

# CUTANEOUS SARCOIDOSIS

M. Pippione and F. Castelli

## ABSTRACT

This is a review of the symptomatic aspects of cutaneous sarcoidosis. Our purpose is to give a view, as complete as possible, as to manifold problems connected with this disease. After mentioning briefly its main characteristics (definition, history, epidemiology, pathogenesis, and clinical manifestations) we present a number of cutaneous manifestations, including histological data. In our opinion, any therapeutic decision must be preceded by an analysis of all the relevant epidemiological, clinical and laboratory data.

## KEY WORDS

Cutaneous sarcoidosis, granulomatous disease

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## DEFINITION

The etiology of sarcoidosis, a granulomatous disease that involves mainly young adults, has not been fully explained. It affects hilar and pulmonary organs, as well as lymph nodes, skin, eyes, liver, spleen and other organs.

Genetic factors may play a role in triggering this disease. Death may be due to pulmonary, cardiac, or renal failure (1,8).

Boeck (1897) and Besnier (1899) described the classical signs of cutaneous sarcoidosis. It was

Schaumann (1914) who gave a full description of the manifold aspects of the disease, and named it "benign lymphoid granulomatosis". Later, arising from Kaposi's definition "sarcoid", the term sarcoidosis was adopted and is still used.

## EPIDEMIOLOGY

Sarcoidosis has a worldwide distribution and it appears in the developed countries more frequently than tuberculosis (11). It seems to be more widely

distributed in the northern hemisphere, especially affecting women as well as young and black people (13).

## PATHOGENESIS

The etiology of sarcoidosis has not been defined yet, but the hypothesis of a multifactorial syndrome is probable. Older clinical observations linked it to a tubercular infection in patients with abnormal reactivity (5). The viral theory suggests a connection between this virus and mycobacteria. An increase of antibodies against Epstein-Barr (E-B) was found in sarcoidosis patients (7). Other possible triggering factors are conifer pollen, zirconium, beryllium, and hair spray (3,4). According to the latest observations sarcoidosis is linked to impaired cell-mediated immunological response, including lymphocytic proliferation and increased circulating immune complexes. The relationship between macrophages, B lymphocytes as well as helper and suppressor T-lymphocytes can be upset, thus provoking the migration of activated helper T-cells to the sites of disease. A depressed cell-mediated immunity to mycotic antigens and DNCB can be demonstrated by intradermal tests in about two thirds of cases. Response to tuberculin becomes typically negative. An increased calcium absorption via the gut, with hypercalcaemia and hypercalciuria, is characteristic. Untreated patients suffering from sarcoidosis display increased serum levels up to 80% of angiotensin-converting enzyme (ACE). However, this observation is not specific (6).

## CLINICAL MANIFESTATIONS OF SARCOIDOSIS

The onset is often deceiving as the general condition may be good. As far as we know, sarcoidosis may involve all organs, except the ovary, suprarenal glands and placenta. Most frequently involved (85% - 90% of cases) are the mediastinal lymph nodes and the lung (Sarcoidosis Upper Respiratory Tract - SURT). The disease develops in three stages classified on the basis of the chest X-ray. At the first stage hilar lymph nodes are affected, blood vessels and bronchi remaining usually uninvolved. Second stage reveals involvement of the lung tissue, often in the form of miliary, reticulo-nodular, or large nodular structures. The last stage "pulmonary fibrosis" or "sclerotic-emphysematous stage" is associated with serious respiratory and functional abnor-

malities (14). Peripheral lymph nodes are often affected (30% - 38% of cases), especially the latero-cervical, subclavicular and epitacheal nodes. They appear enlarged, hard, movable, painless, and suitable for biopsy. Bone and joint involvement is found in about 10% of cases including cystic lesions of distal parts of metacarpal, metatarsal, and phalangeal bones. X-ray examination shows cystic images (geodes), known as Perthes-Jungling's osteitis. Cardiac lesions were found in 20% of cases, whereas spleen and liver lesions were observed in 10% and 5% respectively. Similar figures are also reported in neurological manifestations of sarcoidosis involving mostly cranial and peripheral nerves and causing paralysis and neuritis. Glandular diseases, whether salivary (Heerfordt's syndrome: parotitis, iridocyclitis, facial nerve palsy) or lacrimal (Mikulicz's syndrome) are unusual, but if manifest, typical.

## CUTANEOUS SARCOIDOSIS

Statistically, skin is affected with frequencies between 33% and 44% (9). Many classifications have been suggested, but it seems that the classical outline given by older authors could still be useful:

A) Small nodular sarcoidosis: it appears with small hemispherical papular and nodular lesions, varying from pinhead to hazelnut sizes, with the colors changing from rose to yellowish-brown. They are smooth, of hard consistence, and indolent. The number of lesions varies from a few to several hundred. Favourite sites are the face (Fig. 1), neck, trunk, and the extensor aspects of the limbs. It may begin as an eruptive rash with possible recurrences. Lesions may be confluent. This lichenoid variety is characterized by small homogeneous rose-yellowish papules usually appearing on the face, buttocks, trunk, and limbs (Fig. 2).

B) The large nodular form is one of the most common and appears as nodular lesions of variable sizes but always larger and less numerous than the previous ones. They are clearly outlined, ranging in color from violaceous to brownish, of hard consistence, often smooth, and protruding. Favourite sites are the face, nose (Fig. 3), forehead, trunk, and limbs. In case of confluence of single lesions irregular forms with a possible central atrophy occur, looking like necrobiosis lipidica. Vitropression is a useful diagnostic tool as it reveals the lupoid infiltration as yellowish, fine-grained spots (Fig. 4 and 5).

C) Subcutaneous (or dermal-hypodermic) sarcoidosis, which is quite uncommon, is characterized by roundish



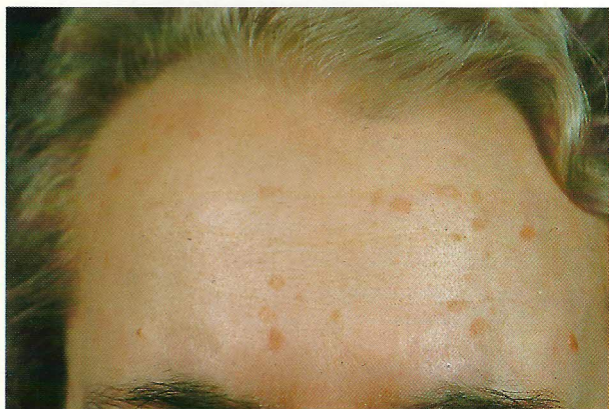


Fig. 1. Small maculopapular sarcoidosis. Yellowish-brown papular lesions on the forehead.



Fig. 4. Atrophic form of sarcoidosis. A large lesion with a red papular edge and an atrophic center.

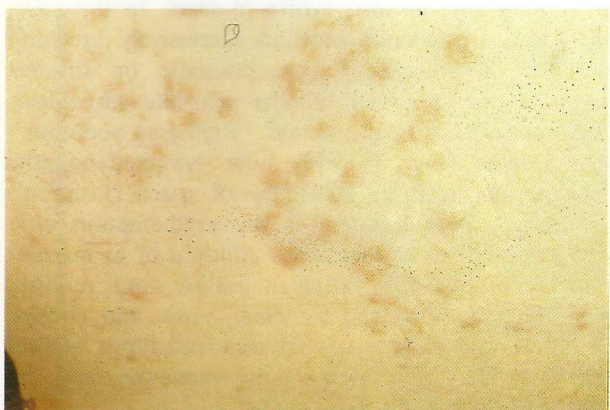


Fig. 2. The same as fig. 1. Lesions on the trunk.



Fig. 3. Nodular sarcoidosis. Red-brown nodule on the nose.



Fig. 5. Annular sarcoidosis. Multiple annular lesions with central atrophy.

or oval nodules of unaffected or violaceous surface on the limbs and trunk. Sometimes it has the appearance of infiltrated plaques of hard consistence. In the rare cases involving the scalp a residual scarring alopecia can be seen.

D) One of the most typical aspects of cutaneous sarcoidosis is lupus pernio (LP) (15). It tends to affect mostly middle-aged women; development is slow and often associated with other systemic locations (one third of patients may present SURT). LP displays violaceous, tumid, smooth, shiny, and indolent plaques, often covered by telangiectasies, occasionally of doughy consistence (Fig. 6). Typical sites are the nose and cheeks (possibly in butterfly disposition), the forehead, ears, and back of the hands. Quite often LP presents bone alterations of the limbs with





Fig. 6. *Lupus pernio* with angiolutoid features. Lesions affecting the cheeks.

typical radiological signs. Cutaneous lesions evolve slowly and may appear as scarred atrophies (rarely as ulcers).

E) Angiolutoid form (Brocq and Pautrier) is characterized by one or a few plaques, well defined, scarcely protruding, rose-violaceous or brownish, covered by smooth thin skin, possibly with telangiectasias. The most common sites are at the bridge of the nose and the adjacent skin, predominantly in women in their forties. The evolution of the lesions is usually slow.



Fig. 7. Sarcoidosis expressed as *erythema nodosum*.

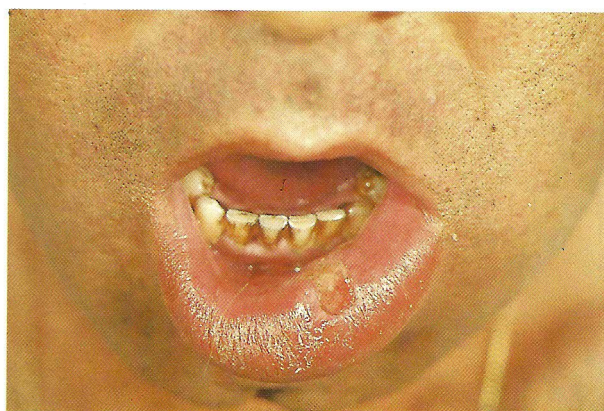


Fig. 8. *Cheilitis granulomatosa* of the lower lip.

F) Sarcoidosis can also evolve in scars. In this case, the onset of rose-violaceous and, successively, brownish nodules in preexistent post-traumatic or surgical scars can be observed. Similar scar-like sarcoidosis may appear after small traumas. "Erythema nodosum"-like lesions (Fig. 7) with hilar lymphadenopathy may be observed in 10%-30% of cases (Lofgren's syndrome). Less frequent is the erythematous type which appears as erythematous infiltrate or as maculopapular lesions with a clear outline and reddish, smooth plaques on the forehead, nose, and cheeks. A differential diagnosis is rosacea and lupus erythematosus. The erythrodermic, the verrucose, and the ulcerated forms are rare (17).

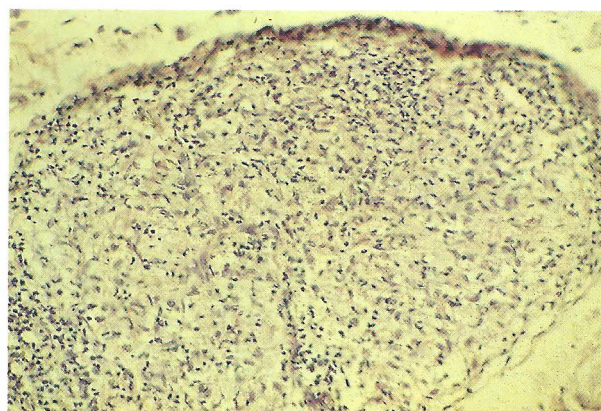


Fig. 9. Histopathologic features of sarcoidosis. Typical appearance of a well defined non caseating granuloma consisting of an aggregate of epithelioid cells and some multinuclear giant cells, with a thin rim of lymphocytes.



Cutaneous sarcoidosis may present an acute, sub-acute, or chronic evolution. Cutaneous sarcoidosis with erythema nodosum often follows an acute course, whereas small, nodular, scar, and erythematous forms are usually of a subacute nature. Other manifestations of sarcoidosis are rather chronic. Granulomatous macrocheilitis (Miescher's cheilitis) (Fig.8) involves mainly the upper lip, assuming an edematous and infiltrated aspect (elephantiasis). Facial nerve palsy may be associated with Melkersson-Rosenthal syndrome (10). Histologically, in this macrocheilitis the same structures as in sarcoidosis can be observed.

## HISTOPATHOLOGY

The histopathology of skin lesions reveals a granulomatous infiltrate of epithelioid cells. The histologic lesions are well defined and surrounded by connective tissue (Fig. 9) with lymphocytes and giant cells, often of the Langhans type. The absence of necrosis, especially of the caseating type, is characteristic. Macrophages as well as B lymphocytes can be demonstrated by immunological methods. The epithelioid granuloma may contain asteroid bodies and a conspicuous reticulin network. This may be useful in differentiating other granulomas. In sarcoidal granuloma fibrosis may develop. Moreover, this granuloma may be hard to separate from other epithelioid cell-rich granulomas, such as foreign-body granuloma, old leishmaniasis and mycobacterial granulomas by histological features alone. Also annular granuloma, particularly its epithelioid, giant-cells, and elastolytic forms, may sometimes pose insurmountable difficulties.

## KVEIM TEST

This is a test of delayed-type immunity response. It is carried out by intradermal injection of sarcoidal tissue suitably prepared. It deserves to be mentioned mainly for historical reasons; in fact it is not used any more in diagnostic procedures.

## DIFFERENTIAL DIAGNOSIS OF CUTANEOUS SARCOIDOSIS

These are some of the main clinical manifestations to be distinguished from cutaneous sarcoidosis:

- Lupus vulgaris
- Tuberculoid leprosy
- Lupoid leishmaniasis
- Necrobiosis lipoidica

- Annular granuloma
- Other granulomatous lesions (foreign-body, etc.)
- Lymphadenosis benigna cutis
- Lymphoma (2)
- Rosacea-like tuberculides
- Rosacea
- Lever's eosinophilic granuloma faciale

## TREATMENT

It is based on antiflogistic, antibiotic, cytostatic, or immunosuppressive drugs. The main medications are:

- Corticosteroids are widely used in doses of 40-60 mg of prednisolone daily (initial dosage). A maintenance dose is administered as long as clinical, radiological, laboratory and functional signs persist. At present, corticosteroids are the most effective agents influencing the course of cutaneous sarcoidosis.

- Chloroquine is particularly useful in the management of the chronic skin lesions. It may also be used together with corticosteroids to reduce the dosage of the latter (18). It is administered in dosages of 250 mg twice a day for 6 months.

Methotrexate or other immunosuppressive drugs (azathioprine, chlorambucil) have been used by some authors in the treatment of cutaneous as well as disseminated sarcoidosis (12, 16).

- Rifampicin, isoniazid, ethambutol, alone or in association with low doses of corticosteroids, have been proposed.

- A therapy with a synthetic peptide, thymopentine, on alternate days over a period of 12 weeks, administered intravenously in dosages of 50 mg/ml, has been suggested.

- Oxyphenbutazone, colchicine, allopurinol, and levamisole have also been tried in the management of sarcoidosis.

- Surgical treatment may include excision of small lesions or skin grafting of extensive sarcoid ulcers.

## CONCLUSION

The Authors suggest that before any decision concerning the treatment is taken all the clinical, epidemiological, and laboratory findings must be thoroughly evaluated.



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## AUTHORS' ADDRESSES

Mario Pippione M.D., professor of dermatology, Department of Dermatology,  
University of Turin, Via Cherasco 23, 10100 Turin, Italy  
Franco Castelli M.D., assistant professor of dermatology, same address