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Management of Mediastino-Pulmonary Sarcoidosis a Prospective Study of 40 Cases

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Abbreviations: PPE: Plasma Protein Electrophoresis; SBB: Staged Bronchial Biopsies; ACE: Angiotensin-Converting Enzyme; EBUS: Endobronchial Ultrasonography; TBNA: Transbronchial Needle Aspiration; HRCT: High-Resolution Computed Tomography; EUS: Esophageal Ultrasonography; FNA: Fine Needle Aspiration; BAL: Bronchoalveolar Lavage

Introduction

Sarcoidosis or Besnier-Boeck-schaumann is a systemic granulomatosis that can affect almost all organs, mediastino-pulmonary involvement the most common. Diagnosis is difficult, given the clinical and radiological polymorphism. Corticosteroid therapy remains the cornerstone of treatment, but it is not always indicated. The aim of this study was to describe the epidemiological, clinical, paraclinical, therapeutic and evolutionary characteristics of patients with mediastino-pulmonary sarcoidosis.

Materials and Methods

Retrospective study of a series of 40 patients spread over a period of 7 years from January 2016 to March 2023 conducted at the Pneumology Department of Ibn Sina Hospital in Rabat.

Results

The mean age was 49.9±10.2, with extremes ranging from 27 to 80 years. There was a clear female predominance, with 30 patients, or 75% of cases. The sex ratio was 0.33 1H/3F, and 47.5% of patients had a history of diabetes (6 or 12.5%), arterial hypertension (4 or 10%), cholecystectomy (5 or 12.5%), dyslipidemia (3 or 7.5%), pulmonary tuberculosis (2 patients) and depression (1 patient). The average hospital stay was 22 days. Dyspnea and intermittent dry cough were the most common respiratory symptoms found in 37 patients. Isolated dyspnea was found in 6 patients (15% of cases), while isolated cough was found in only 3 patients (7.5% of cases). Chest pain was found in 5 patients (12.5% of cases), and hemoptysis was reported by 2 patients (5% of cases). On the other hand, 23 patients with extra-respiratory manifestations were grouped together in (Table 1). General signs were marked by asthenia (52.5%) and anorexia (15%).

As regards the biological work-up, the blood count showed lymphopenia in 9 patients (22.5% of cases). Hypercalciuria was noted in 4 patients (10% of cases), including 1 case of hypercalciuria associated with hypercalcemia. Plasma protein electrophoresis (PPE) was carried out in 6 patients, revealing 4 cases of polyclonal hypergammaglobulinemia and 2 cases of elevated beta 2 globulin levels. Renal function tests were disturbed in 4 patients, i.e. 10% of cases, and liver function tests were disturbed in 5 patients, i.e. 12.5% of cases. For angiotensin-converting enzyme (ACE): Of 15 patients, 9 had elevated ACE levels, i.e. 60% of cases. Chest X-rays performed on all patients showed radiological stage 1 in 17.5%, stage 2 in 65%, stage 3 in 5% and stage 4 in 12.5% of cases. High-resolution thoracic CT scans were performed on 33 patients, and the results are shown in (Table 2).

In addition, 2 patients in our series underwent PET scan showing active hypermetabolic abnormalities in the lymph nodes, predominantly mediastino-hilar, and in the bilateral lungs, possibly related to sarcoidosis. With absence of focus or hypermetabolic abnormalities suggesting myocardial involvement. The histological diagnostic methods used included bronchial fibroscopy, which was performed in 31 patients. Normal

bronchial fibroscopy was found in 9 patients (29%), while 15 had an inflammatory appearance of the bronchial mucosa, in 12 cases presence of thickened spurs in 12, narrowed orifices in 4 and whitish granulations in only one. Only 17 patients underwent bronchoalveolar lavage (BAL), the cytological profile of which was lymphocytic and macrophagic in 15 cases (48.3%) and 2 cases (6%) respectively. Staged bronchial biopsies (SBB) were taken in 31 patients, revealing histological lesions suggestive of BBS in 12. The diagnostic yield of it was therefore 38.7%.

Table 1: Summary of the extra-respiratory manifestations found in our series.

Nature of Damage	Events Found	Frequency of Damage in (%)
Ocular	Painful red eye and/or decreased visual acuity in 6 patients. Xerophthalmia was found in 3 patients.	22.5
Cutaneous	1 case of nodular lesions in both upper limbs; 2 cases of erythema nodosum; 3 cases of lupus pernio; 1 case of sarcoid in both legs.	15
Peripheral lymph node	1 case of right axillary lymphadenopathy1 case of left axillary lymphadenopathy 2 cases of bilateral inguinal lymphadenopathy 2 cases of bilateral cervical lymphadenopathy	12.5
Cardiac	No specific cardiac symptoms were found in our series.	5
Neurosarcoidosis	-	
Hepatic/splenic	1 case of splenomegaly; 1 case of painless homogeneous hepatomegaly without associated jaundice; 2 cases of hepatosplenomegaly; of which: Þ1 case is associated with portal hypertension	10
Renal	Found in 2 patients or 5% of cases, including 1 case of end-stage chronic renal failure	5
ENT	1 case of nasal involvement (nasal obstruction with posterior discharge); 1 case of peripheral facial paralysis (suspected Heerfordt syndrome without any confirmation); 1 case of modification of the landmarks of the nasal bones (associated with lupus pernio). 4 patients reported dry mouth.	17.5
Articular	1 case of diffuse polyarthralgia as part of Löfgren syndrome; 3 cases of diffuse polyarthralgia; 1 case of bilateral knee pain; 1 case of arthralgia with an inflammatory appearance of the large joints, particularly the wrists.	15
Sarcoidosis complicated by pulmonary hypertension	2 cases of pulmonary arterial hypertension	6

Table 2: Frequency of radiological abnormalities in patients in our series.

Radiological Abnormality	Number of Cases
Hilar/mediastinal ADP	8
rmicronodular infiltrates of perilymphatic distribution	16
Centrilobular parenchymal micronodules	5
Frosted glass appearance	7
Honeycomb appearance	4
Condensation syndrome	4
Pulmonary nodule	7

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Accessory salivary gland biopsy was performed in 28 patients and contributed to the histological diagnosis of 7 patients. Its diagnostic yield was therefore 25%. Bronchial echo-endoscopy with mediastinal lymph node needle cytoaspiration (EBUS-TBNA) was performed in just 1 patient. This brought Lymphoid tissue but without granuloma. Mediastinoscopy was performed in 10 patients. The diagnostic yield was 100%. Biopsies performed at other histological sites also contributed to the diagnosis of the patients in our series, namely: 2 skin biopsies, 2 peripheral lymph node biopsies and 2 abdominal adenopathy biopsies, and 1 renal biopsy in a patient with chronic interstitial nephritis associated with proteinuria, with the presence of Schaumann bodies on pathology, leading to end-stage chronic renal failure. Plethysmography was performed in 30 of our patients; it was normal in 16 patients; 12 patients had a restrictive ventilatory disorder and 2 patients had an obstructive ventilatory disorder. Decreased DLCO was observed in 11 of the 30 of those who benefited from the examination or 36.66% of cases.

Therapeutic abstention, combined with close monitoring, was indicated in 5 patients; oral corticosteroid therapy was recommended in 32 patients, and subsequently in 2 radiological type I patients, following unfavorable disease progression. (34 patients in total) The initial dose prescribed was 0.5-1mg/kg/day, tapering off progressively if the disease progressed favorably. Azathioprine-based immunosuppressants were introduced in 1 patient, who developed several adverse reactions to OC. Hydroxychloroquine (Plaquenil*) combined with OC was indicated in 1 patient for cutaneous involvement. Cyclophosphamide (Endoxan*) combined with MTX was indicated in 1 patient for sarcoidosis refractory to corticosteroid treatment. DLO was indicated in 3 patients at the stage of chronic respiratory failure.

In addition, all patients benefited from adjuvant measures, including oral potassium supplementation, a salt-free, low-carbohydrate diet and education on healthy dietary habits. Non-treatment evolution was favourable in 3 patients with radiological type I, and unfavourable following radiological aggrevation in 2 patients with an initial decision to abstain from treatment. Treatment was favourable in 26 patients, marked by regression of clinical and/or radiological and/or functional symptoms. However, worsening was observed in 4 patients, with one case of sarcoidosis refractory to corticosteroid treatment and cyclophosphamide.

Discussion

Sarcoidosis is a systemic inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas in various organs. Mediastino-pulmonary involvement remains the most common. Its incidence and prevalence have always been observed to be highest in Nordic countries and among African Americans [1]. This statement is supported by contemporary estimates provided by recent studies in Sweden [2] and the USA [3,4]. Several recent studies in other populations report a prevalence of sarcoidosis in excess of 0.05%, indicating that the disease may not be as rare as previously thought [1]. At present, we unfortunately have no registry that assesses the incidence and prevalence of sarcoidosis in Morocco. The repeated assertion in the literature that peak onset of sarcoidosis occurs between the ages of 20 and 45 years is not supported by the majority of recent studies, with onset ages closer to 30-55 years. [1] In our study, the mean age was 49.9±10.2 years, in line with the literature.

There was a clear female predominance in our series, with a percentage of 75% compared with 25% of incident male cases. According to Judson et al. [5] the diagnosis of BBS was made in around 50% of subjects 3 months after the onset of symptoms, or after a first visit to the doctor for a symptom of sarcoidosis. 25% of subjects were diagnosed only after 6 months, and around 10% within 2 years. In a large retrospective study of 1607 patients, Silzbach et al. [6] found that sarcoidosis was most often initially recognized on chest X-rays, obtained either routinely or following respiratory symptoms (present in 1/3 of cases). Cadelis et al. [7] estimated that 17.3% of cases were discovered incidentally. In our series, 2.5% of cases were discovered incidentally.

The diagnosis is made on the basis of a clinico-radiological picture that is most often suggestive, the demonstration of granulomas without caseous necrosis, and the exclusion of other causes of granulomatosis. Its clinical presentation is highly polymorphic. The lungs and mediastinal lymph nodes are the organs most frequently affected in patients with sarcoidosis [8,9]. According to Judson et al. [5] the most common initial symptoms of the disease were respiratory. In fact, more than half the individuals had respiratory symptoms, and around half of them only had respiratory symptoms [5]. Among these, persistent cough, dyspnea or chest pain, whether or not associated with mediastinal adenopathy, were the most frequently encountered [10]. Physical examination of the lungs is usually normal [10]. The results of our study are in line with the literature. General signs such as fatigue may be prominent or even isolated.

According to Valeyre D et al. [11] this is estimated to affect almost 70% of patients. Weight loss may accompany Löfgren's syndrome, elderly sarcoidosis or multivisceral disease. Fever is present in Löfgren's syndrome, Heerfordt's syndrome, and liver or kidney involvement. However, outside these situations, the presence of these general signs should prompt a search for a differential diagnosis. In our study, asthenia was observed in 21 patients (52.5% of cases). Weight loss was observed in 6 patients, or 15% of cases. Skin involvement occurs in around 32% of patients [9], Erythema nodosum is the most frequent acute manifestation, affecting the subcutaneous fat [12]. This is an aspecific lesion: biopsy is useless, as it shows no granuloma. The association of erythema nodosum with mediastinal adenopathy, arthralgia and fever constitutes Löfgren's syndrome. Facial lesions in chronic

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sarcoidosis may be due to lupus pernio, whose presence should prompt a search for ENT involvement. Articular involvement is observed in around 0.5 to 7% of patients with sarcoidosis [8,9].

In our series, inflammatory arthralgias were observed in 15% of patients. Ocular involvement is reported in over 11% of patients [8]. This may be anterior, intermediate or posterior uveitis, chorio-retinitis, lacrimal involvement, optic neuritis or conjunctival nodules. Anterior uveitis may present as acute or chronic iridocyclitis, depending on its onset and course [13,14]. On the other hand, posterior uveitis, the most severe form, can cause papilledema, retinal hemorrhage and chorioretinitis, and may be associated with anterior uveitis. It should be systematically investigated, as it can threaten visual prognosis. Cardiac sarcoidosis is noted in at least 2.3-5% of patients with sarcoidosis [7,8], while occult myocardial involvement is probably much higher (>20%) [15]. It may occur in the absence of pulmonary or systemic involvement. Given the potential mortality associated with cardiac sarcoidosis, early diagnosis and treatment are crucial. Currently, cardiac MRI with gadolinium injection is the best test for determining the presence and extent of cardiac involvement [16]. 18FDG PET scans can be useful in determining the extent of granulomatous inflammation in cardiac involvement; Neurological involvement or neurosarcoidosis occurs in 4.6-9% of patients with sarcoidosis [8,9]. It can affect both the central and peripheral nervous systems. All patients with sarcoidosis should have a conventional chest X-ray. It shows an abnormality in over 90% of cases and is often the first examination suggestive of the diagnosis [17-19]. This is essential for both diagnosis and follow-up of the disease.

In our series, 17.5% of patients had stage I, 17.5% had stage II, 65% had stage III (5%) and 12.5% had stage IV. The results of our study are in line with the literature. As part of the diagnostic, high-resolution computed tomography (CT) of the thorax has proved to be of major benefit. It is more sensitive than chest radiography. According to Lynch JP et al. [20] and Nunes H et al. [21], parenchymal involvement most often corresponds to a micronodular and reticulonodular pulmonary infiltrate, bilateral and symmetrical, with a predominance in the upper and middle parts of the lung fields. Lesions suggestive of sarcoidosis are reticulonodular infiltrates of perilymphatic.

Distribution: around bronchovascular bundles ("string of pearls" sign) [22], in the perilobular, subpleural and scissural areas. The "beaded scissure" appearance is almost pathognomonic [23]. These may coalesce into irregular nodules surrounded by micronodules (galaxy sign), the presence of symmetrical, bilateral hilolobar and mediastinal adenopathies that are usually non-compressive and non-necrotic [24] and may calcify in 20% of cases during prolonged forms [25]. Ground-glass is rarely the main radiological lesion in sarcoidosis. Histologically, this lesion may correspond to the confluence of multiple granulomas or to fibrosis lesions. In most cases, cavitary lesions are the consequence of ischemic necrosis [26].

Pulmonary sarcoidosis may be complicated by fibrosis lesions, which predominate in the upper, middle and central perihilar territories [27]. Bronchoscopy is an important and widely used diagnostic option, enabling bronchial biopsies, transbronchial biopsies and bronchoalveolar lavage (BAL) to be taken. This may reveal a macroscopically normal appearance, or a "fundus-like" mucosa with thickened spurs, whitish granulations of the proximal bronchi, and very rarely stenoses [28]. A typical feature of the endobronchial localization of granulomas is a "cobblestone" appearance [29]. An abnormal macroscopic appearance is noted in 22 patients in our series, i.e. 71% of cases. Bronchoalveolar lavage (BAL) analysis: generally, indicates CD4+ LT lymphocytic alveolitis in patients with active disease, with increased CD4/CD8 ratio (> 3.5). Lymphocyte-predominant fluid was found in 15 patients in our series, or 48.38% of cases. BAL can help confirm a diagnosis in patients with atypical radiological findings and clinical features compatible with sarcoidosis [30], particularly in type 0 patients in whom alveolitis may be present. Bronchoscopy is a simple and safe method of histological confirmation of a diagnosis. Even without visual abnormalities, there is a 20% chance of finding non-necrotizing granulomas in a biopsy sample.

According to the results of a study by Shorr A et al. [31], the yield of BBE was 61.8%. In a review of 85 patients, Armstrong et al. [32] demonstrated that BBEs enabled histological confirmation in 57% of cases. The diagnostic yield of BBE in our study was 38.7%. Transbronchial biopsies, guided by thoracic CT, allow samples of parenchyma to be taken. According to Boer de S et al. [33], they are more effective in cases of extensive parenchymal involvement. As accessory salivary gland biopsy is an accessible biopsy site, it is systematically performed after bronchial fibroscopy. According to the results of a study by Michon-Pasturel et al. [34], the overall yield of BGSA was 38.5%, with total safety, whereas Cadelis et al. [7] found a yield of only 9.5%. In the series by Chevalet et al. [35] studying sarcoidosis in elderly subjects (>70 years), the results were positive in 70.6% of cases, and were more informative than bronchial biopsies. Sensitivity was better than in most published series involving younger subjects. Bronchial echo-endoscopy with mediastinal lymph node needle aspiration (EBUS-TBNA) (EBUS: endobronchial ultrasonography, TBNA: transbronchial needle aspiration) is recognized as a first-line diagnostic procedure that should be added to conventional bronchoscopy in cases of suspected sarcoidosis with mediastinal and hilar lymph node involvement [36].

In a study of 304 patients by Von Bartheld et al. [37] (2009-2011), its diagnostic yield was 66%. This technique was performed on only 1 patient in our series. It yielded lymphoid tissue but no granuloma. Esophageal echo-endoscopy for fine-needle aspiration (EUS-FNA) (EUS: esophageal ultrasonography; FNA: fine needle aspiration) is also proving highly promising. In a study by Von Bartheld et al. [37], its diagnostic yield was 88%. Mediastinoscopy is a highly important diagnostic tool, with high sensitivity and specificity for confirming the diagnosis of

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sarcoidosis. It remains the "gold standard" for the diagnosis of mediastino-pulmonary sarcoidosis according to the ATS/ERS/WASOG [17], but the technique is invasive and costly. It should be used as a last resort in the event of non-contributory biopsies using other, less invasive histological diagnostic methods.

Pulmonary function tests are extremely important for estimating the severity of lung damage, and for monitoring both the natural course of the disease and the response to treatment. In pulmonary sarcoidosis, there are three types of ventilatory disorders (restrictive, obstructive and mixed syndromes), with or without impaired gas exchange [25]. Most often, these are restrictive syndromes (defined as total lung capacity below 80% of theoretical) with impaired alveolar-capillary diffusion capacity measured by DLCO, or mixed syndromes. It is not uncommon to find an isolated obstructive syndrome (Tiffeneau<70%), the mechanisms of which are complex and often interlinked in the same patient in cases of significant bronchial distortion and stenosis due to pulmonary fibrosis [38], or proximal endobronchial stenosis [17], or bronchial compression [10].

In the event of dyspnea, the major challenge is to distinguish between respiratory limitation on exercise and a cardiovascular component, or even a mechanism of muscular origin (respiratory muscle damage in the context of the disease), hence the importance of carrying out an exercise test. The 6-minute walk test (TM6) is a useful tool for monitoring functional evolution by showing a reduction in the distance covered and identifying the nadir of desaturation during exercise; it can thus reveal respiratory insufficiency or pulmonary hypertension [10]. Blood gases are generally normal at rest [10].

Treatment aims to control or slow down the disease's negative impact on the various target organs, and thus improve quality of life. There is no cure for sarcoidosis. Prednisone is the glucocorticoid most commonly used in the treatment of BBS, and the induction dose is generally 0.5mg/kg/d of prednisone. Higher doses, 1mg/kg/d of prednisone, for 1 to 3 months are recommended in severe manifestations affecting the CNS or optic nerve requiring an urgent effect, as the probability of response is better with such a dosage. The maintenance phase recommended to reduce OC to a maintenance dose of 5 to 10mg/day for a total of one year of treatment before discontinuation [39]. The rationale for duration is empirical and based on observational data suggesting that relapses are frequent in patients treated for less than 1 year [38]. In asymptomatic type I sarcoidosis, Löfgren's syndrome and asymptomatic patients with normal EFR, the recommended therapeutic attitude is abstention. treatment is recommended in type II-III symptomatic and/or with abnormal EFR (CPT<60%-DLCO<65%) And/or progression, bronchial compression or vascular compression by adenomatous, the presence of obstructive ventilatory disorder or endobronchial stenosis and Type IV with sign of persistent activity and controversial in Type II and III asymptomatic with functional abnormalities. Methotrexate (MTX) is the immunosuppressive agent most commonly used in sarcoidosis [17]. with an initial dose of 5 to 15mg per week is recommended in combination with folic acid supplementation [18]. As a complete response to the addition of MTX can take up to 6 months to achieve, GCs are maintained until they can be reduced below 7.5mg/d or withdrawn. [19] Other immunosuppressants can be used as an alternative to, or in combination with, MTX, although the evidence supporting their efficacy is less strong. These include azathioprine, leflunomide and mycophenolate mofetil.

Follow-up procedures and duration for patients with sarcoidosis are not standardized. In general: -clinical examination and pulmonary function test every 3 months, chest CT scan, ECG and blood tests including creatinine and calcium measurements every 6 months for up to 1 year. -Respiratory function tests: the parameter most frequently affected in pulmonary sarcoidosis is DLCO (which decreases) due to parenchymal damage or the development of PH. However, the most commonly used functional test is FVC, and its association with DLCO may be more accurate in assessing disease progression. An increase in FVC > 10% or DLCO > 15% is considered an adequate response to treatment [40]. Regarding imaging: compared with chest radiography, high-resolution computed tomography (HRCT) is more sensitive and specific for characterizing lesion patterns and the extent of lung involvement.

A relapse rate estimated at 36.6% of cases was found in the study by Rizzato et al. [29]. These relapses generally occurred within the first year following cessation of corticosteroid treatment. In our series, we estimate a relapse rate of 7.5%. The prognosis is mainly linked to the occurrence of complications: such as chronic respiratory failure, pulmonary hypertension, persistent incapacitating symptoms and impaired quality of life; The main complications found in our study are 8 patients presented complications related to sarcoidosis (20%) of cases. Pulmonary hypertension was found in 2 patients in our series, (5%) of cases. Chronic respiratory failure occurred in 3 patients in our series, 7.5%, with a high mortality rate observed in cases of pulmonary hypertension and chronic pulmonary heart disease [17]. Infectious complications are frequent and may be linked either to a defect in mucociliary purification related to architectural distortions of the pulmonary parenchyma, or to iatrogenic immunodepression [41]. It involved 4 patients in our series, or 10% of cases. According to Denning DW et al [42], aspergilla transplantation complicates between 3% and 12% of pulmonary sarcoidosis cases, while Hours et al. [43] estimate a rate of 2%. In our series, we estimate a rate of 5%. Effective treatment with azole antifungals requires at least six months' therapy, but a large percentage of patients fail to achieve a complete response [44]. Certain extra-pulmonary localizations can be functionally life-threatening as (ophthalmological, renal, hepatic) or even life-threatening (neurological and cardiac) [10]. In our series, 1 case

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of end-stage chronic renal failure was identified.

Conclusion

Sarcoidosis is a systemic disease of unknown cause characterized by the presence of granulomas in the affected organs. The diagnosis of this condition is confirmed when a suggestive clinico-radiological presentation is supported by histological evidence, and by the exclusion of possible alternative diagnoses. However, further research is still necessary to better understand the pathophysiology of this disease, and to optimize the therapeutic management of patients.

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