Polymorphous cutaneous and chronic multisystem sarcoidosis

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SUMMARY

Sarcoidosis is a systemic disorder in which cutaneous findings are often prominent. These may be polymorphous to the extent that sarcoidosis may mimic many other cutaneous diseases. We describe a 56-year-old woman with involvement of the skin, eyes, bones, heart, and lung. After an initial presentation 10 years earlier of erythema nodosum with bilateral hilar adenopathy, there were three types of cutaneous changes: subcutaneous, nut-sized palpable nodules localized along the upper and lower extremities, annular plaques on the shins, and erythema nodosum-like palpable and slightly tender nodules. It is very unusual to have all three types of skin lesions, especially the erythema nodosum-like histologically specific cutaneous ones in this setting, which is what prompted this report.

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology characterized by epithelioid noncaseating granulomas in all affected organs. Specific skin manifestations of sarcoidosis are polymorphous, ranging from papules or plaques to nodules, lupus pernio, or ulcerations, with erythema nodosum a characteristic but nonspecific skin finding (1–7). Sarcoidosis frequently involves the lungs, mediastinal and peripheral lymph nodes, eyes, bones, and skin. The clinical course is progressive, although remissions and relapses often occur (8). Sarcoid granuloma formation begins with the presentation of as-yet unidentified infectious antigens or autoantigens to the T lymphocytes.

Some observations suggest that the causes of sarcoidosis are occupational or environmental exposures. The two common target organs, the skin and lungs, are in permanent contact with environmental agents. Some inorganic antigens, such as beryllium, clay, talc, pine pollen, and oxalosis have been suggested as environmental triggers in the development of sarcoidosis (9, 10).

The preceding activation of macrophages participates in lymphocyte stimulation and recruitment. The exact point when sarcoidosis starts is usually unclear. We describe a patient with chronic sarcoidosis affecting the internal organs and accompanied by polymor-

KEY WORDS

sarcoidosis, erythema nodosum, lupus vulgaris, granuloma

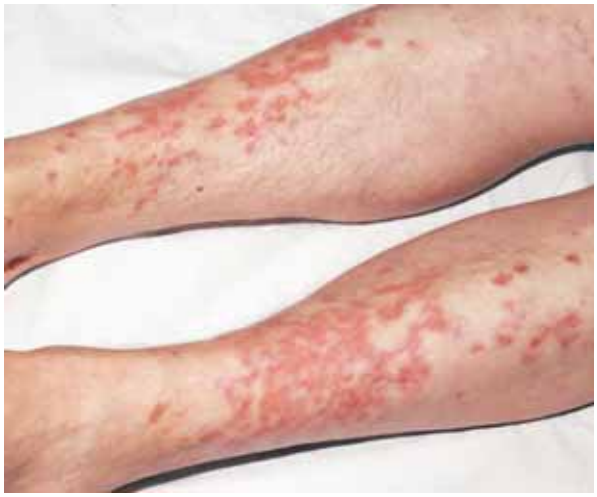

Figure 1. Sarcoidosis, showing multiple annular cutaneous plaques and papular lesions, erythematous in color; lesions localized on both shins.

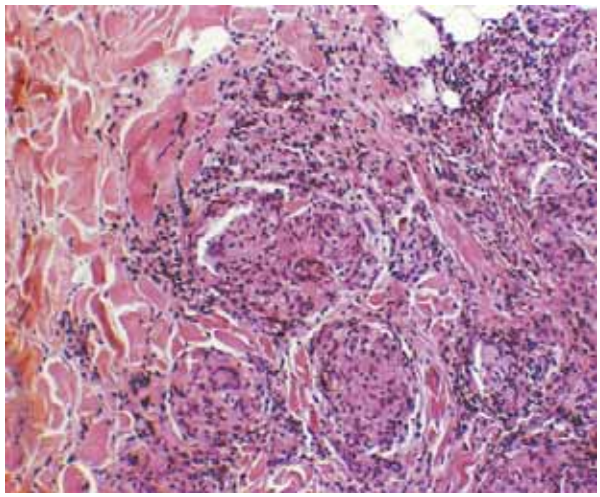

Figure 3. The multiple granulomas in the subcutaneous tissue and the deep dermis, composed of epithelioid cells, multinucleate giant cells, and lymphocytes (Hematoxylin-eosin, original magnification × 200).

phous skin changes. She was remarkable in having both erythema nodosum and histologically specific cutaneous and subcutaneous sarcoidosis simultaneously.

Case report

A 56-year-old woman was seen in January 2005 for multiple painless subcutaneous nodules in a linear pattern and skin lesions on the extremities of 6 months' duration. She complained of weakness, dyspnea, and easy fatigability. She had had erythema nodosum 10 years earlier, associated with hilar lymphadenopathy in a chest X-ray. Mediastinoscopy with histologic examination of the hilar lymph nodes revealed noncaseating epithelioid cell granulomas. Spirometric examination performed at the same time showed normal pulmonary capacity. From 1996 to September 2004 she had no cutaneous findings suggestive of sarcoidosis. Her occupational history was noteworthy for 30 years of exposure to polyvinyl chloride (PVC) and tetrahydrofuran (THF). PCV is one of the most popular plastic materials. There is some evidence associating prolonged exposure to PVC with pulmonary impairment (11). THF is a heterocyclic organic compound that is used us a solvent of intermediate polarity in chemical reactions

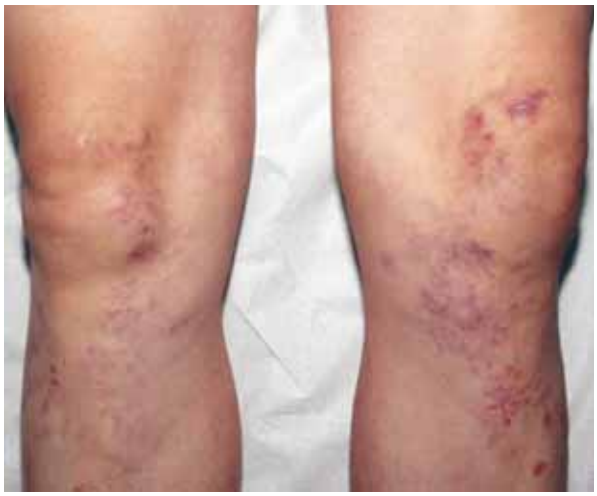

Figure 2. Multiple violaceous skin nodules, deep in the skin, around the knee joints.

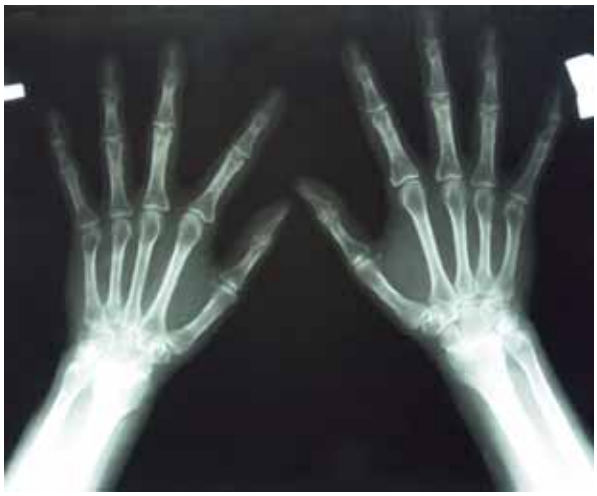

Figure 4. Radiograph demonstrating multiple cystic lesions localized in digital bones.

and industrially to degrease metal parts. THF can also be used as a component to produce polyurethane fibers (12). The patient did not report any skin injuries on the sites of sarcoidosis lesions.

On examination, three different types of skin lesion were observed. The first was subcutaneous, nut-sized palpable nodules localized along the upper and lower extremities with the overlying skin of normal color. Second, the skin of both shins was covered by multiple annular plaques with light surface scaling. Some larger plaques showed central clearing with hyperpigmentation (Fig. 1). On diascopy these lesions exhibited an apple-jelly color, indicating the presence of a sarcoid infiltrate. The third type of lesion was evident on the skin of the knee joints as violaceous, palpable, and slightly tender nodules, deeply placed in the skin (Fig. 2). The diagnosis of cutaneous sarcoidosis was confirmed by histological examination of the skin biopsy specimens. The skin samples were obtained from two different skin lesions: the first was taken from the firm, red-brownish cutaneous plaque localized on the shin, and the second was taken from the subcutaneous nodule on the thigh. Histological examination of the samples from the plaque and nodule revealed noncaseating granulomatous inflammation. The granulomas were well-circumscribed and consisted of epithelioid cells, mononuclear cells, and rare Langhans-type giant cells. A peripheral rim of sparse lymphocytes surrounded the epithelioid histiocytes (Fig. 3). The specimen obtained from the nodule revealed numerous granulomas extending through the entire thickness of the dermis, also partially involving the subcutaneous adipose tissue. Peripheral lymph nodes were not enlarged. The mucous membranes, scalp, and nails were not involved. Direct ophthalmologic examination showed the presence of 3 mm papules on the lower right palpebral conjunctiva that may correspond with granuloma. Other ocular involvement was not established. X-ray examination of the hand bones showed multiple cystic lesions (Fig. 4). Chest X-ray revealed bilateral hilar lymphadenopathy and disseminated small nodules. Computed tomography showed parenchymal infiltration, thickened interlobular septa, and early fibrosis. Cardiac ultrasonography demonstrated enlargement of the right ventricle and maximum pressure in the pulmonary artery of about 40 mm Hg. Spirometry showed decreased diffusing capacity, obstruction, and a restrictive pattern: FEV_1 = 1,160 ml (47% of pred. value), VC = 1,860 (62% of pred. value), MEF_{25} = 440 l/s (31% of pred. value), MEF_{50} = 980 l/s (26% of pred. value), and MEF_{75} = 2,530 l/s (46% of pred. value). Laboratory findings included an ESR of 20; white and red blood cell counts and urinalysis were normal. Liver enzymes and kidney parameters were normal. Calcium metabolism was normal. The sputum was examined and a standard mycobacterial culture was performed to exclude tuberculosis. Stains for acid-resistant bacilli and cultures for fungi were negative. The tuberculin skin test result was negative.

In 1995 the patient was initially treated with aspirin for a few months because of erythema nodosum and bilateral hilar lymphadenopathy, but the gradual exacerbation of pulmonary changes led to the beginning of oral corticosteroid therapy. An initial dose of prednisone of 60 mg per day was given. The pulmonary lesions markedly improved, but 3 months later a perforated peptic ulcer occurred. After a short break in the systemic steroid treatment, prednisolone injections and then oral prednisone (40 mg daily) were prescribed. The chest radiographs markedly improved for almost 5 years. In March 2003, after a 5-year period of systemic corticosteroid therapy, the patient stopped prednisone intake. In September 2004 she developed polymorphous superficial and deep cutaneous lesions associated with progressive pulmonary symptoms. Accordingly, the very potent topical corticosteroid clobetasol and oral naproxen were started. However, both were ineffective, and so additional treatment with chloroquine phosphate (500 mg daily) and topical 0.1% tacrolimus ointment twice daily was initiated. After 2 weeks' therapy with topical tacrolimus, the beginning of the resolution of the plaques on the shins was observed.

Discussion

Sarcoidosis is a granulomatous disease of unknown etiology that is suspected to be the product of a combination of genetic, immunologic, and environmental factors (10). The most common sites involved in sarcoidosis are the lungs, skin, and eyes (13). Nearly one-fourth of sarcoidosis patients have skin lesions (8). They may be divided into two groups: specific skin involvement with typical sarcoid granulomas on histologic examination and nonspecific skin lesions. The most frequent lesion classified as nonspecific is erythema nodosum, which is characteristic of acute sarcoidosis. An erythema nodosum-like eruption with the histological changes of sarcoidosis has also been described (14). Our patient had typical erythema nodosum at the beginning of the disease. The presence of erythema nodosum is the best predictor of a good prognosis in patients with sarcoidosis, but some patients with it do develop chronic sarcoidosis (15). An association with the development of chronic, progressive disease in subjects over 40 has been observed, as is the case with our patient (16–18).

The frequency of various skin lesions in sarcoidosis may be present: erythema nodosum (20.5%), cutaneous plaques (4.3%), subcutaneous nodules (4.3%),

maculopapular rash (3.7%), scar lesions (2.9%), lupus pernio (2.7%), and psoriasiform lesions (0.9%) (19). We describe a patient with pulmonary established sarcoidosis and erythema nodosum at the beginning of disease. She had been given long-term therapy with systemic steroids because of the progression of the pulmonary involvement. A year and a half after the cessation of corticosteroids, marked exacerbation of pulmonary symptoms and new polymorphous skin lesions appeared. On examination there were three types of lesions: subcutaneous painless nodules on the upper and lower extremities, cutaneous tender nodules around the knee joints (erythema nodosum-like lesions), and multiple small plaques on the front and back aspects of the shins. As opposed to erythema nodosum, which is typical for the acute stage of sarcoidosis, these types of skin lesions are characteristic for the chronic stage of disease. More than one type of chronic skin lesions may exist at the same time. Nevertheless, subcutaneous sarcoidosis is rare, especially in white people (20, 21).

Subcutaneous sarcoidosis is usually accompanied by hilar lymphadenopathy, but in our patient subcutaneous sarcoidosis appeared after the progression of the pulmonary changes. These plaques were accompanied by the tender nodules around the knee joints, which were persistent and difficult to treat. The plaques on the shins are responding well to topical tacrolimus. This case is unusual due to the coexistence of polymorphous superficial and deep skin lesions. Our patient's exposure to prolonged and regular occupational contact with PVC and THF should be considered a possible causative agent inducing a cell-mediated immune response in the skin and internal organs.

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