis has a benign course without destruction as seen in the present case. Although our patient had acute onset of arthritis, the other manifestations of sarcoidosis did not reveal Löfgren syndrome.

Treatment of subcutaneous sarcoidosis depends on the localisation of the lesions and presence of systemic disease [**12**]. Potent topical and intralesional corticosteroids result in favourable responses for single lesion without

systemic disease [**12, 13**]. Multiple skin lesions and systemic involvement require systemic agents to control the disease. First line therapy is generally systemic corticosteroids which provide successful outcomes in most of the patients. However, various adverse effects may be seen especially in the elderly. If the patient cannot tolerate this therapy or if systemic steroids are contraindicated, alternative agents such as tetracyclines, doxycyline, MTX, antimalarials, isotretinoin, cyclosporine, allopurinol, pentoxifylline, etanercept, or infliximab may be considered. Doxycycline in 200 mg/d may be required to be used for months to be effective. Cytotoxic agents such as MTX may be considered as a second line therapy in patients with sarcoidosis resistant or intolerable to systemic corticosteroids [**14**]. Methotrexate may be administered as weekly doses of 10-30 mg for at least 6 months [**13, 15**]. The possibility of hematological, gastrointestinal, pulmonary, and hepatic toxicity requires close follow-ups. The use of antimalarials in this disorder is relatively longer than MTX. Antimalarial therapy has been accepted to be a safe and effective alternative treatment in the treatment of cutaneous sarcoidosis [**12**].

In the present case, our observations demonstrated that control of disease activity in subcutaneous sarcoidosis rapidly achieved by systemic steroids, MTX, and hydroxychloroquine. The associated arthritis also responded to therapy as well. However, close follow-up of patients are needed for adverse effects and rapid relapses. Doxycycline therapy may not be a promising agent since it needs a longer time to evaluate the response and may not be helpful to inhibit new lesions. Antimalarials seem to be effective agents especially for the treatment of elderly patients; however, risk of ophthalmological side effects is an important problem.

Arthritis associated with subcutaneous sarcoidosis is extremely rare. Although the drugs may cause some considerable adverse effects, both may regress successfully under appropriate treatment.

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