CASE REPORT

Cutaneous Sarcoidosis – Diagnostic Challenges

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Abstract

Sarcoidosis is a multisystemic granulomatous disease, with unknown etiology, characterized histopathologically by the development in the affected organs of some „empty" (non-caseous) granulomas. Cutaneous lesions can sometimes be the first localization of the disease. We present the case of a patient with known sarcoidosis and autoimmune thyroiditis, who developed a rash spread on the trunk and limbs, for which she was treated with dermatocorticoids and antihistamines, but without significant improvement. A skin biopsy was performed with histopathological examination, which revealed: at the dermal level, lympho-histiocytic infiltrates with nodular distribution, forming several granulomas, without areas of necrosis of caseification, including frequent cells with epithelioid appearance, suggestive for the diagnosis of cutaneous sarcoidosis. The patient underwent systemic cortisone therapy and hydroxychloroquine, with favorable outcome. The challenge of diagnosing this pathology is to differentiate it from a number of conditions, including: ring granuloma, cutaneous Crohn's disease, lipoid necrosis, lupus vulgaris. To establish the diagnosis of certainty, it is necessary to correlate the clinical data with the result of the histopathological examination.

Keywords: sarcoidosis, granulomatous disease, lichen planus, cutaneous Crohn's disease, lipoid necrobiosis, classic ring granuloma.

Rezumat

Sarcoidoza este o boală granulomatoasă multisistemică, cu etiologie necunoscută, caracterizată histopatologic prin dezvoltarea în organele afectate a unor granuloame „goale", fără cazeum. Leziunile de la nivelul tegumentului pot constitui uneori prima localizare a bolii. Prezentăm cazul unei paciente cunoscute cu sarcoidoză şi tiroidită autoimună, care a dezvoltat o erupție diseminată la nivelul trunchiului şi membrelor, pentru care a urmat tratament cu dermatocorticoizi şi antihistaminice, însă fără o ameliorare semnificativă. S-a efectuat biopsie cutanată cu examen histopatologic, care a evidențiat: la nivel dermal, infiltrate inflamator limfohistiocitar dispus nodular, formând câteva granuloame, fără arii de necroză de cazeificare, incluzând frecvente celule cu aspect epitelioid, stabilindu-se astfel diagnosticul de sarcoidoză cutanată. Pacienta a urmat tratament sistemic cortizonic şi cu Hidroxicloroquină, cu evoluție favorabilă. Provocarea diagnosticării acestei patologii constă în diferențierea ei de o serie de afecțiuni, printre care: granulom inelar, boală Crohn cutanată, necrobioză lipoidică, lupus vulgaris. Pentru a stabili diagnosticul de certitudine este necesară corelarea datelor clinice cu rezultatul examenului histopatologic.

Cuvinte cheie: sarcoidoză, boli granulomatoase, lichen plan, boala Crohn cutanată, necrobiosis lipoidica, granulom inelar clasic.

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disorder of unknown origin, that most commonly involves the lungs. Cutaneous manifestations may be the clue to diagnose the disease, as they are present in up to one-third of patients[1]. The disease can affect any organ in the body, and is characterized by the formation of epitheloid cell tubercles, without caseation, although fibrinoid necrosis may be present at the centre of a few, proceeding either to resolution, or to conversion into hyaline fibrous tissue[2]. Sarcoidosis affects both women and men, usually under 40 years old. It can affect any race, but it is more frequent in Nothern European countries[3].

Clinically, the cutaneous lesions consist of translucent-looking papules, with "apple jelly" appereance on diascopy, nodules, and red-blue plaques. Most commonly, they are found on scars. When involving the scalp, scarring alopecia may occur[4].

Erythema nodosum represents the non-specific cutaneous lesion, frequently encountered in sarcoidosis. It presents as painful, erythematous nodules, predominantly found on the anterior surface of the lower extremities. It is undistinguishable from erythema nodosum of other causes. It is important to know that, if it is present, it may indicate the acute form of sarcoidosis. The triad (erythema nodosum, arthritis, bilateral hilar adenophaty on chest radiography) is known as Lofgren syndrome. Patients may also associate fever, malaise. The resolution usually occurs in 3 to 6 months, spontaneous[5].

It is important to know that, general (non-organ specific) manifestations may be present in sarcoidosis: fatigue, small fiber neuropathy and neuropsychological symptoms. Their recognition and impact on patient's life quality is essential for the optimal management of the patient with sarcoidosis[6].

The diagnosis of sarcoidosis requires a compatible clinical picture, the demonstration of non-caseating granulomas on tissue biopsy, and the exclusion of other disorders that can present with similar clinical and histopathological findings. Evaluation for systemic disease should consist in: complete physical examination, chest radiography, pulmonary function tests including diffusion capacity studies, electrocardiogram, assesment for latent tuberculosis (by tuberculin skin test or interferon gamma release assay, ophthalmologic examination, laboratory studies (complete blood count, serum calcium, liver and kidney function tests, baseline serum angiotensin converting enzyme level)[7,8].

Differential diagnosis of cutaneous sarcoidosis includes a variety of other granulomatous disorders: classic ring granuloma, necrobiosis lipoidica, cutaneous Crohn, foreign body reactions, tuberculosis, tuberculoid leprosy[7].

Management of cutaneous sarcoidosis begins with evaluation of the extent and severity of disease to determine the most appropriate treatment pathway. For localized disease, first-line therapy consists in: intralesional or topical corticosteroids. In case of systemic disease, the options are: oral glucocorticoids, antimalaric drugs (hydroxychloroquine or chloroquine), methotrexate, tetracyclines[9,10].

CASE REPORT

We present the case of a 60 years old woman, reffered to our Dermatology for the evaluation of a bilateral, pruritic papular eruption, disseminated at the level of the trunk and the lower limbs, in evolution for 2 years. Her medical history included: pulmonary sarcoidosis diagnosed six years previously, autoimmune thyroiditis, psoriasis vulgaris, papulo-pustular rosacea, lumbar di-

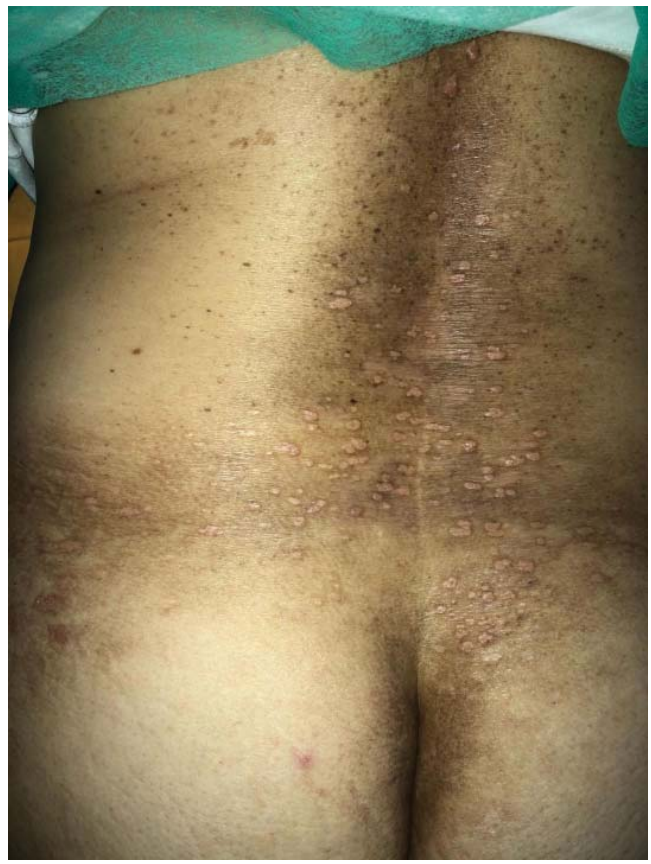

Figure 1. Papular eruption, disseminated at the level of the trunk.

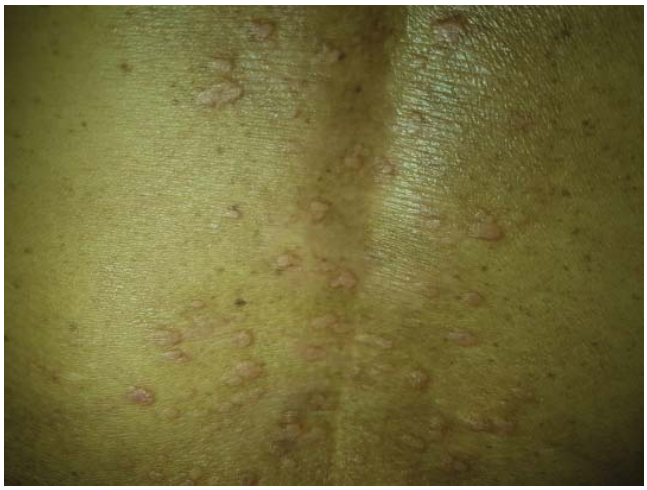

Figure 2. Erythematous papules, well defined, with regular edges, 0.5-4cm in diameter, some of them covered with fine scales, located on the posterior trunk.

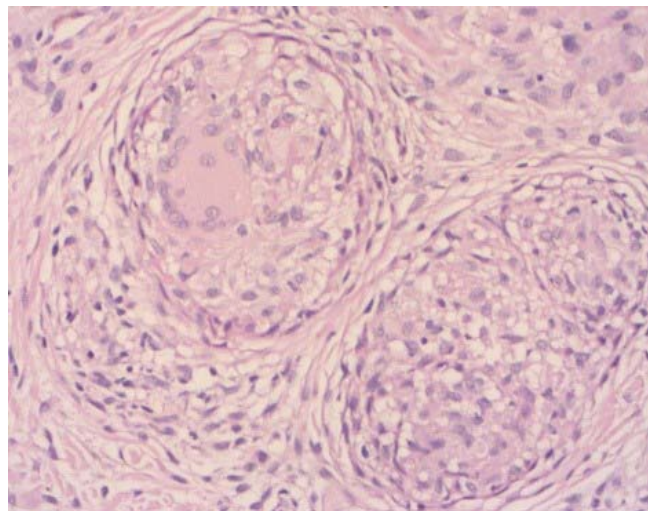

Figure 3. Inflammatory infiltrate with nodular pattern =>granulomas, without areas of necrotizing necrosis.

scopathy, and total hysterectomy (for uterine fibroma). Family history was unremarkable. She was on chronic treatment with levothyroxine 100μg/day and dermatocorticoids.

Physical examination was normal, except skin lesions. On clinical exam of the skin we revealed numerous pruritic, erythematous papules, well defined, with regular edges, 0.5-4cm in diameter, some covered with fine scales, located on the posterior trunk and both upper and lower limbs (Figure 1, Figure 2).

Routine blood work revealed: inflammatory syndrome with elevated CRP and ESR, mixed dyslipidemia. Abdominal ultrasound examination found 2 cm oval-shaped adenopathy in the celiac trunk area. Chest radiography showed the presence of several nodules, with stationary appearance from previous examinations, which were confirmed by CT scan.

We suspected cutaneous sarcoidosis, and we performed a skin biopsy with histopathological examination-to confirm our clinical presumption: at the dermal level, lympho-histiocitary inflammatory infiltrates with nodular distribution, forming several granulomas, without areas of necrosis of caseification, including frequent cells with epithelioid appearance. (Fig 3, Fig 4).

Corroborating the clinical, paraclinical data, and histopathological examination, we set the final diagnosis of cutaneous sarcoidosis.

A tapering course of oral prednisone 0,5mg/kg body weight was started. Because of adverse effects, steroids should be avoided for long term therapy and while slowly tapering the prednisone dosage, we associated hydroxychloroquine 200mg daily, gradually increasing it to 600mg daily[11,12]. The systemic treatment was accompanied with local therapy: dermatocorticoids

CRP	Pozitiv (negative)
VSH 1h	28 mm/1h (0-20)
Fibrinogen	602 mg/dl (238-498mg/dl)
Hemoglobin	14g/dl (11.7-15.9 mg/dl)
Platelets	321*10^3 /μl (150-400 /μl)
Neutrophil%	61.2% (37-80%)
Leukocytes	14*10^3 /μl (4.6-10.2)
Creatinine	0.74mg/dl (0,83)
Urea	54mg/dl (15-50)
ALT	19 U/L (9-52)
AST	18 U/L (14-36)
Cholesterol	248 mg/dl (<200mg/dl)
Triglycerides	200mg/dl (<150mg/dl)

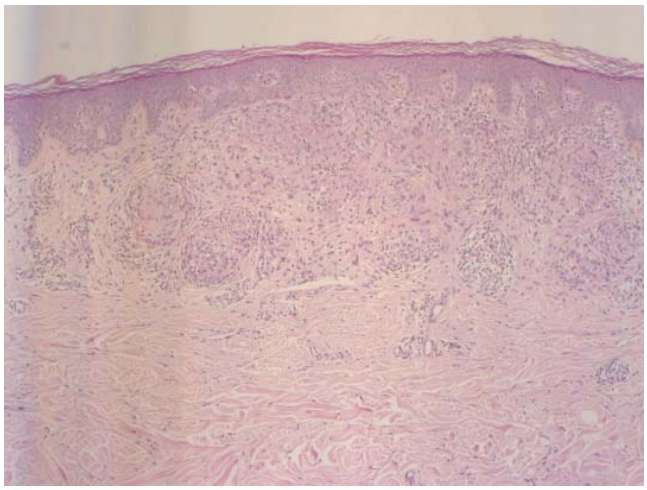

Figure 4. Thickened collagen bands.

and emollients.

Two months after starting the treatment, the patient presented for revaluation. On history taking and clinical examination, significant improvement in symptoms and lesions was seen (Figure 5).

DISCUSSIONS

Sarcoidosis is a granulomatous disease that can affect any organ, and the differential diagnosis represents the major challenge of cutanous sarcoidosis. First, the differentiation from lichen planus. It usually occurs in women, at 30-60 years old. Clinically it presents as multiple flattened pruritic papules, with pinkish-purple color, polygonal, glossy in appearance, disseminated on flex areas, with a tendency to generalize. Pathogenesis is based on cell-mediated immunity. As for the histopathological examination, it is characterized by: hyperkeratosis, granular layer growth, acanthosis degeneration with basal cell layer liquefaction; mononuclear cells in the band around the epidermis; keratinocyte apoptosis at the dermo-epidermal junction[13].

We may also differentiate sarcoidosis from non-infectious granulomatous dermatitis. Granuloma annulare appears more frequently at women, 30 years old, as symmetrical papules and plaques with central hyperpigmentation, located on hands and feet. The forms are: localized, generalized, subcutaneous. Usually, there are around 10 lesions. The pathogenesis is not well understood. It has been theorized that some triggering factors may contribute: vaccination, viral infections, trauma, insecte bite reactions. Granuloma anulare is mediated by Th1, and studies showed elevations in IL-2R-positive lymphocytes, IFN-γ-producing

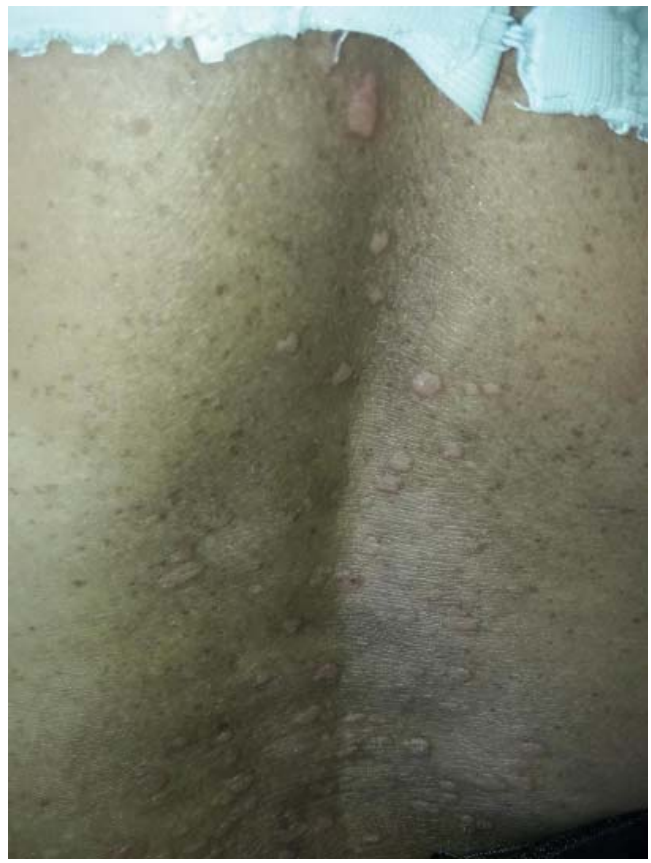

Figure 5. Improvement of the lesions.

lymphocytes, and TNF production by macrophages. The mechanism is based on release of cytokines (accumulated within the dermis), and release of lysosomal enzymes (which lead to degradation of connective tissue). The pathognomonic element in the histopathological examination is mucin deposition, and focal degeneration of collagen and elastic fibres, perivascular and interstitial lympho-histiocytic inflitrate in the upper and mid dermis. Treatment must be adjusted to the clinical form: in case of localized disease, therapeutic alternatives are dermatocorticoids or intralesional corticosteroids, cryosurgery or topical tacrolimus. Antimalarials or phototherapy are reserved to more extensive forms.

Necrobiosis lipoidica affects women, 30 years old. At clinical examination, we can find violaceous or red-brown plaques, with elevated edges, central telangiectases. Usually, the patient presents 1 to 3 lesions, which initially appears as a reddish-brown papule that slowly evolves into a well-defined waxy plaque. Histopatholo-

gical examination reveals: sclerosis, obliteration of the fascicular pattern of collagen, necrobiosis, microangiopathy.

Most commonly, local corticosteroid treatment is sufficient, but, in the case of a non-responsive ulceration to this treatment, excision of the lesion and covering with graft is recommended. Up to one third of patients associate diabetes mellitus, but the severity of the disease is not related to the severity of diabetes[15,16].

Cutaneous lesions in Crohn's disease can occur anytime in the evolution of the disease, sometimes even preceding the formal diagnosis of inflammatory bowel disease. From the wide range of extraintestinal manifestations, skin involvement in Crohn's disease is the most common one and includes specific lesions (with histopathological features consistent with Crohn's on biopsy), reactive lesions (inflammatory in nature but without specific histopathological findings of Crohn's), associated lesions (such as erythema nodosum) or therapy (particularly anti-TNF) induced lesion. The specific lesions can occur as a direct extension of bowel lesions to the skin or as metastatic lesions, meaning non-contiguous with the gastrointestinal tract. These latter lesions include erythema, vegetative papules, ulceration, lymphedema[17,18].

In conclusion, sarcoidosis can be defined as „the great imitator" as several other conditions may mimic the clinical and histopathological picture of the disease. A diagnosis of certainty can not be achieved by a single examination; history taking, physical examination, imaging tests, tissue sampling with histopathological examination revealing non-caseating granulomas and exclusion of other causes are required. In patients with longstanding evolution of the disease, checkups are required as involvement of other organs or systems can occur.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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