Subcutaneous Sarcoidosis with Neurological Involvement: An Unusual Combination

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Sarcoidosis is a multisystem granulomatous disorder of unclear cause. It is a global disease that affects both genders, in all races and age groups. The peak incidence occurs between the second and third decade, with a second peak occurring in woman between the fourth and sixth decade.

Cutaneous involvement occurs in 20–35% of patients with systemic sarcoidosis and may occur without systemic disease. Cutaneous sarcoidosis is known as one of the "great imitators" in dermatology, as skin lesions of patients with the disease may exhibit many different morphologies, including patches, papules, nodules, plaques, subcutaneous nodules, scar sarcoidosis, erythroderma and even ulcerations. The heterogeneous skin lesions are classified as specific and non-specific on the basis of the presence or absence of sarcoidal granulomas.

Subcutaneous sarcoidosis is a specific subset of cutaneous sarcoidosis and is also known as Darier-Roussy sarcoid. Five percent or less of patients with sarcoidosis have subcutaneous nodules. Subcutaneous sarcoidosis is characterized by a peak incidence during the fourth decade, female predominance, asymptomatic to slightly tender subcutaneous lesions typically involving the upper extremities, and cutaneous lesional multiplicity and clustering. It is diagnosed by identifying non-infectious sarcoidal or epithelioid granulomas with minimal lymphocytic inflammation involving predominantly the panniculus. Subcutaneous sarcoidosis is the only specific subset of cutaneous sarcoidosis frequently associated with systemic disease. In most patients the systemic disease consists of bilateral hilar adenopathy. Other identified systemic involvements in patients with subcutaneous sarcoidosis are arthritis, renal involvement, uveitis, parotitis, dactylitis and mucositis (nasal, oral and conjuctival) [1]. Neurological involvement is rare. It is characterized by a favorable response to oral corticosteroids therapy [1,2].

Neurosarcoidosis is reported in about 5% of patients with sarcoidosis. Cranial neuropathies are the most common manifestations, seen in approximately 50–75% of patients with neurosarcoidosis. The neuropathies may be caused by increased intracranial pressure, nerve granulomas or, most commonly, by granulomatous basal meningitis. Facial palsy is the most frequent cranial neuropathy, being unilateral in 65% and bilateral in 35%. A prominent meningial reaction around the brainstem appears to be the underlying cause. This fact is supported by the often abnormal brainstem auditory evoked potentials and cerebrospinal fluid findings. Facial nerve palsy alone appears to be associated with good prognosis, but other presentations of neurosarcoidosis are reported to have poor outcome [3].

At present there is no curative treatment for sarcoidosis. Immunosuppressive and/or immunomodulatory drugs, however, are used for controlling the disease, with corticosteroids remaining the mainstay of therapy. They function by suppressing the pro-inflammatory cytokines and chemokines that are involved in cell-mediated immune responses and granuloma formation. Methotrexate or hydroxychloroquine may be added, especially if the response to steroids is inadequate. Although the chemokine and cytokine pathways that regulate granuloma formation are not well understood, tumor necrosis factor-alpha is implicated. TNFα antagonists such as pentoxifylline and thalidomide are reported to be useful in refractory systemic disease and neurosarcoidosis. Infliximab (a monoclonal antibody against TNFα) in particular has a growing body of literature supporting its effectiveness, and appears to be a safe treatment with a good steroid-sparing effect.

Subcutaneous sarcoidosis with neurological involvement

As mentioned above, both subcutaneous sarcoidosis and neurosarcoidosis are infrequent manifestations of sarcoidosis. Their co-occurrence is therefore extremely rare. Only five case reports of subcutaneous sarcoidosis with neurological involvement have been reported in the literature after the first original article published in 1904 by Darier and Roussy.

The first case was reported by Vainsencher and Winkelman in 1984. They described a 54 year old woman known to be suffering from sarcoidosis with systemic manifestations including uveitis, iritis and parotitis, with tender, pink to flesh-colored,1–3 cm subcutaneous nodules on her legs, and neuritis of the right facial nerve. Examination one year after diagnosis revealed a decrease in size of the lesions after treatment with chaulmoogra oil (chaulmestrol) and local X-ray therapy – treatment used in the 1940s for granulomatous disease. During the year, she had one lesion on the left arm that healed spontaneously within 6 months.

TNFα = tumor necrosis factor-alpha

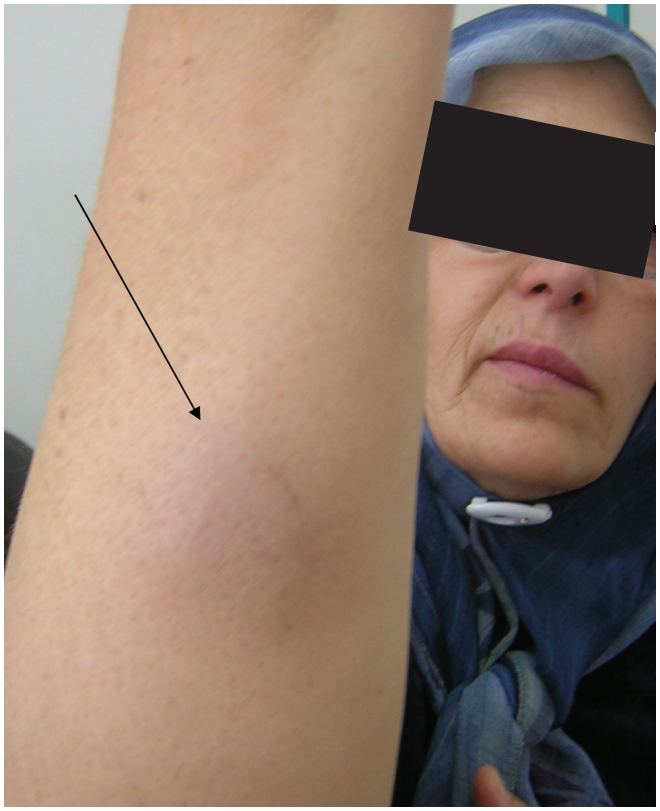

Figure 1. Woman with subcutaneous sarcoid nodule of her right forearm (arrow) and facial nerve palsy.

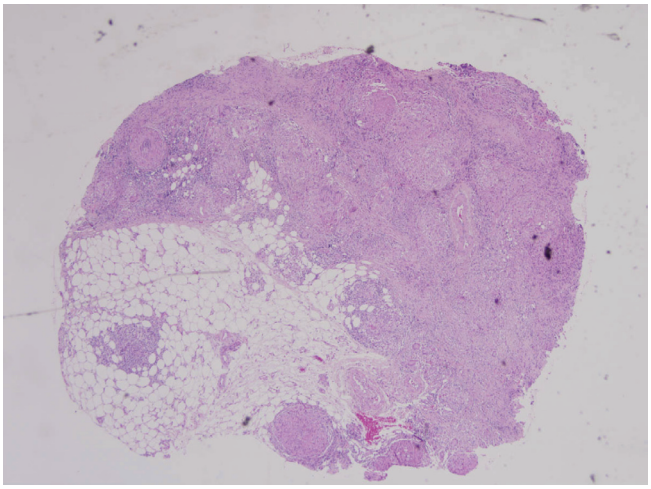

Figure 2. Low magnification slide of skin biopsy specimen showing subcutaneous non-caseating granulomas.

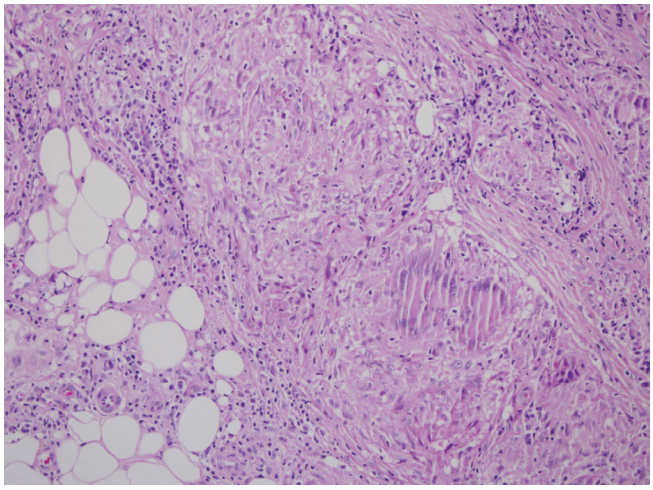

Figure 3. Skin biopsy specimen showing subcutaneous non-caseating granulomas under high magnification.

In the largest series of cases describing 54 patients with subcutaneous sarcoidosis published by Iftikhar and Sujata from the Mayo Clinic in 2005 [1], there were two patients with peripheral neuropathy. Unfortunately, from the article it is impossible to determine other characteristics of those patients.

In 2002, Chiang et al. [4] reported a case of a 32 year old woman with hypo-pigmented lesions on the trunk and extremities. Less than a year after the appearance of these lesions, which were diagnosed by biopsy as subcutaneous sarcoidosis, she developed obstructive hydrocephalus necessitating the placement of a shunt. She also had pulmonary involvement, according to chest X-ray. She was treated, and apparently responded to systemic corticosteroids.

The last case reported in the literature was by Watanabe and co-workers in 2006 [5]. The case involved a 70 year old woman who presented with mixed paralysis of the limbs. Electrophysiological studies were compatible with polyneuropathy. In retrospect, she reported two asymptomatic nodules on her lower extremities, one on each leg. The presence of bilateral hilar adenoapthy led to the diagnosis of sarcoidosis. Skin biopsy provided a confirmation of the diagnosis. The sarcoid granulomas were also adjacent to many peripheral nerves, which probably compressed them, causing her symptoms. She was treated with oral prednisolone and showed a gradual improvement.

In our case a 53 year old woman was referred due to painful nodular lesions on all four extremities. Shortly after the appearance of these lesions, she developed facial nerve palsy [Figure 1]. She also complained of fatigue and arthralgia. Chest X-ray and computed tomography showed mediastinal and symmetrical hilar adenopathy. Biopsy of the skin lesions showed subcutaneous non-caseating granulomas [Figures 2 and 3] and a diagnosis of subcutaneous sarcoidosis was made. Treatment with steroids resulted in a quick resolution (within 2 months) of the subcutaneous and pulmonary lesions, and slower resolution (6 months) of the nerve palsy.

Those cases reveal some common features. Most (if not all) of the patients were females in their third to sixth decade. In all the cases, the dermatological manifestations preceded the neurological ones, even if only by a short time. All the patients suffered from systemic sarcoidosis with hilar adenopathy being the most common presentation. The skin lesions were usually on the limbs. The neurological involvement was varied, being both central and peripheral.

Comment

Our case, as well as the other few published in the literature, represents a rare subcutaneous involvement in systemic sarcoidosis and even rarer association between subcutaneous sarcoidosis and neurological involvement. The common characteristics of the few cases published are female gender, systemic involvement (which is mild, represented by bilateral hilar adenopathy), and favorable response to oral corticosteroid.

Subcutaneous sarcoidosis with facial nerve palsy as a manifestation of systemic neurological involvement is a unique entity characterized by non-severe cutataneous involvement with rapid cutaneous resolution, a slower neurological resolution but a good prognosis. Most of the patients were diagnosed by dermatologists, using skin biopsies. In some of the cases the skin lesions preceded the neurological event, sometimes by years, but they were not investigated or diagnosed until then. Diagnosis of subcutaneous sarcoidosis depends primarily on suspicion and then on the histological examination of the involved subcutaneous tissue. Early and correct diagnosis and treatment may possibly prevent the systemic involvement.

Conclusions

Subcutaneous sarcoidosis with facial nerve palsy as a manifestation of a systemic neurological involvement is a unique entity characterized by non-severe cutaneous involvement with rapid cutaneous resolution and a slower neurological resolution but a good prognosis. Other presentations of neurosarcoidosis are reported to have poorer prognosis.

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