

RETROSPECTIVE STUDY OF ELDERLY ONSET SARCOIDOSIS IN TUNISIAN PATIENTS

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ABSTRACT. Background: Sarcoidosis is a systemic granulomatous disease of unknown etiology. It affects mostly young adults. In the elderly, the presentation of this disease is different, often posing positive diagnosis problems. **Objectives:** We intend to describe the various clinical features and the management of sarcoidosis in elderly patients (age ≥ 65 years) compared to the younger ones. **Methods:** We performed a retrospective, descriptive and comparative study in the Department of Internal Medicine in the University Hospital Hedi Chaker, Sfax, Tunisia, between 1996 and 2016. **Results:** From a series of 80 patients, we found sixteen patients (20%) with sarcoidosis diagnosed after the age of 65 years. A female preponderance (81,25%) was noted. Intrathoracic involvement concerned 13 patients (81,3%). Extrapulmonary signs were also frequent (93,8%). The main extrathoracic manifestations were ganglionic involvement (75%), an alteration of the general health (31,3%), hepatic involvement (31,3%), cutaneous involvement (25%) and ocular involvement (25%). Biological manifestations were hypercalcemia, hypercalciuria, lymphopenia and hypergammaglobulinemia noted in respectively 12,5%, 12,5%, 31,3% and 50% of the cases. Angiotensin-converting enzyme (ACE) level was elevated in 100% of the patients. Lymphadenopathy and cutaneous biopsies were important contributing factors to diagnosis (respectively: 100% and 75% were positive). Oral corticosteroid therapy was required in 50% of cases. Evolution was marked by pulmonary fibrosis in two cases. Satisfactory course of the disease was observed in the other patients. **Conclusion:** Young and elderly subjects had common characteristics of sarcoidosis, except for more co-existing chronic morbidities, no erythema nodosum and more frequent high levels of ACE in the elderly group.

KEYWORDS: Sarcoidosis, Elderly subjects, Uveitis, Interstitial lung disease

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INTRODUCTION

Sarcoidosis is a granulomatous disease of unknown etiology characterized by the infiltration of organs by non-caseating granulomas. Lungs and lymph nodes are commonly involved (1). But any other organ

of the body may be concerned, especially organs exposed to environmental factors such as eyes and skin (2,3). This disease occurs throughout the world, affecting both sexes and all ethnicities (4). It generally affects young subjects (5). In Scandinavian and Japanese studies, a second peak of incidence is reported in women over 50 years old (6). Elderly-onset sarcoidosis (EOS) has a low incidence, the clinical features and the course of the disease can be different, making the diagnosis challenging in some cases (7). But once this particular clinical presentation of the disease is recognized, elderly patients can benefit from suitable treatment and improved quality of life.

In the current report, we presented the main epidemiological, clinical, paraclinical and therapeutic characteristics in a population of EOS from southern Tunisia. In addition, we compared the different features of EOS and younger-onset sarcoidosis (YOS). We report, to our knowledge, the first study of EOS in the Arab population.

MATERIALS AND METHODS

This retrospective study concerned elderly patients (≥ 65 years of age) in whom the diagnosis of sarcoidosis was made after admission to our department of internal medicine in Sfax in southern of Tunisia between 1996 and 2016.

In this study, the cases with compatible clinical and radiological findings and histological non-caseating granulomas were accepted as sarcoidosis, after exclusion of other causes of granulomas such as tuberculosis.

The clinical characteristics, laboratory data at diagnosis and therapy were compared between the elderly and the younger (< 65 years of age) patients.

Statistical analysis was done by SPSS 20 package program. Groups were compared using chi-square and student's test; p values < 0.05 were considered as statistically significant.

RESULTS

GENERAL CHARACTERISTICS

From a series of 80 patients, sixteen patients (20%) with sarcoidosis diagnosed after age 65 years were included (mean age: 71 years, range: 66-79 years). The study population consisted of 13 women (81,25%) and 3 men (18,75%). All our patients were white. There was no family sarcoidosis history. The average time of diagnosis (period from the appearance of the first sign to the date of the diagnosis of sarcoidosis) was 7 months, with a range from 10 days to 2 years. The mean duration of hospitalization was 11 days (range: 1-50 days). Associated metabolic and cardiovascular illnesses were noted in 11 patients (68,8%) (high blood pressure: 7 cases, type 2 diabetes: 6 case, ischemic heart disease: 1 case and atrial fibrillation: 1 case). Only two patients had a smoking history of about 15 and 20 pack year.

DIAGNOSTIC CIRCUMSTANCES

Only one patient among the elderly was asymptomatic at the time of diagnosis. Sarcoidosis was revealed in this case by abdominal ultrasound showing abdominal lymphadenopathy. Pure extra pulmonary manifestations revealed sarcoidosis in ten cases (62,5%).

INVOLVEMENT

We identified three presentations of sarcoidosis in our patients: pure intra-thoracic sarcoidosis (1 case: 6,25%), intra and extra thoracic sarcoidosis (12 cases: 75%) and pure extra thoracic sarcoidosis (3 cases: 18,75%).

Pure intra-thoracic sarcoidosis

The case of pure intra-thoracic sarcoidosis was a 67-year-old woman. She presented a dry cough. The thoracic densitometry in this case showed bilateral hilar lymphadenopathy without parenchymal abnormalities. Mediastinoscopy with biopsy was performed revealing noncaseating granulomas. Biologically, she presented hypergammaglobulinemia. Therapeutic abstention was recommended in this case and the patient was lost of view in less than three months.

Pure extra-thoracic sarcoidosis

Two men and a woman presented pure extrapulmonary sarcoidosis. The woman manifested general signs, anterior uveitis, hepatomegaly with cholestasis, xerostomia, functional renal insufficiency due to hypercalcemia, hypergammaglobulinemia, lymphopenia, and high ACE level. Salivary gland biopsy was positive. She received oral corticosteroid therapy starting at 1 mg/kg/day of prednisone equivalent, with a good outcome. The second patient was transferred from the ear-nose-throat (ENT) department after parotidectomy and cervical adenopathy biopsy with histology showing non-caseating granulomas in both cases. The third patient had inguinal lymphadenopathy. He also manifested xerostomia. Biopsy of the lymph node and of the salivary glands showed non-necrotizing granulomas. Therapeutic abstention was recommended to both of the patients with a good outcome.

Intra and extra-thoracic sarcoidosis

Clinical and Radiologic Signs

Dyspnea and/or cough were observed in eight cases (66,6%). Thoracic densitometry was performed in 10 cases (83,3%), showing isolated mediastinal lymphadenopathy (n=1), mediastinal lymphadenopathy with parenchymal infiltration (n=6), isolated parenchymal infiltration (n=1) and parenchymal fibrosis (n=2). The spirometry was performed on 11 patients. We found a restrictive lung disease (n=2) and obstructive lung disease (n=2). Among the extra-pulmonary manifestations noted in this group, we found general signs (asthenia and/or fever and/or weight loss) in 4 cases (33,3%) and hepatomegaly in 3 cases (25%). Specific dermatological manifestations characterized histologically by the presence of non-caseous granulomas were found in 4 patients (25%): three maculopapular lesions and two purple plaques. There have been no cases of erythema nodosum. Two patients presented inflammatory arthralgia with arthritis in one case. Ocular involvement concerned 3 patients: uveitis in 2 cases (18,8%) (1 case of granulomatous anterior uveitis and 1 case of hyalitis) and orbital pseudotumor in one case, revealed clinically by a swelling in the external border of the wright eye and confirmed by the orbital RMI and the biopsy. Xerostomia was noted in 2 cases (11%), superficial adenopathy in 2 cases (16,6%), and ENT manifestations in 2 patients (12,5%). We have also noted a case of an eyelid nodule. Only one patient presented pulmonary hypertension (PH) secondary to pulmonary fibrosis. It was estimated at 40 mmHg on a transthoracic echocardiogram. No other cardiac damage has been found. In particular, the atrial fibrillation observed in one patient was diagnosed many years ago and was stable under treatment. The tuberculin skin test result was negative in all elderly and young patients.

Biological Abnormalities

Biological data were as follows: accelerated ESR (50%), polyclonal hypergammaglobulinemia (60%), lymphopenia (33,3%), hypercalcemia (9,1%), hypercalciuria (25%) and cholestasis in 2 cases (16,7%).

Serum levels of angiotensin-converting enzyme (ACE) were measured in 6 cases and were always high (100%).

Treatment and Outcome

General corticosteroids were prescribed in seven cases (58,3%) starting at 0.5 mg/kg/d or of prednisone equivalent in 3 cases and 1 mg/kg/d in 4 cases. The indications were symptomatic pulmonary involvement, with evolution to pulmonary fibrosis in two cases and a good outcome in the other cases. Orbital pseudotumor and multisystemic involvement including mainly general signs and hepatic damage were the other indications of systemic corticosteroids with a satisfactory course. Topical corticosteroids were successfully used to treat two patients with anterior uveitis and hyalitis. Antimalarial drugs were used to treat maculopapular lesions in a patient, and non-steroidal anti-inflammatory drugs were prescribed to treat arthritis in one case. Surgical removal of the eyelid nodule was performed in one case. Information on the main demographics, clinical characteristics, laboratory investigations, and treatment of both late-onset and young-onset sarcoidosis groups in this series are described in table 1.

BIOPSIES PERFORMED

Histological confirmation of sarcoidosis was performed in all patients. Twenty nine histological samples were performed for diagnostic purposes in the elderly group. They were positive in 21 cases (72,4%). Four patients had at least 2 positive biopsies (Table 2).

STATISTICAL ANALYSIS

In an analytical study, and comparing the data of the older then the younger patients, it was noted that the elderly group had a higher range of associated metabolic and cardiovascular illnesses (68,8% vs. 29,7%; $p=0,004$). The two groups were statistically similar in terms of pulmonary involvements. Significant difference was found between the two groups for the frequency of the erythema nodosum, which was not noted in the elderly group, and found in 16 young patients ($p=0,032$). The serum levels of ACE were more frequently high in the elderly population (100% vs. 52,5%; $p=0,032$) (Table 1).

DISCUSSION

Sarcoidosis is a ubiquitous disease, characterized by a large variation according to geographical

Table 1. Clinical Features, biological Abnormalities and Treatment

		Elderly patients n=16	Young patients n=64	p
General characteristics (%)	Female gender	81.2	84.4	0.7
	Associated cardiovascular and metabolic illnesses	68.8	29.7	0.04
Pulmonary manifestations (%)	Dyspnea	26.7	28	1
	Cough	43.8	29.7	0.28
iExtra- pulmonary manifestations (%)	General signs	31.2	31.2	1
	Specific Cutaneous manifestations	25	22	0.7
	Erythema nodosum	0	25	0.032
	Uveitis	18.8	17.2	1
	Articular manifestations	12.5	29.7	0.21
	Peripheric lymph nodes	12.5	35.9	0.07
	Hepato-splenic manifestations	43.8	29.7	0.28
	Xerostomia	18.8	18.8	1
	ENT manifestations	12.5	9.4	0.65
	Renal manifestations	6.2	3.1	0.5
	Laboratory Findings (%)	Hypercalcemia	13.3	7.9
Hypercalciuria		20	14	0.63
Accelerated ESR		46.7	62.3	0.27
Hypergammaglobulinemia		61.5	57.7	0.8
Lymphopenia		31.2	35.9	0.72
Elevated angiotensin-converting enzyme levels		100	52.5	0.032
Treatment (%)	Corticosteroids	50	70.3	0.12

Table 2. Tissue Biopsy Sites

Biopsy site	Patients (n)	Result		Profitability (%)
		+	-	
Salivary gland biopsy	12	5	7	41.6
Lymph node biopsy	5	5	0	100
Bronchial biopsy	5	3	2	60
Cutaneous	4	3	1	75
Nasopharyngial biopsy	2	2	0	100
eyelid biopsy	1	1	0	100
Orbital tumor biopsy	1	1	0	100
Médiastinoscopy	1	1	0	100
Laparotomy	1	1	0	100

location, ethnicity, sex and age.

Previous epidemiological data showed that sarcoidosis mainly affects young people, with a peak frequency between 25 and 45 years (5,8). These results are not confirmed by the majority of recent studies that show a peak age at the time of onset of the disease between 30 and 55 years (9,10). In Eu-

rope and Japan, a second peak frequency is described in women over 50 years old. Sarcoidosis is rare in people under 15 years and over 70 years⁶. There is a female predominance of sarcoidosis, with a sex ratio that often varies between 1 and 2 (11–14).

Increased female predominance may be observed in EOS with a sex ratio of 5/1, suggesting the presence of hormonal factors influencing on the activity of sarcoidosis (15,16).

Few studies focus on the features of sarcoidosis in elderly patients. From a series of 293 Turkish patients, eight (2.7%) were 70 years old or older; 7 (87.5%) of them were females. Twenty-three (7.8%) of the cases were aged over 65 years and 19 (83%) of them were women (17). Chevalet et al reviewed 30 elderly patients; they noted a female preponderance in 70% of the cases (18). Standyk et al. found that 7.8% of sarcoidosis patients were aged over 65 years¹⁹. Yanardağ et al found 102 patients (17.7%) aged more than 50 years (19). In the same way, Lerner et al found almost half of their patients older than 50 years of age at the time of initial diagnosis (20).

Table 3. General and Clinical Data in the literature

	Chevalet ¹⁸	Varron ²⁸	Our study
No. of patients	30	30	16
Female gender(%)	70	83.3	81.25
Age (years)	74	70.6 +/- 5.3	71
Intrathoracic signs(%)	57	36.7	81.3
Peripheral lymph nodes (%)	17	16.7	18.8
Arthralgia/arthritis (%)	13	6.7	12.5
Skin involvement (%)	13	36.7	25
Uveitis(%)	3.3%	33.3	18.8
General signs(%)	53	33.3	31.2
Renal involvement (%)	6.6	-	6.2

In our study, the frequency of sarcoidosis in elderly patients (≥ 65 years) was of the order of 20% with a female preponderance in 81,25%.

Familial sarcoidosis was found in some series (17,21,22). We have not found any familial history in our study.

Occupation and environmental exposure have been reported to be potential triggers of sarcoidosis in genetically susceptible patients (3,23). We didn't identify any occupational exposure in our patients.

Coexisting comorbidities are more common in EOS group, making the diagnosis and the treatment more difficult in some cases (15,24). In our series, 68,8% of the old patients presented associated comorbidities vs. 29,7% of the young patients ($p=0,004$).

An alteration of general health usually dominates the clinical features in the elderly population, with the possibility of prolonged unexplained fever leading to the diagnosis of tuberculosis or malignancies (15,18,25). In our study, general signs were noted in 31,2% of the cases in the EOS group.

Pulmonary manifestations remain the predominant signs, as with the younger group. They range from 57 to 82% of cases (18,19,26). They were observed in 81,3% in our study. Symptoms of cough and dyspnea, are the predominant findings (56,25% in our series).

The prevalence and distribution of extrapulmonary involvement varies among the series.

In the study of Yanardag et al (27), extrapulmonary involvement was more commonly observed in older patients, while Löfgren syndrome, erythema nodosum, and uveitis were less frequent. Erythema nodosum was also less frequent in the EOS groups

in other series, affecting no patient in the study of Varron et al (28) and only one patient in the study of Chevalet et al (18).

In our series, erythema nodosum was not noted in the EOS group, while it was found in 16 young patients ($p=0,032$).

Biopsies are essential to the diagnosis of sarcoidosis. Warron et al (28) found that proportion of patients with accessory salivary glands and skin biopsies was more often contributory

to the diagnosis in elderly patients. Histological confirmation was performed in all our patients. Lymph node biopsy, nasopharyngeal, orbital tumor and eyelid biopsies were the most profitable (100%). However, salivary glands and bronchial biopsy were the least profitable, as they are often performed blind. Nevertheless, their minimally invasive nature should encourage the clinicians to perform them whenever possible to support the diagnosis.

Corticosteroids are the cornerstone of the treatment and allow a disease remission (29). Half of our patients have received general corticosteroid vs 70,3% in the younger group. This result is expected on the one hand because sarcoidosis can regress spontaneously, and on the other hand, because it is always recommended to spare the elderly, when possible, from heavy therapy and all its side effects. A good course was observed in most of our patients. Two cases have developed pulmonary fibrosis.

CONCLUSION

Despite her affinity to young people, sarcoidosis may also concern elderly patients. We reported a series of sixteen sarcoidosis patients older than 65 years. According to our study, 81,25% of patients were women. We found some distinct characteristics in elderly people compared with younger subjects: more coexisting chronic morbidities, no erythema nodosum and more frequent high levels of ACE in the EOS group. The recognition of particular signs of sarcoidosis in elderly patients helps to avoid delays in the diagnosis of this disease, and thus to benefit from treatment and improved quality of life.

CONFLICTS OF INTEREST: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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