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Original Research

Prevalence and characteristics of cutaneous sarcoidosis in Argentina

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ABSTRACT

Background: Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The incidence is higher in women than in men, according to some studies. Studies regarding prevalence and characteristics of cutaneous sarcoidosis in our region are scarce.
Objective: This study aimed to describe the characteristics of patients with cutaneous sarcoidosis and to estimate its prevalence.
Methods: A cross-sectional study was conducted of patients with cutaneous sarcoidosis between January 1, 2004 and April 30, 2019 at the Hospital Italiano de Buenos Aires in Argentina. We included all patients age >17 years with biopsy-proven cutaneous sarcoidosis. Isolated cutaneous sarcoidosis was defined as the presence of epithelioid noncaseating granulomas on a skin biopsy without further evidence of systemic involvement. To estimate period prevalence, we only considered the subgroup of patients affiliated with our private health system.
Results: A total of 38 patients with cutaneous sarcoidosis were included. The median age at the time of diagnosis was 55.5 years. There was a striking female predominance in our series (73.7%). Overall, 15 patients (39.5%) had isolated cutaneous sarcoidosis and 23 (60.5%) had systemic sarcoidosis with cutaneous involvement. The median follow-up of the study population from histological diagnosis was 50 months (interquartile range, 24–10 months). Regarding skin involvement, 28 patients (73.7%) presented with only sarcoidosis-specific lesions, 6 (15.8%) presented with erythema nodosum, and 4 (10.5%) presented with both sarcoidosis-specific lesions and erythema nodosum. Treatment was given to 29 patients (73.6%), with systemic and topical corticosteroids being the most frequent. The crude prevalence of cutaneous sarcoidosis was 16.9 (95% confidence interval, 10.6–25.5) per 100,000 persons.
Conclusion: One of the major findings of our study was that 40% of patients had isolated cutaneous sarcoidosis.

Introduction

Sarcoidosis is a multisystemic, chronic, and granulomatous disease of unknown etiology. The prevalence ranges from 10 to 64 per 100,000 persons and varies by geographic location, race, and sex (Haimovic et al., 2012a; 2012b;; Iannuzzi et al., 2007; NOE and Rosenbach, 2017; Wanat and Rosenbach, 2014). The incidence is higher in women than in men (Hillerdal et al., 1984; Rybicki and Iannuzzi, 2007; Rybicki et al., 1997). In a large population-based study, the female-to-male ratio was 2.1:1 (Ungprasert et al., 2016a, 2016b), whereas in a smaller retrospective analysis the ratio was 1:4.1 (Tong et al., 2014).

Skin lesions are present in at least 20% of sarcoidosis cases. The most frequent clinical manifestations are macules and plaques (Haimovic et al., 2012a; 2012b;; Iannuzzi et al., 2007; NOE and Rosenbach, 2017; Wanat and Rosenbach, 2014). There is a debate in the scientific community regarding whether isolated cutaneous sarcoidosis exists (Judson and Baughman, 2014; Ungprasert et al., 2016a). Some authors state that sarcoidosis is, by definition, a multisystemic disease; therefore, there is no such thing as isolated cutaneous sarcoidosis without systemic involvement. They postulate that this may represent an initial presentation and that systemic involvement will eventually be observed. These authors also affirm that the diagnosis of sarcoidosis cannot be determined by the presence of granuloma in a single organ, such as the skin (Costabel et al., 2007). However, some authors state that, despite being rare, isolated cutaneous involvement can be diagnosed in patients who do not develop systemic disease in the long term

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(Ishak et al., 2015; Ungprasert et al., 2016b; 2017a;; Wanat and Rosenbach, 2014).

The epidemiology of cutaneous sarcoidosis is not well characterized because most previous studies were based on referral-based studies (Ungprasert et al., 2016a; 2016b; 2017a; 2017b). To date, precise data on cutaneous sarcoidosis and its prevalence are lacking in Latin America. The present study aimed to describe the clinical characteristics of patients with cutaneous sarcoidosis and to estimate its prevalence.

Methods

We performed a cross-sectional study to evaluate the clinical and histopathologic features of patients with cutaneous sarcoidosis between January 1, 2004 and April 30, 2019 at the Hospital Italiano de Buenos Aires in Argentina. The institution is composed of two central hospitals and 24 peripheral centers and offers comprehensive health and medical services to approximately 140,000 outpatients. However, patients enrolled in other prepaid health providers can also receive medical attention. The Department of Dermatology has 80 physicians and 7 nurses, with up to 16,000 medical consultations per month. At our center, all medical care interventions are centrally registered in a computerized data repository with only one electronic health record per person.

We included all patients age >17 years with biopsy-proven cutaneous sarcoidosis (evidence of epithelioid noncaseating granuloma). Other granulomatous diseases were ruled out. Patients who did not undergo a systemic evaluation were excluded (Costabel et al., 2007; Haimovic et al., 2012a; Iannuzzi et al., 2007; Ishak et al., 2015; Judson and Baughman, 2014; NOE and Rosenbach, 2017; Wanat and Rosenbach, 2014). All individual medical records of the identified patients were reviewed by a dermatologist specifically trained to do so.

The following patient data were obtained: sex, age at the time of diagnosis, area of involvement of cutaneous manifestations, presence or absence of systemic involvement disease (Haimovic et al., 2012a; Wanat and Rosenbach, 2014), histopathologic findings (erythema nodosum, sarcoidal granulomas), time between first visit to a specialist and diagnosis, and treatments. Classification of skin lesions was defined according to histological findings: specific lesions such as alopecia, plaque, maculopapular, scar, and subcutaneous nodules, presenting with sarcoidal granulomas. Nonspecific lesions, such as erythema nodosum, were defined by the absence of these granulomas.

Cutaneous sarcoidosis was defined as suspected clinical lesion with histopathologic findings of sarcoidal granuloma and exclusion of other granulomatous diseases by special stains for microorganisms and cultures. Alternatively, cutaneous sarcoidosis was also considered when noncaseating granulomas were diagnosed elsewhere and compatible skin manifestations were found.

Isolated cutaneous sarcoidosis was defined as the presence of epithelioid noncaseating granulomas on skin biopsy without further evidence of systemic involvement or infection (Costabel et al., 2007; Haimovic et al., 2012a; Iannuzzi et al., 2007; Ishak et al., 2015; Judson and Baughman, 2014; NOE and Rosenbach, 2017; Ungprasert et al., 2016b; Wanat and Rosenbach, 2014). Systemic sarcoidosis with cutaneous involvement was considered in any of the following scenarios: presence of noncaseating granulomas in any extracutaneous organ and in the skin, and presence of noncaseating granulomas in any extracutaneous organ and clinical evidence of cutaneous sarcoidosis. To classify patients into subgroups, medical records were reviewed, including skin biopsy with special stains and cultures, routine blood and urine tests, detection of erythrocyte sedimentation rate and serum angiotensin-converting enzyme, chest computed tomography, pulmonary function test, tuberculin skin test, and electrocardiography.

For patients with isolated cutaneous sarcoidosis, the time from diagnosis to the last visit carried out was registered to evaluate whether systemic involvement appeared. These patients did not present systemic involvement at diagnosis or during follow-up.

Sampling and statistical analysis

Sampling was consecutive. Categorical variables are reported with absolute numbers and percentages. Numerical variables are reported with median and 25% to 75% interquartile range (IQR). To estimate period prevalence, we only considered the subgroup of patients who belonged to the closed health system of the Hospital Italiano de Buenos Aires. The prevalence was constructed using the number of affiliates to the closed health system who were age > 17 years as of June 15, 2011 as the denominator. Prevalence is reported with its corresponding 95% confidence interval (CI). The statistical software STATA (StatCorp, version 14.2) was used for calculations.

The institutional review board revised and approved the study (protocol number 3344). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2018.

Results

A total of 299 electronic medical records were identified, with sarcoidosis reported as a diagnosis during the study period. Of these, 171 had biopsy-proven sarcoidosis and were further analyzed. Of those, only 45 patients (26.3%) were found to have cutaneous involvement. Seven patients with biopsy-proven cutaneous sarcoidosis did not undergo systemic evaluation and were excluded. Thus, 38 patients were included in this study (Fig. 1). Fig. 2.

The median age at the time of diagnosis was 55.5 years (IQR, 42–60 years), and 28 patients (73.7%) were female. All patients were Hispanic or Latin. Overall,15 patients (39.5.%) had isolated cutaneous sarcoidosis and 23 (60.5%) had systemic sarcoidosis with cutaneous involvement (Table 1). The median follow-up of the study population from histological diagnosis to inclusion in the study was 50 months (IQR, 24–101 months). The median follow-up of patients with isolated cutaneous sarcoidosis from histological diagnosis to inclusion in the study was 59 months (IQR, 24–101 months).

Of the 23 patients with systemic involvement, five initially presented with isolated cutaneous involvement and developed systemic disease during a median of 6 months (IQR, 2–6 months). On the other hand, eight patients presented with systemic involvement and developed cutaneous compromise during a median time of 19.5 months (IQR, 6–24 months). Finally, 10 patients had both systemic and cutaneous involvement at the same time.

The most frequent extracutaneous manifestations were lymph nodes and lung in 20 (91%) and 17 patients (72.3%), respectively. Heart and liver involvement was observed in one patient (4.5%) each. Regarding skin manifestations, 28 patients (73.7%) presented with only sarcoidosis-specific lesions, 6 (15.8%) presented with erythema nodosum, and 4 (10.5%) presented with overlap. Four patients presented with both specific and nonspecific lesions. We did not find any particular cutaneous morphologies or distributions that were more likely to be seen in patients with systemic involvement. Further information regarding histology, clinical manifestations, site of involvement, and complementary studies are detailed in Tables 1 and 2.

Treatment was given to 29 patients (76.3%), eight of whom (27.6%) received more than one drug. Systemic and topical corti-

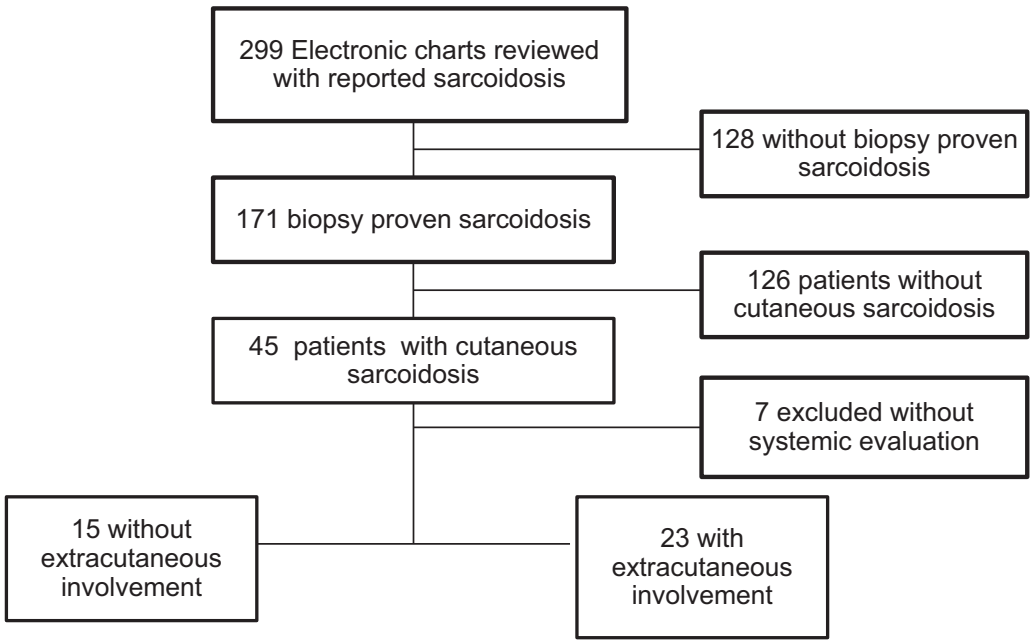

Fig. 1. Study flow diagram: selection criteria and final diagnosis.

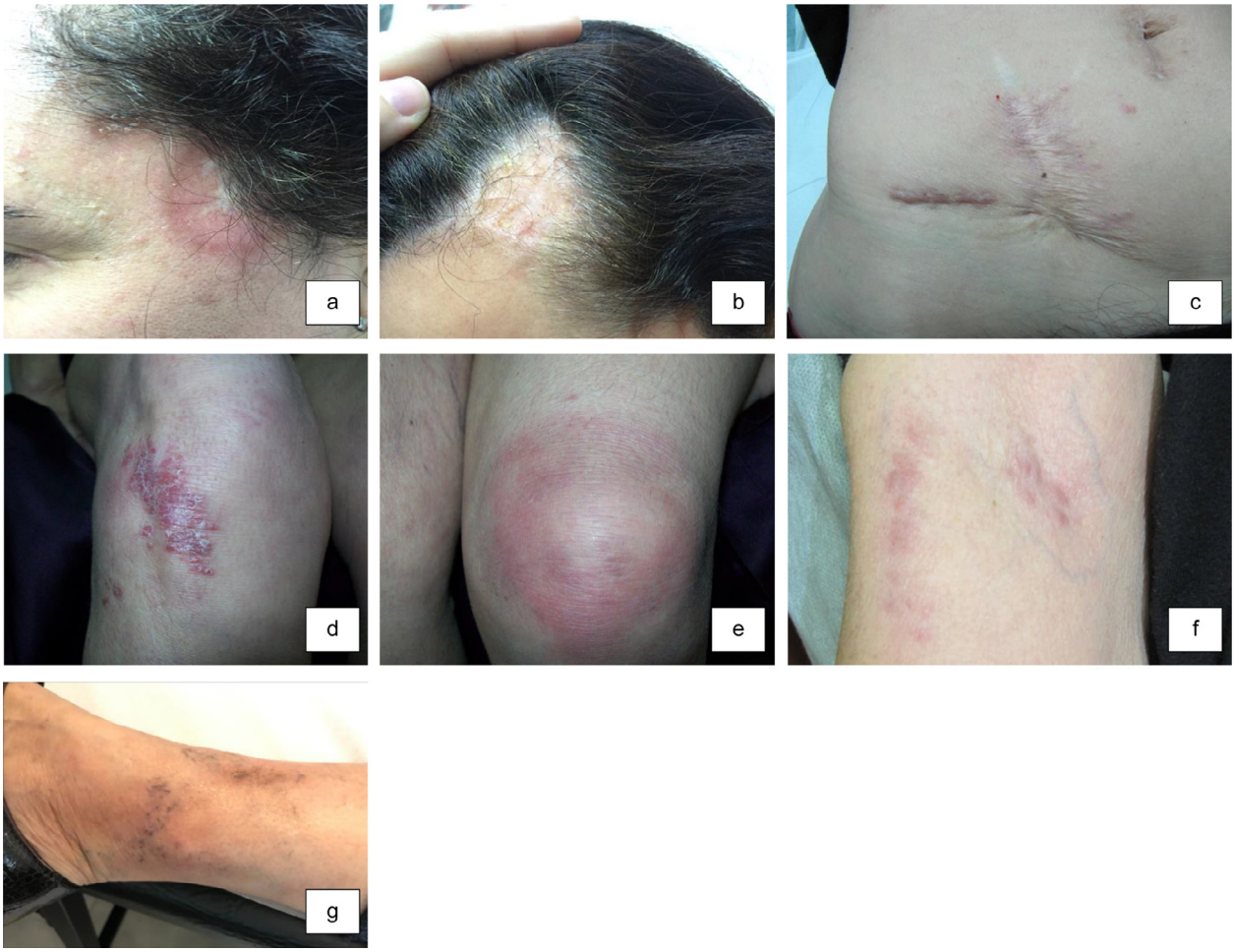

Fig. 2. Different types of specific lesions of sarcoidosis: (a) plaque; (b) alopecic; (c) scar; (d) plaque (predominant); (e) maculopapular; (f) papular; and (g) subcutaneous nodule.

Table 1
Patient characteristics, collected at the Hospital Italiano between January 1, 2004 and April 30, 2019.

Variable	Result (n = 38)
Female, n (%)	28 (73.7)
Age at diagnosis, years, median (IQR)	55.5 (42–60)
Type of sarcoidosis, n (%)	
Isolated cutaneous sarcoidosis	15 (39.5)
Systemic sarcoidosis with cutaneous involvement	23 (60.5)
Months to diagnosis, median (IQR)*	2 (1–8)
Biopsied organ, n (%)	
Skin	27 (71.1)
Skin + lung	1 (2.6)
Skin + liver	1 (2.6)
Lymph node	5 (13.2)
Skin + lymph node	4 (10.5)
Involved areas, n (%)	
1	26 (68.4)
≥2	12 (31.6)
Region of involvement, n (%)†	
Lower limbs	20 (52.6)
Upper limbs	15 (39.5)
Abdomen	2 (5.3)
Chest	4 (10.5)
Back	2 (5.3)
Face and neck	14 (36.8)
Scalp	1 (2.6)
Clinical presentation, n (%)	
1 type	28 (73.7)
≥2 types	10 (26.3)
Types of cutaneous sarcoidosis, n (%)	
Specific lesions	
Alopecic	2 (5.3)
Plaque	9 (23.7)
Maculopapular	8 (21)
Scar	6 (15.8)
Tumoral	2 (5.3)
Subcutaneous nodule	14 (36.8)
Nonspecific lesions	
Erythema nodosum	10 (26.3)
ACE absolute‡, median (IQR)	46.5 (32–77)
ACE elevated§, n (%)	15 (39.5)

ACE, angiotensin-converting enzyme; IQR, interquartile range
Categorical data are expressed with absolute numbers and percentages. Numerical data are expressed in median and IQR.
* Time between clinical diagnosis and histological confirmation.
† Sum of percentages is > 100 because each patient might present lesions in > 1 localization.
‡ Available in 20 patients.
§ Available in 28 patients.

Table 2
Patient characteristics with isolated cutaneous sarcoidosis, collected at the Hospital Italiano between January 1, 2004 and April 30, 2019.

Variable	Result (n = 15)
Female, n (%)	13 (86.7)
Age at diagnosis, years, median (IQR)	59 (42–72)
Months to diagnosis, median (IQR)*	3 (1–10)
Involved areas, n (%)	
1	11 (73.3)
≥2	4 (26.4)
Region of involvement, n (%)†	
Lower limbs	6 (40)
Upper limbs	7 (46.7)
Abdomen	0 (0)
Chest	2 (13.3)
Back	2 (13.3)
Face and neck	6 (40)
Scalp	0 (0)
Clinical presentation, n (%)	
1 type	12 (80)
≥2 types	3 (20)
Type of cutaneous sarcoidosis, n (%)	
Specific lesions	
Alopecic	0 (0)
Plaque	3 (20)
Maculopapular	3 (20)
Scar	3 (20)
Tumoral	2 (13.3)
Subcutaneous nodule	6 (40)
Nonspecific lesions	
Erythema nodosum	2 (13.3)
ACE absolute‡ median (IQR)	37 (15–43)
ACE elevated§, n (%)	9 (6)

ACE, angiotensin-converting enzyme; IQR, interquartile range
Categorical data are expressed with absolute numbers and percentages. Numerical data are expressed in median and IQR.
* Time between clinical diagnosis and histological confirmation.
† Sum of percentages is > 100 because each patient might present lesions in > 1 localization.
‡ Available in nine patients.
§ Available in nine patients.

costeroids were the most frequently used treatments, in 18 (62%) and 15 (51.7%) patients, respectively. Other treatments such as hydroxychloroquine, intralesional corticosteroids, and surgery were used in 6 (20.7%), 2 (6.9%) and 1 (3.4%) patients, respectively.

Of the 38 patients included, 22 (57.9%) were affiliated with our private health system. The crude prevalence of cutaneous sarcoidosis estimated in this subgroup of patients was 16.9 (95% CI, 10.6–25.5) per 100,000 persons.

Discussion

In this study, we present the characteristics of cutaneous sarcoidosis. One of our major findings was that 40% of patients had isolated cutaneous sarcoidosis. Additionally, we estimated the prevalence of cutaneous sarcoidosis, which was 16.9 (95% CI, 10.6–25.5) per 100,000 persons.

In our study population, cutaneous sarcoidosis was more frequent in middle-aged women and presented most frequently in the lower extremities with subcutaneous nodules, plaques, papules, and scar sarcoidosis, similar to what was reported in other publications (Benatar, 1977; Costabel et al., 2007; Haimovic et al., 2012a; Iannuzzi et al., 2007; Ishak et al., 2015; NOE and Rosenbach, 2017; Ungprasert et al., 2016b; 2017a;; Yanardağ et al., 2003). In the same line, eritema nodosum was the most frequent finding among nonspecific lesions.

Interestingly, Wu and Lee (2013) reported that facial involvement was much more frequent (59%) in Taiwanese patients, and similar findings were reported in India (Sharma et al., 2007). However, in Western countries, approximately 25% of cutaneous lesions occured on the face (Cardoso et al., 2009; Sharma et al., 2007). In line with this finding, our data are similar to that of Western countries. In our study, 10 patients were initially diagnosed with systemic and cutaneous sarcoidosis simultaneously. On one hand, Ungprasert et al. (2016b); (2017a;)) found that skin lesions were often the initial presentation. A diagnosis of skin disease was present in 47% of patients in the sarcoidosis-specific lesions cohort and 38% of patients in the EN cohort before the diagnosis of systemic sarcoidosis (Ishak et al., 2015; Ungprasert et al., 2016b; 2017a). On the other hand, Ishak et al. (2015) reported that their patients were more often initially diagnosed with systemic sarcoidosis before presenting with cutaneous disease.

Among specialists, there is a longstanding debate regarding the existence of isolated cutaneous sarcoidosis. Our results shed light on this matter because 39.5% of patients in our study presented with isolated cutaneous sarcoidosis, followed by a multidisciplinary team for a median of 50 months. Some authors support the existence of isolated cutaneous sarcoidosis, although it is rare (Ishak et al., 2015; Ungprasert et al., 2016b; 2017a;; Wanat and Rosenbach, 2014). In a recent study from Latin America, sarcoidosis remained confined to the skin in 14 patients (19%; Torquato et al., 2020). However, other authors defend sarcoidosis as being a mul-

tisystemic disease and maintain that the presence of granuloma in a single organ, such as the skin, is not sufficient to establish a diagnosis (Costabel et al., 2007).

The reported rate of cutaneous involvement in our study (26.3%) in patients with systemic sarcoidosis is in line with what is published (9%–37%; Baughman et al., 2001; Benatar, 1977; Ishak et al., 2015; Ungprasert et al., 2016a, 2016b; Yanardağ et al., 2003). All of our patients were examined by well-trained physicians who conducted clinical and histopathological examinations to give a correct diagnosis and appropriate treatment.

The major limitations of our study are those expected of a retrospective study. Moreover, because we analyzed a closed, all-white population with fast access to the private health care system, some of our findings may not be extrapolated to the general population. Also, we should highlight that the follow-up time was very variable, from 5 to 180 months, which leads to difficulties when analyzing the obtained data. The identification of cases relied on patients contacting the medical system and could underestimate the incidence of mild forms of cutaneous sarcoidosis not requiring patient consultation. Despite isolated instances of cutaneous sarcoidosis being found mostly in women (86.7%), we do not have enough evidence to state that this subtype is more common in this population than the diffuse type.

Conclusion

To our knowledge, this is the first study in Argentina to explore the clinical manifestations of cutaneous sarcoidosis in a closed population. We identified that approximately 39.5% of patients with cutaneous sarcoidosis did not develop systemic disease in the long term. Therefore, we have evidence to believe in the existence of isolated cutaneous sarcoidosis, although this is still a matter of debate in the current literature. Further studies are needed to verify our hypothesis. Due to the highly different clinical features according to ethnicity, we are not able to corroborate that the present results are relevant to other populations; thus, pursuing a similar approach in other areas worldwide will be valuable.

Conflicts of interest

None.

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None.

Study approval

The author(s) confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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