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MASTER THESIS

"SARCOIDOSIS CUTÁNEA: CORRELACION CLINICO-PATOLOGICA"

Tiago Castro Esteves

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1 - ABSTRACT

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Background: Sarcoidosis is a multi-system disease that may involve any organ or system. Cutaneous manifestations occur in 25-30% of patients with sarcoidosis. Recognition of cutaneous lesions is important because they provide a clue about the diagnosis and provide an easily accessible source of tissue for histopathologic examination. Sarcoidosis can present with reactive non-specific lesions like erythema nodosum or specific manifestations showing granulomatous microscopic pathology including papules, plaques, lupus pernio, scar sarcoidosis, and rare morphologies such as alopecia, hypo-pigmented patches and ichthyosiform lesions.

Several genetic polymorphisms are associated with an increased risk of developing sarcoidosis, suggesting that genetic susceptibility to sarcoidosis is probably polygenic. Environmental factors may also modify the susceptibility to sarcoidosis. Evidence favoring an infectious etiology has been accumulating, but the results of studies are conflicting. Recent studies have linked infectious agents including mycobacterial and propionibacterial organisms with sarcoidosis. However, the current concept is that the pathogenesis of sarcoidosis involves a T-helper-1-mediated immune response to environmental antigens in a genetically susceptible host. Although tremendous advances have been made, there is a significant gap between the vast knowledge accumulated on sarcoidosis in recent years and the understanding of this disease.

Objective: The aim of this work is to describe the main clinical and histopathological findings of cutaneous sarcoidosis, to investigate the relationship of these skin lesions with systemic involvement and to provide a comprehensive overview on the current updates in the treatment approach of cutaneous sarcoidosis.

Material and methods: A retrospective review of all patients who were diagnosed with cutaneous sarcoidosis and confirmed by histopathologic examinations, at the Department of Dermatology of Hospital de Vall d`Hebron, Universidad Autónoma de Barcelona. The clinical features were analyzed through review of medical records, and histopathologic and laboratory examinations.

Results and conclusion: At presentation, the age of the patients ranged from 37 to 71 years, with a mean age of 54 years. There were 24 females (83%) and 5 males (17%). Clinically, skin lesions consisted of macules or papules in 19 patients (65,5%), nodules in 12 (41%), plaques in 8 (27,5%) and lupus pernio in 4 (14%). Systemic

organ involvement was observed in 17 out of the 29 cases (59%). Intralesional or topical corticosteroids were the most frequent treatment used.

Histologically, the extent of the granulomatous infiltrate was mild in 6 cases (20%), moderate in 13 (43%) and severe in 11 (37%). Sarcoidal granulomas were located at superficial dermis in 3 cases of 30 biopsies (10%), superficial and mid dermis in 13 cases (43,3%), mid dermis in 3 (10%), entire dermis in 10 (33,3%) and 1 case (3%) with dermis and hypodermis involvement. In all cases, naked sarcoidal granulomas, with or without few lymphocytes, were present.

In conclusion, this retrospective study of cutaneous sarcoidosis showed a clinical spectrum of lesions with a good correlation with the granulomas´ localization in the biopsies.

2 - INTRODUCTION

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In Greek, sarcoidosis means a fleshlike condition (*sarco* means "flesh," *eidos* means "like," and *osis* means "condition"). [1] Actually, sarcoidosis is a multisystem disorder of unknown origin, characterized by the accumulation of lymphocytes and mononuclear phagocytes that induce the formation of noncaseating epithelioid granulomas.

Multiple organs may be involved, including lungs, mediastinal and peripheral lymph nodes, liver, spleen, skin, eyes, and parotid glands; central nervous system, heart, upper respiratory tract, bones, and joints are less frequently but usually more severely involved. [2,3]

Sarcoidosis is characterized by local immune reaction associated with clinical anergy. [4] The pathogenesis of sarcoidosis is suspected to be a host immunologic response to an antigenic exposure. [5] The development of noncaseating granulomas is thought to be the result of the local presentation of an antigen by macrophages to T lymphocytes, CD4 T cells/helper T cell type 1 (T_H1) phenotype. [6,7] The T cells most likely act in a twofold manner: in antigen recognition and in amplification of the local cellular immune response. [6] In addition, dendritic cells have been shown to have a prominent role in the immunopathological processes operating in this disease. [8,9]

Clinicians and scientists have entertained a number of possible causes, including infectious agents, genetic mutations, and various environmental exposures, with inconclusive results. The notion of a single causative agent is not in keeping with the worldwide distribution of disease. On the other hand, if there are multiple causes, then the near uniform reaction of patients with sarcoidosis to a common antigenic challenge (ie, the Kveim-Siltzbaum reagent) is difficult to reconcile. Based upon the available evidence, it seems likely that multiple factors, including host genetics and environmental exposures, independently contribute to the pathogenesis of sarcoidosis.

Sarcoidosis has a worldwide distribution and affects all ages, races and both sexes. [10] The prevalence of sarcoidosis has been reported to be the highest in Scandinavian countries and in the African-American population in the United States. [11] Onset of this disease is most often observed in adults under the age of 40 years in both sexes, with a peak incidence between 20 and 29 years. [11] A second peak in incidence has

been reported in women aged above 50 years in Scandinavian countries and Japan. [10,11] The prevalence is slightly higher in women than in men. [10]

Cutaneous involvement in sarcoidosis occurs in about one-quarter of the patients and is generally observed at the onset of the disease process although it may occur coincident with or after systemic involvement. [12,13] Therefore, cutaneous lesions can be an initial presentation and are probably an important factor in the investigation of the etiology of sarcoidosis.

The cutaneous manifestations are variable, sometimes being very obvious and at other times perplexing. [14] They mimic a wide array of dermatological conditions posing a diagnostic challenge to dermatologists worldwide. Hence, the disease is aptly referred to as the 'great imitator'. [12,14-16]

Cutaneous sarcoidosis lesions are classified as specific when the histologic examination shows typical sarcoid granulomas. Nonspecific sarcoidosis skin lesions show a nondiagnostic inflammatory reaction pattern on histologic evaluation. Nonspecific skin lesions are often associated with an acute presentation of sarcoidosis and, in general, portend a good prognosis of the skin lesions and of the visceral sarcoidosis. [17] Specific skin lesions tend to be more problematic than nonspecific lesions and are associated with worse outcomes. [17] Common specific sarcoidosis skin lesions are manifested as maculopapules, nodules, plaques, subcutaneous nodules, infiltrative scars and lupus pernio. Most common non-specific lesions are erythema nodosum, erythema multiforme, calcifications and prurigo. [18,19]

The diagnosis of sarcoidosis is established on the basis of compatible clinical and radiologic findings, supported by histologic evidence in one or more organs of noncaseating epithelioid-cell granulomas in the absence of organisms after an exhaustive study (special stains, microbiological cultures and serologic studies). The presence of foreign bodies has been classically considered an exclusion criteria for sarcoidosis, although several reports indicate that foreign bodies may serve as an inciting factor to induce granuloma formation. Therefore, these particules should not be interpreted as an evidence to exclude the diagnosis of sarcoidosis. A diagnosis of sarcoidosis is reasonably certain without biopsy in patients who present with Lofgren's syndrome. In all other cases, a biopsy specimen should be obtained from the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva. If diagnosis requires pulmonary tissue,

transbronchial biopsy by means of bronchoscopy has a diagnostic yield of at least 85% when multiple lung segments are sampled.

3 – MATERIALS AND METHODS

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We retrospectively identified 29 specimens with histopathological diagnosis of Cutaneous Sarcoidosis (CS) obtained between 1991 and 2012 (a 22-year period) in a single institution, Hospital Universitari Vall d´Hebron, Spain. Diagnosis of CS was confirmed by clinicopathological correlation and laboratory findings. The medical records, clinical photos at the time of biopsy, pathologic slides, and laboratory data for documentation of extra-cutaneous involvement were reviewed.

Systemic sarcoidosis was defined as cutaneous and extra-cutaneous involvement. We used the ACCESS instrument [20] (A Case Control Etiologic Study of Sarcoidosis) to define the organ involvement in Sarcoidosis. Only the patients with cutaneous involvement (specific cutaneous lesions) were reviewed. Biopsies of non-specific skin lesions were excluded from this study.

All cases showed non-caseating granulomas in the formalin-fixed and paraffin-embedded skin biopsy specimens. It was confirmed that special stains (like periodic-acid Schiff, alcian blue, Ziehl Neelsen stain and others) and cultures for bacterial, mycobacteria and fungi were negative and other granulomatous diseases were excluded. [21]

The pulmonary involvement of Sarcoidosis was confirmed by chest radiography, chest computed tomography, respiratory function tests and, in some cases, bronchoscopy, bronchoalveolar lavage and pulmonary or transbronchial lymph node biopsy. Radiographically, sarcoidosis of the lung was staged [22]: stage 1, bilateral hilar lymphadenopathy without infiltration; stage 2, bilateral hilar lymphadenopathy with infiltration; stage 3, infiltration alone; and stage 4, fibrotic bands, bullae, hilar retraction, bronchiectasis, and diaphragmatic tenting.

Other laboratory tests, including routine biochemistry, urinalysis, gallium-67 (Ga-67) scan, tuberculin skin test, and serum levels of angiotensin-converting enzyme (ACE) were performed on some patients based on clinical settings.

Central nervous system involvement was considered to exist if a lesion was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) and diagnosed by a consultant neurologist. For evidence of ocular sarcoidosis, all patients were screened by an ophthalmologist.

The clinical variables assessed were sex and age, as well as the type and localization of lesions.

Histologically, the following characteristics were evaluated:

1. Epidermis (normal, atrophic, ulcerated, focal lichenoid infiltrate);
2. Characteristics of the granulomatous infiltrate: Extent (+ mild, ++ moderate, +++ severe); Localization (superficial dermis, mid dermis, deep dermis and hypodermis); Distribution (perivascular, periannexial, irregular/interstitial); Coalescence of granulomas;
3. Characteristics of the granulomas: Type (naked sarcoidal or tuberculoid); Celular types such as multinucleate giant cells (0 absence, + mild, ++ moderate, +++ numerous); Other cellular types; Presence of necrosis and fibrosis; Foreign material (0 absence, + presence); Schaumann bodies (0 absence, + presence); Asteroid bodies (0 absence, + presence).
4. Interstitial infiltrate (type and density).

Finally, evolution of the disease and treatment outcomes were also evaluated.

4 – RESULTS

4 – RESULTS

4.1 – Clinical outcomes

The clinical characteristics of the 29 patients are summarized in **Table 1**.

At presentation, the age of the patients ranged from 37 to 71 years, with a mean age of 54 years. There were 24 females (83%) and 5 males (17%). Ethnicity was documented for all patients; 26 were white and 3 Afro-American **(Figure 1)**.

The clinical diagnosis at the time of skin biopsy included sarcoidosis (n=20), cutaneous tuberculosis (n=6), granuloma annulare (n=5), lupus erythematosus (n=3), lymphoma or pseudolymphoma (n=3), atypical micobacterial infection (n=3) and one case of each of the following diagnosis: vasculite, syphilis, Hansen's disease and foreign body granuloma.

Clinically, skin lesions consisted of macules or papules in 19 patients (65,5%) **(Figure 2)**, nodules in 12 (41%) **(Figure 3)**, plaques in 8 (27,5%) **(Figure 4)** and lupus pernio in 4 (14%) **(Figure 5)**. The less common presentations of cutaneous sarcoidal lesions, in our series, were: ulcerated form (1 patient) **(Figure 6)**, scar sarcoidosis (1 patient) and cicatricial alopecia (1 patient). Thirteen patients had more than one type of skin lesion.

Concerning localization of skin lesions, the most frequently affected areas were the lower limbs in 15 patients (of these, 6 in the knees) as well as the head and neck in 15 patients (4 in the nose, 3 in the forehead, 3 in the lower lip, 2 in zygomatic region, 2 in pre-auricular zone and 1 in malar zone), followed by the upper limbs in 10 patients (of these, 2 in the elbows), and trunk in 10 patients (with the back accounting for 3 of these cases). Lesions were present in more than one location in 16 patients.

According to the date available, the duration of skin lesions at diagnosis ranged from 1 month to 15 years, with a mean duration of 25 months.

During a median follow-up period of 6,8 years (minimum 3 months, maximum 21 years), systemic organ involvement was observed in 17 out of the 29 cases (59%). Among these patients, cutaneous lesion was the first manifestation in 88% (15 patients) and respiratory complaint was the first manifestation in 12% (2 patients) of cases.

The most frequent extracutaneous manifestation was dyspnea followed by arthralgia, fever and fatigue.

Systemic involvement most commonly affects the lung (15 patients) followed by lymph nodes (10 patients), liver (3 patients), central nervous system (2 patients) and one patient with ocular involvement. Ten patients had more than one organ involvement.

Systemic disease occurred frequently in patients with lupus pernio (4/4), scar sarcoidosis (1/1), cicatricial alopecia (1/1), plaques (6/8) and nodular variant (9/12). The less frequently clinical skin manifestation associated with systemic involvement was the maculopapular variant (9/19).

Chest radiography was done in all patients with cutaneous sarcoidosis (**Figure 7)**. On radiological staging (at the time of diagnosis), the vast majority of patients had normal chest radiograph (48,2%), followed by stage II (24,1%), stage I (17,2%), stage III (6,9%) and finally stage IV (3,5%) **(Table 1)**. The relation between each type of cutaneous lesion and the radiological staging is also shown in **Table 2**.

The most frequent CT findings were hilar and mediastinal adenopathy, followed by widespread nodules distributed among the bronchovascular bundles or subpleurally, interstitial infiltrates, and consolidation and architectural distortion with bronchiectasis and fibrotic changes of the lung parenchyma.

Of the 4 patients receiving Ga-67 scan, 3 showed abnormal findings compatible with sarcoidosis (**Figure 8)**. All of these 3 patients had normal chest radiography at the time of initial clinical investigation.

Among the 19 patients with routine blood biochemistry and urinalysis, one had hypercalcemia (serum calcium >10,5 mg/dl), two had anemia, two had elevated erythrocyte sedimentation rate and 10 (52,6%) had high serum angiotensin-converting enzyme (ACE) levels (>40 U/L). In all cases, the ACE level was less than twice the normal value. Systemic disease was identified more commonly in those with raised serum ACE levels (80% vs. 33,3% with normal ACE).

Mantoux test was performed in 20 patients, of which 18 were negative. The overall findings in these two cases (positive tuberculin test) were consistent with sarcoidosis, possibly in association with old pulmonary tuberculosis.

From a total of 29 patients studied, three patients were lost to follow-up. Duration of follow-up ranged from 3 months to 21 years (mean 6,8 years). Of the remaining 26 patients, in 19 of them (73%), the disease followed a chronic course, with persistence

of disease activity for more than 2 years **(Table 3)**. Regarding the evolution of skin lesions, in 9 cases (9/26), cutaneous disease was present unchanged or active, in 5 (5/26) there was a partial resolution and in 12 (12/26) the lesions had fully resolved. At last evaluation, 8 patients had ongoing systemic sarcoidosis. In four patients, pulmonary sarcoidosis had resolved, on the basis of normal chest radiography, but cutaneous lesions persisted. One patient died of liver cirrhosis (hepatitis C virus).
In terms of treatment received and response to treatment, our data are limited, as records, particularly documenting treatment response, were sometimes incomplete. Intralesional or high-potency topical corticosteroids were the most frequent treatment used (20 patients), followed by systemic corticosteroids (16 patients), chloroquine phosphate (4 patients), methotrexate (3 patients), doxycycline (1 patient), metronidazole (1 patient) and thalidomide (1 patient).

4.2 – Histological outcomes

A total of 30 formalin-fixed and paraffin-embedded skin biopsy specimens from the 29 cases of specific sarcoidosis skin lesions were reviewed. Twenty-eight patients had a single cutaneous biopsy and one patient had two biopsies performed at different occasion. The pathological findings are summarized in **Table 4 and 5**.

4.2.1 – Epidermis

Twenty-three specimens (77%) showed epidermal changes, including slight epidermal atrophy in 11 cases (37%), acanthosis in 11 cases (37%) and focal lichenoid infiltrate in 1 case (3%).

4.2.2 – Characteristics of the granulomatous infiltrate

The extent of the granulomatous infiltrate was mild in 6 cases (20%), moderate in 13 (43%) and severe in 11 (37%) **(Figure 9)**. Sarcoidal granulomas were located at superficial dermis in 3 cases of 30 biopsies (10%), superficial and mid dermis in 13 cases (43,3%), mid dermis in 3 (10%), entire dermis in 10 (33,3%) and 1 case (3%) with dermis and hypodermis involvement **(Figure 10)**. Grenz zone was respected in 20 cases (67%) **(Figure 11)**.

Perivascular distribution of granulomas was seen in two cases (6,6%) **(Figure 12)**, and periannexial distribution in five samples (16,6%). However, in 3 cases, we observed perivascular and periannexial distribution, simultaneously (10%). In the rest of the cases (66,6%), the distribution was irregular/interstitial.

Concerning the only case of subcutaneous fat involvement, it showed a lobular distribution as well as a septal distribution.

Coalescence of granulomas was observed in 24 biopsies (80%).

4.2.3 – Characteristics of the granulomas

The inflammatory infiltrate consisted of nodular aggregates of epithelioid histiocytes with variable amounts of multinucleated giant cells and lymphocytes **(Figure 13)**.

In all cases, naked sarcoidal granulomas **(Figure 14)**, with or without few lymphocytes, were present, with absence of mycobacterial and fungal organisms. In the majority of the cases (80%), we observed a small number of lymphoid cells around the granulomas. In the rest of the cases, there was an absence of lymphoid cells.

Multinucleated giant cells were found in 29 biopsies (97%). The presence of these cells was mild in 23 cases (77%) and moderate in 6 (20%).

Focal fibrinoid necrosis among granulomas was present only in one case. We didn't observe any case with the presence of fibrosis.

Foreign material was detected in 5 biopsies (17%), all of them without the use of polarized light microscopy. Asteroid bodies were seen in 1 case (3%) **(Figure 15)**, as well as Schaumann bodies, with only 1 case (3%).

4.2.4 – Interstitial infiltrate

Concerning the interstitial infiltrate, lymphocytes were present in 20 cases (67%). Other cellular types were seen only in a minority of biopsies: plasma cells in 7 cases (23%) and histiocytes in one case (3%).

In most patients, the interstitial infiltrate was multicellular

5 - DISCUSSION

5 – DISCUSSION

5.1 – Clinical outcomes

Sarcoidosis is a common systemic, noncaseating granulomatous disease of unknown etiology. While numerous organs may be involved, the lungs, lymph nodes, and skin are most commonly affected. [23]

The incidence of sarcoidosis varies widely throughout the world, probably because of differences in environmental exposures, surveillance methods, and predisposing HLA alleles and other genetic factors. In the United States, the disease prevalence is estimated to be between 10 to 40 cases per 100,000 persons, [24] with a much higher annual incidence in African Americans (35.5-64 cases/100,000 population) than in whites (10.9-14 cases/100,000 population). [25,26] Scandinavia has the world's highest prevalence of reported cases (64 cases/100,000 population). [27] In other countries, the incidence of sarcoidosis is reported as follows: United Kingdom, 20/100,000; France, 10/100,000; Germany, 9/100,000; Greece, 7/100,000; Spain, 1.4/100,000; Japan, 1.4/100,000 and Korea, 0,125/100,000. [15,28-30]

Sarcoidosis affects all races and all ages. Most commonly it presents in winter and early spring, [31] and usually develops before the age of 50 years. [25] The onset of sarcoidosis peaks during the third and fourth decade of life in the general population. [25] In black Americans, the peak incidence occurs later in life, in the fourth decade. [25] In Japan, the peaks are in the third decade of life, [32] while in Scandinavian women, the incidence appears to be bimodal, with one peak at 25 to 29 years of age and another at 65 to 69 years of age. [33]

The disease affects both sexes, with a slight preponderance among females [34], especially in the second peak. [29,35] The female predominance is particularly high, ranging from 71 to 76%, in patients with cutaneous sarcoidosis. [21,36-38]
In our series, 89% of the patients were between 40 and 60 years of age, with a peak during the fifth decade of life, slightly higher than what is described in the literature

(western countries). [15,25,28,29,39] In our study of cutaneous sarcoidosis, there was a marked female predominance (83%), which is in consonance with other series. In Hanno's series, [40] 83% were female, and in Yanardag's [41] series of 170 patients with cutaneous sarcoidosis, 80% were female. Estrogen may play a role in the development of skin lesions, [21] which could explain the predominance of women in reports of cutaneous sarcoidosis. Another factor which may explain this difference between the two sexes, is that women may be more likely than males to notice and report cutaneous lesions.

The phenotypic expression of sarcoidosis varies across different races or regions. [25,36] Sarcoidosis is more frequent in individuals of Afro-American origin. In addition, skin involvement in these individuals may be more acute and severe than in other races. [42] In contrast to this, cases affecting white persons have a tendency to be asymptomatic with a more favorable prognosis. [43] In our series we had only 3 patients afro-americans, nevertheless all of them had systemic involvement of the disease.

Clinical suspicion and characteristic histologic findings are important for diagnosis. [21,44-45] Skin lesions may present with a wide spectrum of different morphologies, so, the diagnosis of sarcoidosis becomes a challenge, especially when the lesions are nonspecific or when there is no systemic involvement. [17,40] In fact, there were several differential diagnoses in our study that share similar clinical features with cutaneous sarcoidosis, which included cutaneous tuberculosis, granuloma annulare, lupus erythematosus, lymphoma or pseudolymphoma, atypical micobacterial infection, vasculite, syphilis, Hansen's disease and foreign body granuloma. Therefore, histologic examination was very important in order to determine a definite diagnosis of sarcoidosis.

Cutaneous sarcoidosis lesions are classified as "specific" (the histologic examination shows typical sarcoid granulomas) or "nonspecific" (nondiagnostic inflammatory reaction pattern on histologic evaluation). Specific skin lesions develop in 9% to 37% of all sarcoidosis patients. [46] These lesions have highly variable clinical manifestations and can simulate many skin diseases. Common specific skin lesions manifest as maculopapules, nodules, plaques, subcutaneous nodules, infiltrative scars,

and lupus pernio. [17,47-49] Maculopapular lesions are the most common specific cutaneous manifestations of sarcoidosis. [17,48,50] Normally, these lesions favor the neck, trunk, extremities, and mucous membranes. [48,51] In our cases, maculopapular eruption was the most common type of cutaneous lesions (65,5%).

Another clinical aspect we want to emphasize is that, cutaneous involvement in sarcoidosis, can manifest itself through multiple skin lesions. In addition, different clinical forms can occur in the same patient during the course of the disease, as occurred in our study. The association of different clinical manifestations in the same patient makes more difficult the classification into classical forms.

Concerning distribution of the lesions in our series, the lower limbs (51,7%), and the head and neck region (51,7%) were the most frequent localizations. In western reports, about 25% of cutaneous sarcoidosis occurs on the head region. [21,37] In contrast, head involvement was much more frequent (51,7%) in our series, and similarly high rates have been reported by other series from Taiwan (50– 58%) [52-54] and India (65%). [55]

Skin involvement was the onset of sarcoidosis in the majority of patients (88%), as previously described. [17,36] This fact provides a valuable opportunity for early diagnosis of this disease because of easy accessibility to skin biopsy.

In general, specific skin lesions have no prognostic significance, do not show any correlation with the extent of systemic involvement, and do not indicate a more serious form of sarcoidosis. [17,40,56] However, in our study, we found that maculopapular variant was the type of cutaneous lesion with a better prognosis. This variant was associated with systemic involvement in only 47,4% (9/19), radiological stage I (4/8) and duration of < 2 years of sarcoidosis activity (7/16). In contrast, our 4 cases of lupus pernio were associated with systemic involvement, radiological stage II (3/3) and duration of > 2 years of sarcoidosis activity. This observation has been previously pointed. Furthermore, we also found that, as in lupus pernio, plaque-type and nodular lesions were more common in chronic forms of the disease and were more persistent, as shown in **Table 3**. These observations are consistent with the literature.

Systemic involvement was detected in 59% of our patients. The lung (88%) and lymph nodes (59%) were the two most commonly affected extracutaneous organs, followed by the liver (18%), central nervous system (12%) and the eye (6%). In contrast, in 12 out of the 29 cases (41%), demonstrable sarcoidosis skin involvement was documented without extracutaneous symptoms. This is a high percentage, however, our findings are coincident with Veien's report, [56] as well as other reports. Hanno [40] found that 33% of the patients had no systemic involvement, and in a series of 25 patients in Singapore, [57] 60% of them had no systemic involvement. One explanation for the high percentage of patients without systemic symptoms, in our study, may be the duration of the follow-up in these 12 patients. Some of these patients were recently diagnosed; therefore, a longer follow-up time (cutaneous involvement in sarcoidosis may precede systemic involvement several years) and a more extensive investigation might reveal extracutaneous involvement in these patients with apparently isolated cutaneous disease.

The Mantoux test is commonly used to distinguish sarcoidosis and tuberculosis. A negative Mantoux test has a high sensitivity value for the diagnosis of sarcoidosis irrespective of the BCG vaccination status. A positive Mantoux test (independently of the size of reaction) in a suspected case of sarcoidosis, should arouse strong suspicion of an alternate or an additional diagnosis of TB. [58] In our study, Mantoux test was performed in 20 patients, of which 18 were negative.

Sarcoidal granulomas produce angiotensin-converting enzyme (ACE), and serum ACE levels are elevated in 30%-80% of patients with sarcoidosis. However, ACE is not specific for sarcoidosis and is elevated in many diseases. [59-62] So, the value of serum ACE levels in diagnosing or managing sarcoidosis remains controversial. There is a false-positive rate of 10% and a false-negative rate of 40% when serum ACE levels are used to diagnose sarcoidosis. [1,63] In some cases, ACE levels may be useful as an adjunct, but not for specific and definitive diagnosis. [63] In the same way, determination of ACE levels is generally not a useful guide for disease progression or therapeutic response. [1,64-66]

Elevated levels of serum ACE were observed in 52.6% of our patients (10/19). We also note that systemic disease was identified more commonly in those with raised

serum ACE levels (80% vs. 33,3% with normal ACE). Although the sample is small, we want to emphasize the fact that, the difference between these 2 groups was significant.

Regarding the treatment, skin lesions of sarcoidosis are not dangerous to life, and treatment of patients should focus upon the systemic abnormality. [67-69] Corticosteroid therapy remains the cornerstone of the treatment regimen. In patients with lesions confined to the skin, topical or intralesional corticosteroid therapy may be adequate while patients with systemic involvement may need systemic corticosteroids or combination therapy.
In our study, partial or complete resolution of skin lesions was the rule (17/26). Curiously, treatment response in our results depended upon the association with systemic symptoms. Among the twelve patients who showed complete resolution of cutaneous lesions, seven of them had no associated systemic symptoms. It is known that the prognosis of cutaneous sarcoidosis depends on systemic involvement and death from sarcoidosis is mostly due to pulmonary fibrosis. Our study also indicated that cutaneous lesions of sarcoidosis associated with systemic symptoms have a lower treatment response compared with patients who only have cutaneous lesions.

5.2 – Histological outcomes

The histological spectrum of cutaneous sarcoidosis, including some uncommon histopathological findings, has been previously described. [21,36,37]

Epidermal changes are usually non-specific and consequently of little diagnostic value in sarcoidosis. However, they are relatively frequent, as previously described. [44] We found epidermal alterations in 23 specimens (77%), mostly atrophy (11 cases) and acanthosis (11 cases).

The extent of the granulomatous infiltrate was moderate or severe in the majority of our cases (24/30). Sarcoidal granulomas were located, mostly, at superficial and mid dermis, however, one aspect we want to emphasize is that, the entire dermis can also

be affected, as well as, exceptionally, the hypodermis. In more than half of cases, granulomas had an irregular distribution. Nevertheless, perivascular and periannexial distribution could also be observed in one third of cases, approximately.
In our series, the granulomas´ location correlated well with the clinical form, being deeper for more infiltrated skin lesions, particularly the nodular form **(Table 4)**. In contrast, the number of granulomas was not correlated with a more or less extensive clinical presentation. In the same manner, the number of granulomas and the extent of lymphocyte infiltration did not correlate with the treatment response and prognosis of our cases.

In all cases of our study, naked sarcoidal granulomas (with or without few lymphocytes) were present, with absence of mycobacterial and fungal organisms. This fact confirms that typical naked non-caseating granulomas are a sensitive and characteristic histological finding in cutaneous sarcoidosis. However, this type of granuloma is not specific of sarcoidosis, and it may be found in other diseases (immunodeficiency disorders, lymphoproliferative disorders, as a response to infectious agents, foreign bodies, etc). [21]

Asteroid and Schaumann bodies were found only in one case each one (3%), which proves that, this histological finding, is little sensitive, as well as non-specific. [21] Nevertheless, this percentage (3%) is lower than other reports.
On the other hand, foreign material could be demonstrated in 17% of our biopsies, slightly lower than what is described in the literature (22-77%). [21] We used conventional light microscopy rather than polarized microscopy, which can explain this low number. Foreign bodies may serve as an inciting factor to induce granuloma formation, [21] and the presence of foreign bodies, birefringent or not, also should not be interpreted as an evidence to exclude the diagnosis of sarcoidosis. [21,36,37,54] In fact, sarcoidosis and foreign material can exist together. [70-72]

Focal fibrinoid necrosis among granulomas was present only in one case. Obviously, when necrosis is found within granulomas, caution needs to be taken in excluding an infection, particularly tuberculosis. [21] However, we concur with other authors that the

presence of this uncommon histological feature should not automatically exclude the diagnosis of sarcoidosis. [36]

6 - CONCLUSIONS

6 – CONCLUSIONS

Sarcoidosis is a multisystem disease in which the skin lesions may present with a wide spectrum of different morphologies. For this reason, the clinical diagnosis of cutaneous sarcoidosis is often difficult.

This retrospective study of cutaneous sarcoidosis showed a clinical spectrum of lesions with a good correlation with the granulomas´ localization in the biopsies.
The clinical-histological correlation and, in much cases, the use of special stains, have a great importance in the differential diagnosis with other granulomatous skin diseases, particularly when the histological features are atypical or non-specifics.

Cutaneous involvement in sarcoidosis is not only useful for diagnosis but may also discriminate progressive disease. Specific lesions like lupus pernio and nodules may have a prognostic significance.

Extracutaneous involvement is frequent and our series indicates that the prognosis of cutaneous lesions depends on the existence of systemic symptoms.

Typical naked non-caseating granulomas are a sensitive and characteristic histological finding in cutaneous sarcoidosis. Another important histological finding is the presence of foreign bodies. In fact, sarcoidosis and foreign material can exist together.

A complete dermatologic examination, ideally by a dermatologist, including chest X-ray, blood chemistry and biopsy of suspicious skin lesions, should be routinely included in the diagnostic evaluation.

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8 – TABLES

9 – FIGURES