Introduction

Sarcoidosis is a multisystemic granulomatous disease of unknown etiology, which most often involves the lungs and lymphatic system. Skin involvement is found in approximately one-third of patients.[1] Among the cutaneous manifestations, subcutaneous sarcoidosis is particularly rare.[2] The prevalence in general population is unknown, but it has been reported to occur in 1.4–6% of patients with systemic sarcoidosis.[3] In a recent series by Marcoval et al.,[4] it was observed in only 2% of patients with systemic sarcoidosis and represented nearly 12% of specific cutaneous lesions. However, published cases or series about this peculiar variant of sarcoidosis are still scarce.[5,7]

Subcutaneous sarcoidosis: A case series of 19 patients

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ABSTRACT

Subcutaneous sarcoidosis is a rare variant of this disease, whose relationship with systemic disease is still controversial. Our objective was to describe the clinical characteristics of a series of patients with subcutaneous sarcoidosis and to investigate the relationship between these skin lesions and the disease’s activity, severity, and prognosis. Nineteen patients with biopsy-confirmed subcutaneous sarcoidosis between 2009 and 2019 were selected. Mean age at diagnosis was 53 years. Lung involvement was detected in 10 patients (52.6%), mainly in stages I and II. Only two patients (10.5%) had additional systemic signs and five patients (26%) suffered from other autoimmune diseases simultaneously. Six patients (31.6%) had elevated angiotensin-converting enzyme levels (mean level 174.5 U/L). Eight patients (42%) received treatment, mainly systemic corticosteroids, and all patients except for one had a favorable clinical outcome. Subcutaneous sarcoidosis is frequently associated with a mild form of systemic disease, and the prognosis seems favorable regardless of treatment. Sarcoid nodules could be an early finding of systemic disease, allowing for less invasive procedures for histological confirmation.

KEY WORDS: Darier-Roussy’s sarcoid, disease severity, sarcoidosis, skin, subcutaneous nodules

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Given the limited number of published cases, the prognosis of the systemic disease in patients with subcutaneous lesions has not been fully clarified. The purpose of our study was to review a series of patients with subcutaneous sarcoidosis, evaluate their clinical characteristics, and explore the severity, activity, and prognosis of the disease in terms of outcome.

Case Series

A retrospective case-series study was conducted. Approval by the Ethical Committee for Clinical Research was obtained with internal code 2020.180. All patients with biopsy-confirmed subcutaneous sarcoidosis treated at our hospital in northern Spain between 2009 and 2019 were
reviewed. The histopathological diagnostic criterion was the presence of noncaseating granulomas in subcutaneous tissue, with or without extension to the dermis [Figure 1], once the presence of tuberculosis (TBC) was ruled out by either Ziehl–Neelsen staining or mycobacterium PCR performed on the biopsy specimen. Additionally, all patients had been tested for TBC at the time, and all showed a negative intradermal reaction of Mantoux or interferon-γ release assays. The following information was obtained from the patient’s clinical records: Location and number of the subcutaneous nodules (single or multiple), presence of other sarcoidosis skin lesions, initial clinical manifestation, pulmonary or systemic involvement, concomitant autoimmune disorders, angiotensin-converting enzyme (ACE) levels, serum calcium levels, treatment received, and disease outcome.

A total of 19 patients fulfilled the inclusion criteria. The clinical characteristics of the patients are displayed in Table 1. All patients were Caucasian. The age at diagnosis was 53 ± 10 years (mean ± sd), with a clear predominance of women (2:1 ratio). In 17 patients (89.5%), sarcoid nodules were the reason for consultation. The most frequent location of the lesions was upper extremities [Figure 2]. Nine patients (47%) showed other sarcoidosis skin lesions, which in most cases (7/9) were specific lesions such as papules, plaques, or scar sarcoidosis, while two patients presented nonspecific manifestations (erythema nodosum and granuloma annulare). Lung involvement was evaluated with a CT-scan in all patients. Seven out of 10 patients with lung disease underwent a pulmonary function test (PFT) and a carbon monoxide diffusing capacity (DLCO) test. Additional targeted examinations, including ophthalmologic evaluation, were performed only in symptomatic patients.

Ten patients (52%) had lung involvement according to CT-scan results. Altered PFT/DLCO was found in one patient with stage II pulmonary disease. Two patients had additional systemic manifestations such as arthritis, uveitis, and muscular sarcoidosis. Five patients (26%) had other concomitant autoimmune diseases. Disease activity was measured by ACE levels. All patients, except for 2, had an ACE determination. ACE levels were elevated in 6 of 17 patients (35.3%) (range 0–207 U/L, mean level 174.5 U/L; normal range in our laboratory 20-95 U/L). None of the patients developed hypercalcaemia (range 8–9.9 mg/mL, mean level 9.2 mg/mL; normal range in our laboratory 8.4–10.4 mg/mL). Eight patients (42%) received treatment. Six patients with extracutaneous disease and one patient with multiple skin lesions only were prescribed oral prednisone at 0.5 mg/kg. Three patients were treated with high-potency topical corticosteroids and/or topical calcineurin inhibitors. One patient with a single lesion received high-potency topical steroids and intranasal betamethasone. All patients experienced disease resolution except for one, who has presented several recurrent outbreaks of subcutaneous nodules to date. This patient received hydroxychloroquine additionally.

Most patients were diagnosed by dermatologists. Patients with extracutaneous involvement were followed up by internal medicine specialists or pneumologists, who decided the indication of systemic treatment. The duration of follow-up ranged from 6 months to 10 years, depending on the time of diagnosis.

**Discussion**

Sarcoidosis cutaneous lesions may be specific or nonspecific, based on the presence or absence of sarcoid granulomas. Furthermore, subcutaneous sarcoidosis is the less common of the specific cutaneous lesions of sarcoidosis.[8]

It usually manifests as asymptomatic firm nodules covered by normal-appearing skin, mostly on the forearms and legs. The diagnosis may require a high suspicion, but the fact that sarcoid nodules tend to appear at an early stage of the systemic disease may be useful in its diagnosis.[4,9] In most patients of our series (17/19), subcutaneous nodules were the clinical manifestation that allowed the diagnosis of systemic sarcoidosis. Other lesions that may resemble subcutaneous sarcoidosis on clinical examination include lipomas, cysts, subcutaneous granuloma annulare, foreign body granulomas, or cutaneous manifestations of lymphoproliferative malignancies. However, when subcutaneous lesions appear in a patient with...
Table 1: Clinical features in the patients with subcutaneous sarcoidosis

| N  | Gender | Location                          | Number | Other skin lesions | Initial symptom | Extracutaneous involvement | PFT/DLCO | Other AI | ACE Levels U/L | Treatment with steroids | Clinical outcome |
|----|--------|----------------------------------|--------|--------------------|-----------------|---------------------------|----------|----------|----------------|------------------------|-------------------|
| 1  | 56/M   | Upper extremity                  | Multiple | No                 | Lung Arthritis/muscle Lung (I) | Yes | No | 153.5 | Oral (b) | Remission |
| 2  | 63/F   | Lower extremity                  | Multiple | Plaques            | Skin Lung (II) | Yes | No | 16.9  | Oral (b) | Remission |
| 3  | 53/F   | Upper extremity                  | Single   | No                 | Skin Lung (I) | No | No | 87.1  | Oral (b) | Remission |
| 4  | 58/M   | Lower extremity                  | Multiple | No                 | Skin No         | No | No | 150   | No | Remission |
| 5  | 66/F   | Upper extremity                  | Multiple | No                 | Skin Lung (I) | No | No | 150   | No | Remission |
| 6  | 62/F   | Upper extremity and trunk        | Multiple | NE                 | Lung Lung (I) | Yes | No | 200   | No | Remission |
| 7  | 55/F   | Lower extremity                  | Single   | No                 | Skin Lung (I) | Yes | No | NR    | No | Remission |
| 8  | 61/F   | Lower extremity                  | Multiple | Plaques papules    | Skin Arthritis/eye | No | PsA | 0     | Oral (b) | Remission |
| 9  | 39/F   | Upper and lower extremity        | Multiple | GA                 | Skin Lung (I) | No | No | 53.9  | Oral (b) | Remission |
| 10 | 38/F   | Upper and lower extremity        | Multiple | Plaques            | Skin Lung (I) | No | No | 25.3  | No | Remission |
| 11 | 41/M   | Upper extremity                  | Single   | Scar lesion        | Skin No         | No | No | 187.9 | No | Remission |
| 12 | 39/M   | Neck                             | Single   | No                 | Skin No         | No | RA | NR    | No | Remission |
| 13 | 48/F   | Upper and lower extremity        | Multiple | Papules            | Skin No         | No | No | 187.9 | No | Remission |
| 14 | 60/M   | Forehead                         | Single   | Plaques scar       | Skin Lung (II) | Yes(a) | No | 207.2 | No | Remission |
| 15 | 65/M   | Neck                             | Single   | No                 | Skin Lung (I) | Yes | GP | 60    | No | Remission |
| 16 | 41/F   | Upper extremity, lower extremity and trunk | Multiple | No | Skin No | No | No | 40    | No | Remission |
| 17 | 51/F   | Upper extremity                  | Single   | Plaques scar       | Skin Lung (I) | Yes | HT | 31    | Oral (b)+Oral (c) | Recurrence |
| 18 | 41/M   | Upper extremity and trunk        | Multiple | No                 | Skin No         | No | No | 50.2  | Topical (d)+Other (e) | Remission |
| 19 | 65/F   | Upper extremity                  | Single   | No                 | Skin No         | No | No | 40    | Topical (d)+Intralesional (f) | Remission |

AI: Autoimmune disease; NE: Nodosum erythema; GA: Granuloma annulare; PFT/DLCO: Pulmonary function test/carbon monoxide diffusing capacity; RA: Rheumatoid arthritis; HT: Hypothyroidism; PsA: Psoriatic arthritis; GP: Granulomatous with polyangiitis; ACE: Angiotensin-converting enzyme; NR: Not requested; Chest X-Ray stage: (I) hilar lymphadenopathy; (II) lymphadenopathy and pulmonary infiltrates; a. PFT/DLCO altered results; b. Prednisone 0.5 mg/kg; c. Hydroxychloroquine; d. High-potency topical corticosteroids; e. Tacrolimus; f. Betametasone

diagnosed systemic sarcoidosis, the diagnosis is generally straightforward.

In agreement with other authors, our series confirms a higher incidence in women with a 2:1 ratio. It is suggested that the overall female predominance may reflect a real difference in the disease, with cutaneous involvement occurring more often in women. However, women may be more prone to notice and report cutaneous lesions, which could explain this difference.

We also found a high prevalence of bilateral hilar lymphadenopathy in our case series, present in 10 patients (52%). However, subcutaneous sarcoidosis seems to be the only specific type of cutaneous sarcoidosis frequently associated with mild systemic disease, based on the chest X-ray stage. None of our patients indeed developed chronic or severe complications, such as pulmonary fibrosis. Moreover, skin biopsy saved the need for hilar lymphadenopathy biopsy, thus causing less morbidity. On the other hand, five patients in our series with single nodules had a systemic disease. Therefore, according to our data, the extent of subcutaneous involvement does not seem to predict the presence of systemic disease.

ACE is produced by epitheloid cells that are derivatives of activated macrophages and is correlated with the amount of whole-body granuloma. In this regard, ACE levels have been thought to reflect the disease activity. Moreover, some studies have shown that prednisolone therapy leads to a reduction in ACE levels. In our series, we observed that the degree of skin involvement was not necessarily accompanied by elevated ACE levels.

The prognostic significance of subcutaneous nodules has not been fully established. Some authors have suggested a strong association between subcutaneous sarcoidosis and mild systemic involvement, although other authors have not found this...
relationship.\textsuperscript{[6]} In our series, all patients except for one had complete remission, which would support the theory that subcutaneous involvement is a marker of systemic disease with a good prognosis.

The coexistence of different types of specific cutaneous lesions has been documented in earlier series.\textsuperscript{[4,7,9]} In our study, nine patients (47\%) showed other cutaneous lesions. Furthermore, scar infiltrates and plaque lesions were more frequent in patients with lung involvement, particularly stage II pulmonary disease. Interestingly, five patients (26\%) had other autoimmune diseases, including hypothyroidism, rheumatoid arthritis, psoriatic arthritis, and granulomatous polyangiitis. This phenomenon has also been described by Dalle et al.\textsuperscript{[7]}

There are several limitations to our study, the main one being a retrospective study conducted at a single center, including a modest number of patients. However, it seems relevant to communicate our results since they support the importance of ruling out systemic disease when subcutaneous sarcoidosis manifests. Furthermore, our results are in line with the findings in other published series: Subcutaneous sarcoidosis appears to be a marker of good prognosis of systemic disease.

**Conclusion**

According to our findings, subcutaneous sarcoidosis is frequently associated with systemic disease, but not with a severe form. The overall prognosis of this particular variant of sarcoidosis seems to be favorable, given the excellent clinical outcome of most patients regardless of the treatment received. Moreover, ACE levels do not seem to reflect the cutaneous disease extension. Finally, we suggest that sarcoid nodules could be an early finding of systemic disease. Therefore, a detailed physical examination and the ability to recognize these lesions provide not only a valuable tool for early diagnosis but also an opportunity to save the patient more invasive procedures for histological confirmation.

**Declaration of patient consent**

The authors certify that appropriate patient consent was obtained.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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