

Sarcoidosis at onset of Psoriasis: a common immunopathogenesis. Review and case report

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Abstract. – Sarcoidosis is an inflammatory systemic disease that may present in many different ways. The pathophysiological mechanisms are not still well known, although sarcoidosis results from an exaggerated Th1 immune response. About 30% of sarcoidosis patients may suffer from skin lesions during the course of the disease and, occasionally, psoriasisiform lesions have been observed. Sarcoidosis may present associated with other diseases and psoriasis is actually one of them, even though not particularly frequent. Few cases of patients who showed clinical and histological features compatible with both pulmonary sarcoidosis and psoriasis vulgaris have been reported. We report an interesting case of a patient affected by sarcoidosis at the onset of psoriasis and discuss immunopathogenetic mechanisms that can be associated with these conditions. Recent data confirm that sarcoidosis is a Th1/Th17 multisystem disorder. These clarifications may be helpful in the management of the diseases and in identifying patients at risk.

Key Words:

Sarcoidosis, Psoriasis, Pathogenesis, Cutaneous lesions, Treatment, Th1, Th17.

Abbreviations

BAL = Broncho-Alveolar Lavage; APC = Antigen Presenting Cell; ACE = Angiotensin Converting Enzyme; DC = Dendritic Cell; TNF α = Tumor Necrosis Factor α ; Th = T helper; IL23R = Interleukin 23 receptor.

Introduction

The first description of sarcoidosis goes back to 1899 when a famous norwegian dermatologist, Ceaser Boeck, described the cutaneous alterations as skin nodules characterized by compact, sharply defined foci of “*epithelioid cells with large pale nuclei and also a few giant cells*”.

Since it resembled sarcoma, he called them “*multiple benign sarcoid of the skin*”¹. Sarcoidosis is a system disorder frequently presenting with bilateral hilar lymphadenopathy, pulmonary infiltration, skin and ocular lesions. The lymph nodes, salivary glands, liver, spleen, heart, muscles, bones, and nervous system may also be involved². Sarcoidosis is characterized by the presence of non-caseating granulomas in involved organs, affecting the lung in about 90% of cases. The granulomatous reaction occurs in the absence of a clearly defined immunological target, although a reaction to an unidentified antigen is suspected². Increased number of CD4+ T cells in the broncho-alveolar lavage (BAL) fluid is characteristic of the disease³. CD4+ T cells interact with Antigen Presenting Cells (APC) to initiate the formation and maintain the granulomas⁴.

Diagnosis of sarcoidosis can be made based on a compatible clinical and/or radiological characteristics. Histological findings of non-caseating granulomas are highly suggestive of sarcoidosis, but they should be posed in differential diagnosis with other diseases with similar histological features². Granuloma formation and T cell alveolitis have been characterized as T helper (Th)-1 responses. These observations have led to the hypothesis that sarcoidosis results from an exaggerated Th1 immune response after presentation of an unidentified antigen by the APC⁵.

About 30% of patients with sarcoidosis may present skin lesions². The skin involvement is often overlooked or misinterpreted. Macules, papules, and plaques may be isolated or gathered. The zones involved include the neck and upper back, extremities, and trunk. Lupus pernio located on the nose, cheeks, lips, and ears can be disfiguring, eroding into underlying cartilage and bones. Women are more affected by these lesions than men⁶. Erythema nodosum occurs in about 10% of cases with sarcoidosis and usually lasts for 3 weeks.

Pulmonary sarcoidosis can be radiologically classified into 5 stages: *stage 0* with a normal chest radiograph, 5-10% of patients at presentation; *stage I* with hilar or mediastinal nodal enlargement only, 45-65% of patients at presentation; *stage II* with nodal enlargement and parenchymal disease, 25-30% of patients at presentation; *stage III* with parenchymal disease only, 15% of patients at presentation; *stage IV* with end-stage lung and pulmonary fibrosis³.

On the other hand, psoriasis is a common inflammatory skin disorder characterizes by erythematous, sharply demarked papules and rounded plaques, covered by silvery micaceous scales which most commonly appear on the elbows, knees, umbilicus, lumbar area, and scalp⁷. Skin biopsy may is usually diagnostic in early lesions or at the advancing edge of the well-established plaque. Histological features in psoriasis include proliferation of epidermal keratinocytes and hyperkeratosis as infiltration of immunocytes and subsequent typical thickening of the erythematous skin².

We present and discuss a case report with clinical and histological features of both sarcoidosis and psoriasis vulgaris showing a peculiar temporal relationship. The main clinical difficulty is the differential diagnosis between psoriasiform lesions and psoriasis. The common immunopathological mechanisms have been taken into account, in order to define clinical and genetic characteristics of sarcoidosis and psoriasis, analyzing the literature and the reported cases with both diseases.

Case Report

A 38 years old male was admitted to our Respiratory Unit in Day Hospital regimen for sarcoidosis in October 2011. His past medical history included a surgical procedure on the right knee for angioma removal, tonsillectomy, and an Achilles tendon surgical procedure post rupture. The rest of his past medical history was unremarkable.

About two months before admission, patient reported symptoms as mild dyspnea, asthenia, and fever (37.2°C). A chest X-ray showed an increased hilar lymph node component without pulmonary infiltrates. A chest TC confirmed a prevalent mediastinal and hilar lymphadenopathy. Blood exams, blood pressure, HR, and saturation were normal, with only an increased C reactive protein and Angiotensin Converting Enzyme (ACE). Pulmonary function tests and arter-

ial blood gas analysis were normal. Diagnosis of sarcoidosis was made based on the histological pattern of a lymph node biopsy executed in mediastinoscopy. Patient started a therapy with prednisone 25 mg twice daily for two months, and subsequently once daily for the following 4 months. At six-months control, the patient was in good conditions without symptoms, and a chest CT confirmed the completed resolution of lymphadenopathy. Therapy with prednisone 5 mg once daily was continued for other 4 months.

During follow-up for sarcoidosis with a low dose of corticosteroid, patient reported skin eruptions on the palm of his hands, lips, and on the frontal part of the scalp. No arthralgia and skin lesions on the elbows and lower extremities were reported. An ACE dosage was normal (value 10 µg/L). Chest CT was executed for sarcoidosis restaging with absence of lymphadenopathy and pulmonary infiltrates. Cutaneous lesions disappear as soon as the dose of cortisone was increased to 25 mg daily for 1 month. One month after oral cortisone discontinuation, the patient returned for a control visit. Physical examination showed the presence of erythematous-desquamative skin lesion on the palm of the hands, lips, and retroauricular region. No other regions were affected and no arthralgia was reported (Figure 1).

According to a dermatologic consultation, skin biopsy of the right hand palm lesions was performed. Histological analysis showed a pattern characterised by hypercheratosis, paracheratosis with intercorneal granulocitous micro abscesses, focal absence of the granulous, papilomatosis and spongiosis. The dermal surface was charac-



Figure 1. Erythematous-desquamative skin lesion on the palm of the hands. Skin biopsy was performed for differential diagnosis between sarcoidosis and psoriasis cutaneous lesions.

terized by a lymphohistiocitary type inflammatory infiltrate, disposed mainly in the perivascular region (Figure 2).

The anatomopathological pattern was compatible with psoriasis. Therapy with oral cortisone for 2 weeks and omega (ω)-3 fatty acids for 6 months controlled signs and symptoms of psoriasis. After 1 year, no recurrence of sarcoidosis was reported with normal radiological and blood exams, and psoriasis events have been treated and kept under good control with an omega (ω)-3 fatty acids therapy.

Discussion

Recent reviews⁸⁻¹¹ have raised the question whether sarcoidosis and psoriasis, when occurring together, may be a coincidence or an association with common immunopathological mechanisms. Sarcoidosis is a granulomatous disease characterized by an exaggerated immune response against an antigen difficult to distinguish³. Dendritic cells (DCs) are APCs

playing an important role in the pathogenesis of sarcoidosis. In the lung, they are responsible for presentation of antigen in draining lymph nodes, inducing T cell activation and proliferation^{12,13}. Pulmonary granuloma formation is dependent on the presence of DCs and DC-induced T cell proliferation in lymph nodes¹⁴. DCs were observed in skin, lymph node and lung lesions from sarcoidosis patients^{12,15}. Conversely, decreased immune reactivity of DCs was reported in blood samples from patients with pulmonary sarcoidosis, suggesting to be phenotypically and functionally immature¹². However, a recent work has shown at the site of disease DCs are mature, immunocompetent and involved in granuloma formation. Ten Berge et al⁵ noted that the number of DCs in BAL, but not in blood, from sarcoidosis patients was increased in comparing with healthy controls, and that DCs purified from BAL of sarcoidosis patients induce T cell proliferation and differentiation. These findings implicate increased local DC activation in granuloma formation or maintenance in pulmonary sarcoidosis. In addition, Ten Berge et al⁵ observed that pul-

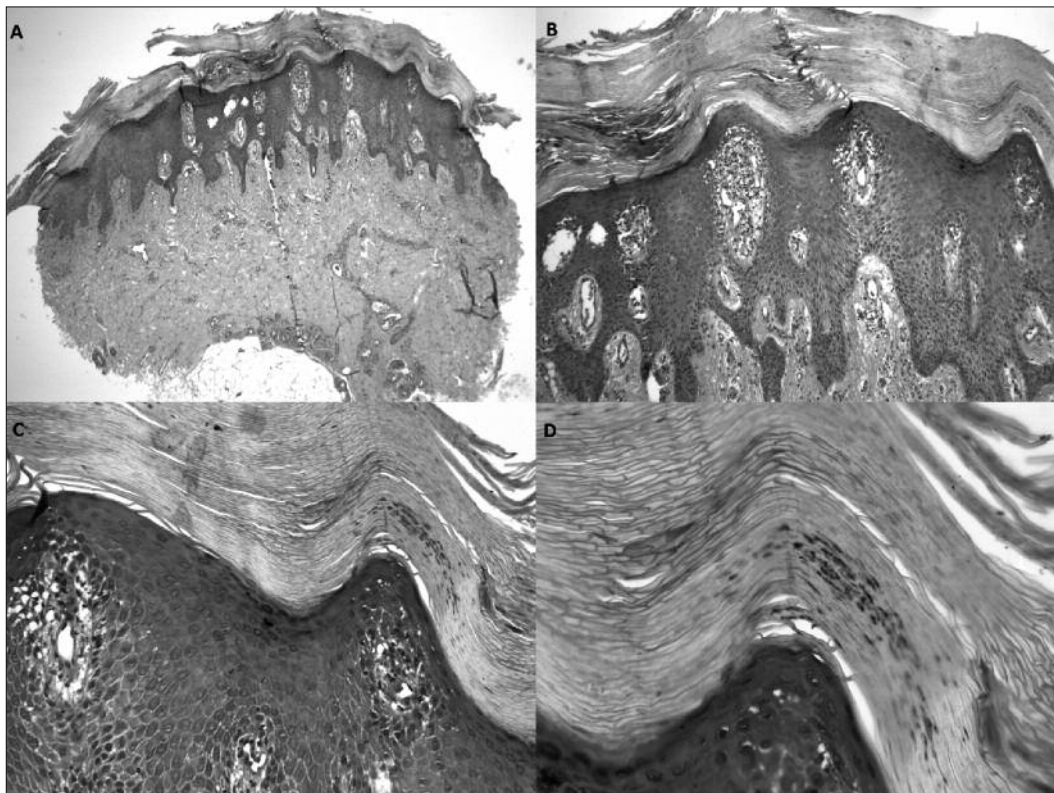


Figure 2. Skin biopsy showing hyperkeratosis, parakeratosis with intercorneal granulocytous micro abscesses, and lymphohistiocitary type inflammatory infiltrate disposed in the perivascular region. Haematoxylin-eosin, magnification $\times 10$ (**A**), $\times 20$ (**B**), $\times 40$ (**C**), $\times 100$ (**D**).

monary sarcoidosis is associated with increased numbers of mature, functionally competent DCs inducing increased levels of the central mediator Tumor Necrosis Factor alpha (TNF- α). TNF α is a mediator of granuloma formation and maintenance, playing an important role in sarcoidosis pathogenesis¹⁶. An enhanced TNF- α secretion by BAL macrophages is observed in sarcoidosis³, and TNF- α is also expressed by Th1 and Th17 cells and both T helper cell subsets¹⁷. Moreover, polymorphisms in the TNF- α locus were associated with different sarcoidosis phenotype and prognosis, and they have been linked to altered TNF- α expression^{18,19}. These data confirm that TNF- α may be an essential target for the treatment of the disease²⁰. Sarcoidosis is a well-known highly polarized Th1 profile disease and infrequently is associated with other diseases characterized by a Th1/Th2 imbalance, such as autoimmune diseases⁸. The presence *in vivo* of a Th1/Th17 population has been widely demonstrated in different diseases characterised by an exaggerated inflammatory response, including psoriasis²¹, rheumatoid arthritis²², Crohn's disease²³, hypersensitivity pneumonitis²⁴, and tuberculosis²⁵. High levels of IL-17+/CD4+ T lymphocytes were detected among cells retrieved from the BAL of patients with sarcoidosis¹⁷. It is well known that sarcoidosis is characterized by a compartmentalisation of CD4+ Th1 lymphocytes and activated macrophages in involved organs, including the lung. Recently, Facco et al¹⁷ have shown that Th17 effector CD4+ T cells are involved in the pathogenesis of granuloma formation, and Th17 cells participate in the alveolitic/granuloma phase and also to the progression towards the fibrotic phase of the disease. The chemokine CCL20 may drive the recruitment of this cell subset¹⁷.

Sarcoidosis has rarely been associated with psoriasis or psoriatic arthritis. A review of 517 patients with sarcoidosis collected over a 36-year period identified only 4 patients who also had a diagnosis of psoriasis⁹. Since 3 of the 4 patients were female and having the same blood group and HLA profiles, Fischer et al²⁶ have assumed that genetic factors may predispose some individuals to these 2 distinct diseases. They identified chromosome 11q13.1 (rs479777) as a novel locus influencing susceptibility to sarcoidosis with genome-wide significance. So interesting, the locus was previously reported to be associated with Crohn's disease, alopecia areata, leprosy and psoriasis. The pathogenesis of psoriasis in-

cludes hyperproliferation and aberrant differentiation of keratinocytes, inflammation, and dermal angiogenesis. Dermal infiltration of inflammatory T cells, DCs, macrophages, and neutrophils are typical features of the disease²⁷. Th1 and Th17 lymphocytes contribute to the pathogenesis of psoriasis through the release of inflammatory cytokines that promote recruitment of immune cells, keratinocyte proliferation, and sustained inflammation²⁸. Several studies suggest that psoriasis is a Th17 cell-mediated disease controlled by IL-23²⁹, and also TNF- α stimulates CD11+ inflammatory DCs to produce IL-23 and IL-20 and seems to be a critical cytokine for many of the pathogenetic features of psoriasis³⁰. In addition, interleukin 23 receptor (*IL23R*) gene has been reported as a genetic factor strongly associated with psoriasis, inflammatory bowel disease, ankylosing spondylitis, and sarcoidosis. Thus, *IL23R* may be a common susceptibility gene shared by several autoimmune disorders, including psoriasis and sarcoid uveitis³¹.

Sarcoidosis is a multisystem disease and cutaneous lesions may be present in 20%-35% of the patients. Skin manifestations in sarcoidosis are not always granulomatous and may result from a systemic immunological reaction. Therefore, this reaction might justify the presence of psoriatic lesions in a patient with sarcoidosis, and the coexistence of sarcoidosis and psoriasis might not be coincidental. Skin lesions of sarcoidosis are classified as *specific* and *non-specific*. Specific skin lesions consist in typical sarcoid granulomas on histologic examination and tend to be chronic, requiring therapy for resolution. These skin lesions have a varied clinical appearance and often can be distinguished by their yellow translucent character. Lupus pernio lesions are nodular violaceous specific skin lesions found predominantly on the face associated with poor prognosis. Specific lesions include maculopapules, plaques, nodules, scar infiltration, ulcerative lesions, hypopigmentation, and alopecia. Non-specific skin lesions are often associated with an acute presentation of sarcoidosis and generally associated to a good prognosis. Erythema nodosum is the most common non-specific skin manifestation. Others may include erythema multiforme, prurigo, calcifications, nail clubbing, and Sweet syndrome. Systemic and topical corticosteroids are the most effective treatments for cutaneous sarcoidosis.

We observed that both diseases share common pathogenic pathways and the occurrence of psoriasis in a sarcoidosis patient might result from a

variable response to a common antigenic stimulus. This is supported by the enhancement of the Th1 immune response in both diseases. In fact, in our case the peculiar timing of the onset of sarcoidosis and psoriasis confirm the common contemporary immunopathogenesis. In addition, it has been reported that the expression of a psoriatic scale antigen (pso p27), linked to the pathogenesis of psoriasis, is markedly increased in the lungs of patients with pulmonary sarcoidosis³².

Experimental evidences suggested that immunopathogenesis of psoriasis is T-lymphocyte based, so least in part it may resemble sarcoidosis. The immigrant immunocytes interact with resident epithelial and mesenchymal cells to generate psoriatic lesions. Once activated, T-lymphocytes excrete a panel of Th1-type proinflammatory cytokines, which explain many of the histopathological changes observed in psoriatic skin³³. Supporting this hypothesis, the application of anti-TNF alpha agents, such as infliximab, adalimumab and etanercept, has demonstrated promising results in both sarcoidosis and psoriasis patients⁸.

In confirming the central role of TNF- α , about 10 cases of pulmonary sarcoidosis were reported in patients receiving anti-TNF- α agents, developing a sarcoid-like granulomatosis while receiving monoclonal anti-TNF- α antibodies³⁴. It is interesting to consider that a wide range of different cutaneous manifestations, ranging from classic erythematous plaques to palmoplantar pustulosis, have been reported over recent years as "psoriasis-induced by anti-TNF- α ".

Our case report is a clear example of the evidence reported in recent years on the common pathogenetic mechanisms of diseases with different phenotypic expressions but with possible common target of therapy.

Conclusions

In conclusion, skin involvement was diagnosed in approximately one-third of sarcoidosis patients with a generally female predominance. Involvement of DCs in antigen presentation and granuloma formation at the site of disease in pulmonary sarcoidosis patients is evident and intrinsic genetic alterations in key APCs may underlie the characteristic exaggerated immune response of Th1 profile diseases. Concomitant sarcoidosis and psoriasis suggest that common pathogenesis involving the Th1 and Th17 pathways may be re-

sponsible for this association. The presence of Th17 cells in the lung and the blood of patients with sarcoidosis, particularly in those patients with the active form of the disease, suggest a role in sarcoidosis progression. *IL23R* may be a common susceptibility gene shared by several autoimmune-disorders including sarcoidosis and psoriasis. All these findings confirm that psoriasis and sarcoidosis pathogenesis is a complex interaction among genetic, immunological, and environmental components.

Our case report highlights the importance of an accurate differential diagnosis before starting therapy in cutaneous lesions of sarcoidosis, because different diseases with common pathogenic mechanisms may coexist or simulate the recurrence of the pre-existing condition.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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