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(CASE REPORT)

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Beyond the lungs: Multisystemic sarcoidosis as a rare infertility cause

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Abstract

Sarcoidosis is a systemic granulomatous disease of unknown origin, characterized by non- necrotizing granulomas that can affect various organs, notably the lungs, lymph nodes, skin, and eyes. Diagnosis relies on clinical presentation, histological evidence, and exclusion of other granulomatous diseases. This case report discusses a 49-year-old Moroccan man who was initially treated for pulmonary tuberculosis based on clinical, radiological, and histological findings. Despite treatment, his condition worsened, prompting further investigation. Symptoms included dyspnea, xerostomia, xerophthalmia, polyarthralgia, paresthesia, and recurrent oral ulcers, along with significant weight loss and infertility. Clinical examination revealed a range of symptoms, including neurological deficits and elevated angiotensin-converting enzyme (ACE) levels. Imaging studies showed diffuse interstitial lung involvement. A bronchial biopsy was suggestive of sarcoidosis, supporting the diagnosis. The patient also exhibited ocular, neurological, and urogenital manifestations, including azoospermia. This case highlights the complexity of diagnosing sarcoidosis, particularly when symptoms mimic other conditions, and underscores the importance of considering sarcoidosis in differential diagnoses to avoid misdiagnosis and ensure timely treatment.

Keywords: Sarcoidosis; Granulomas; Tuberculosis; Diagnosis; Ocular; Neurological; Azoospermia

1. Introduction

Sarcoidosis is a systemic granulomatous disease of unknown origin, resulting from a complex interaction between infectious or environmental triggers and genetic factors, leading to an aberrant immune response [1].

The diagnosis of sarcoidosis is not standardized, but it is based on three major criteria: a compatible clinical presentation, the presence of non-necrotizing granulomatous inflammation in one or more tissue samples, and the exclusion of alternative causes of granulomatous disease [2].

The disease especially affects the lymph nodes, lungs, skin and eyes. It is an infrequent but not rare disease, especially in northern Europe, the United States and India [3]. People with darker skin, including a portion of Arab populations, are more frequently and severely affected (African Americans, for instance, have four times the risk of developing the disease) [4]. Sarcoidosis is estimated to impact 2 to 160 per 100,000 people globally [5].

Sarcoidosis affects more women and is diagnosed between the ages of 30 and 50. The evolution of the disease is variable, as is the indication for systemic treatment, based on the use of corticosteroids as first-line option, the use of immunosuppressants as second-line therapy, and anti-TNF agents in severe and/or refractory cases [3].

A thorough understanding of the disease is essential due to its numerous complications and the potential for confusion with tuberculosis, especially in Morocco, where tuberculosis is prevalent [4].

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2. Case report

We report the case of a 49-year-old Moroccan man, a non-smoker who is married but childless. At age 47, he was treated for pulmonary tuberculosis based on clinical (dyspnea and overall health decline), radiological (mediastinal and hilar lymphadenopathy with bilateral micronodular lung findings on chest CT), and histological (chronic granulomatous tuberculoid bronchial inflammation without necrosis from a bronchial biopsy) evidence. Despite this treatment, there was no clinical or radiological improvement, leading to his referral to our pulmonology department due to worsening symptoms and the need for specialized care.

His symptoms began at age 47 with stage II dyspnea, which has progressed to stage IV over the past four months according to Sadoul's classification. He also experienced a dry cough, but no hemoptysis or chest pain. Extrathoracic symptoms started 1 year and 8 months ago and include xerostomia, xerophthalmia, polyarthralgia affecting large joints, paresthesia in all four limbs, torticollis, headaches, and decreased vision in the left eye. He also reported recurrent oral ulcers (more than three times per year) but no genital ulcers for the past 14 years. These symptoms were accompanied by fever and significant weight loss of 30 kg over two years. Additionally, the patient had been diagnosed with infertility at age 37, confirmed by a spermogram showing total azoospermia (with a normal testicular Doppler ultrasound conducted in 2013).

Upon admission, the physical examination revealed that the patient was alert with a Glasgow Coma Scale score of 15/15, a WHO performance status of 1, a respiratory rate of 22 breaths per minute, an SaO2 of 97% on room air, a heart rate of 76 beats per minute, and a blood pressure of 100/60 mmHg. The pleuro-pulmonary examination was normal. Neurological examination showed a tetrapyramidal syndrome with brisk, widespread deep tendon reflexes in all four limbs, a hint of the Babinski sign, but intact sensation throughout.

Laboratory tests revealed an elevated angiotensin-converting enzyme (ACE) level of 131 U/L (normal range 20–70 U/L), while other tests such as complete blood count, liver and kidney function tests were normal. C-reactive protein and sedimentation rate were elevated at 39 g/dL and 60 mm/h, respectively, indicating chronic inflammation. Serum protein electrophoresis indicated an inflammatory syndrome with a strong immune response. Phosphocalcium balance in blood and urine, total protein, and 24-hour proteinuria levels were normal. Tests for HIV, hepatitis B, hepatitis C, hepatitis E, syphilis (VDRL, TPHA), QuantiFERON-TB Gold, antinuclear antibodies, and various autoimmune markers were negative. Lipid profile, thyroid function, coagulation, and glucose levels were all within normal limits. Gene expert and acid-fast bacilli (BK) tests in sputum were negative.

2.1. lung involvement

Radiologically, a frontal chest X-ray revealed an interstitial syndrome similar to the previous year's findings (fig.1).

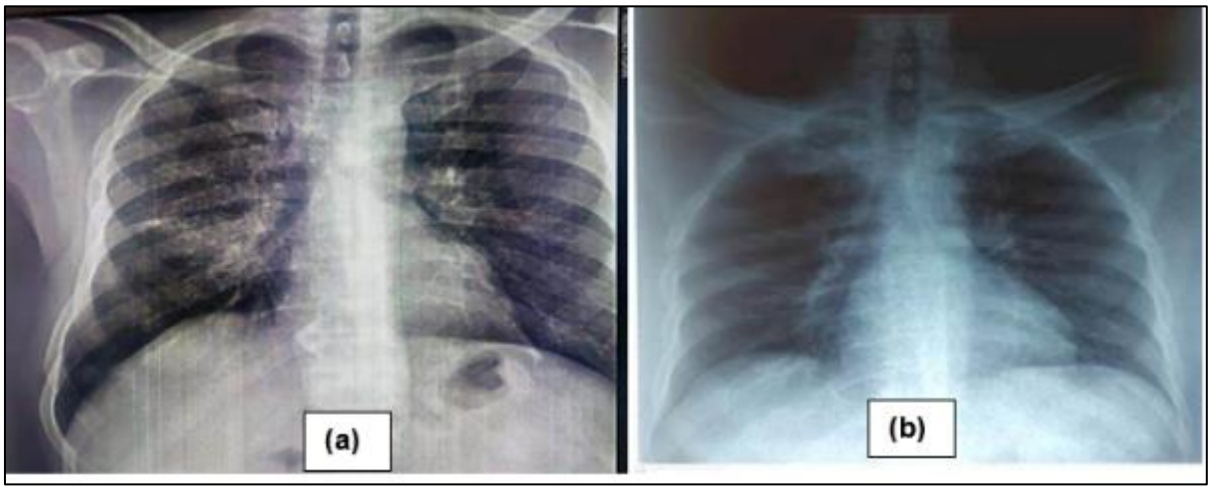

Figure 1 A comparison between a chest X-ray taken upon his admission to the service (b) and a chest X-ray taken two years ago (a) revealed a similar involvement consistent with an interstitial syndrome

Upon admission, a chest CT scan revealed diffuse interstitial involvement consistent with Stage III sarcoidosis. The imaging showed micronodules scattered throughout the lung parenchyma, subpleural regions, and scissures, diffusely distributed across both lung fields. These micronodules displayed a peribronchovascular and perilymphatic

distribution extending from the hilum to the periphery. Ground- glass opacities were observed in the middle lobe and both lower lobes. Additionally, there was diffuse thickening of septal and non-septal lines, bilateral thickening of scissures and associated "pearly" scissures, and thickening of peribronchovascular structures. A few centrolobular and para-septal emphysematous bullae were also present.(fig.2-6).

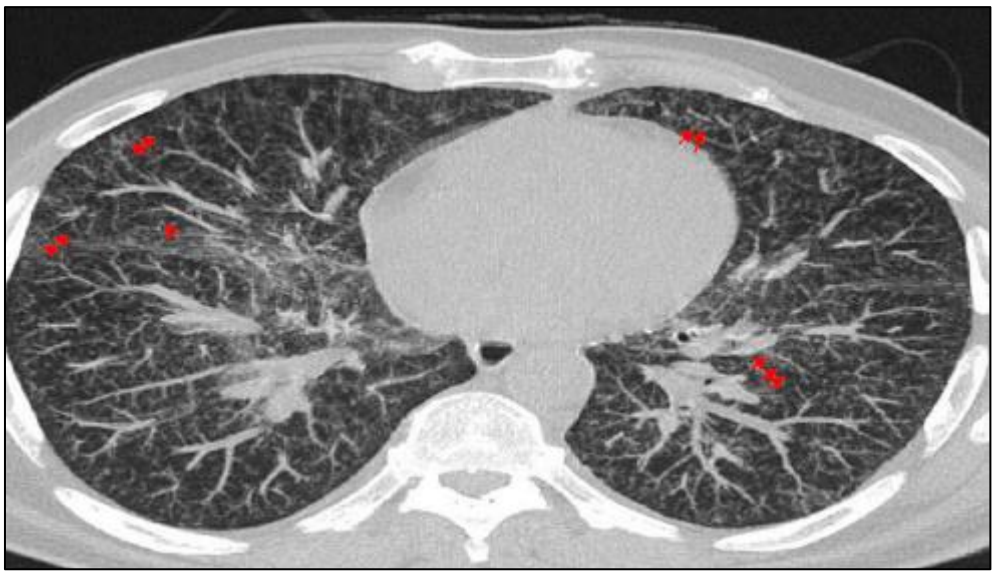

Figure 2 Axial section of thoracic CT scan showing micronodules

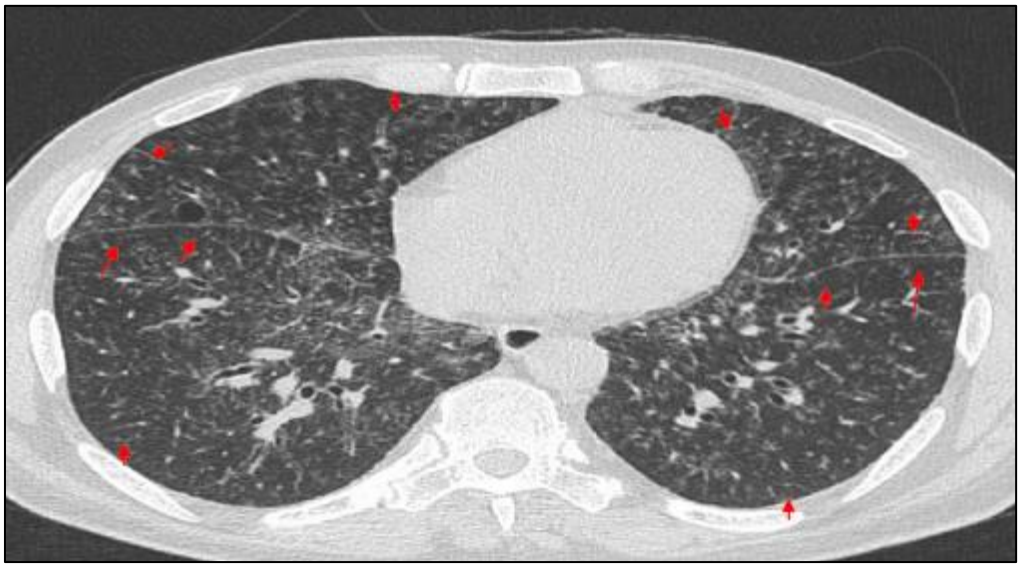

Figure 3 Axial section of thoracic CT scan showing septal, non septal and scissural thickening

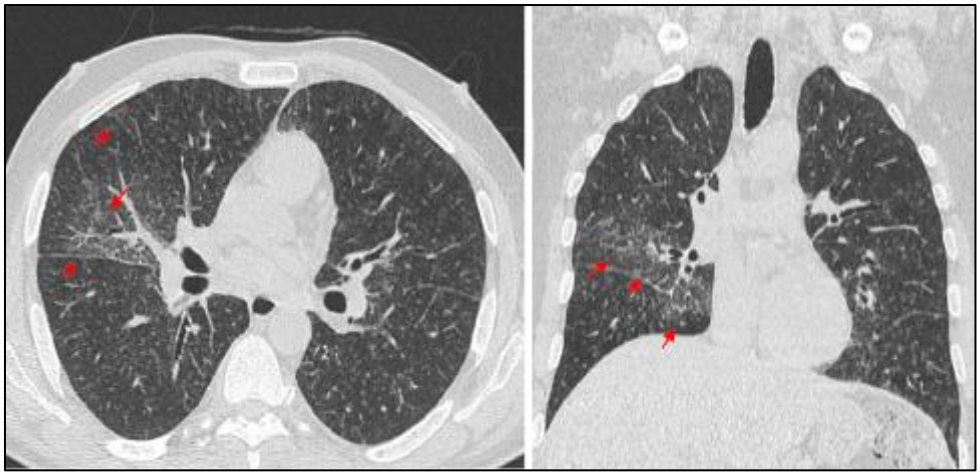

Figure 4 Axial and frontal sections showing ground glass foci

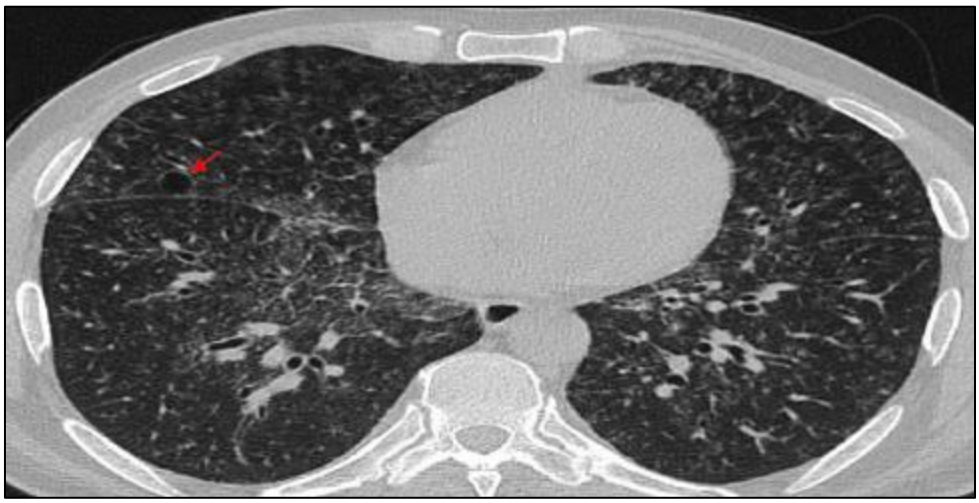

Figure 5 Axial section showing an emphysema bulla

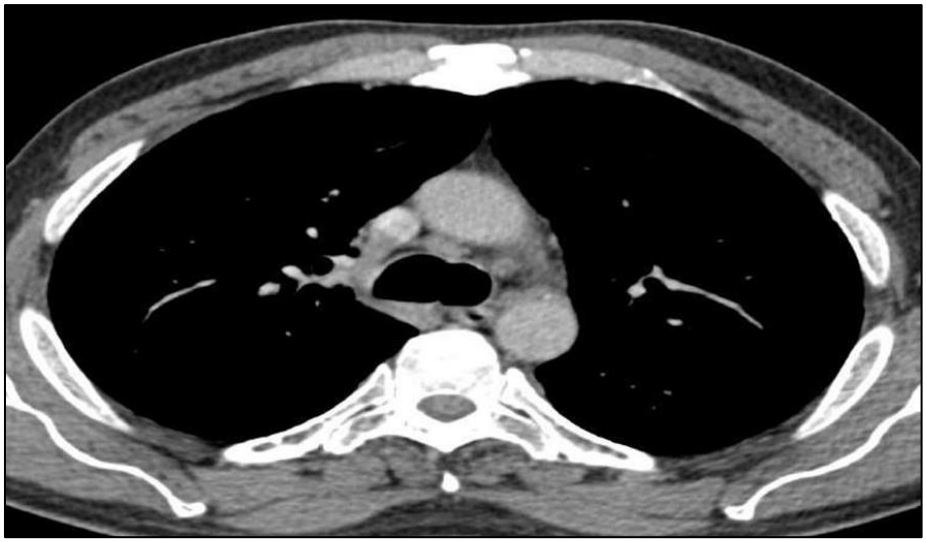

Figure 6 Mediastinal window showing mediastinal lymph nodes visible at inferior mediastinal level, precarinal, barety lodge of subcentrimetric size

A chest CT scan conducted 3 months before admission to our service showed similar radiographic findings, while a CT scan from 2 years earlier had revealed bilateral mediastinal and hilar lymphadenopathy along with bilateral intraparenchymal micronodular images.

A second bronchoscopy was performed, revealing diffuse inflammation of the bronchial tree without visible thickening or budding. The staged bronchial biopsy with histopathological study indicated tuberculoid granulomatous lesions of the bronchial mucosa with some foci of fibrinoid necrosis. (fig.7) The bronchoalveolar lavage showed polymorphic inflammatory cytology with a predominance of macrophages and no signs of malignancy. The GeneXpert test on bronchial aspirations was negative.

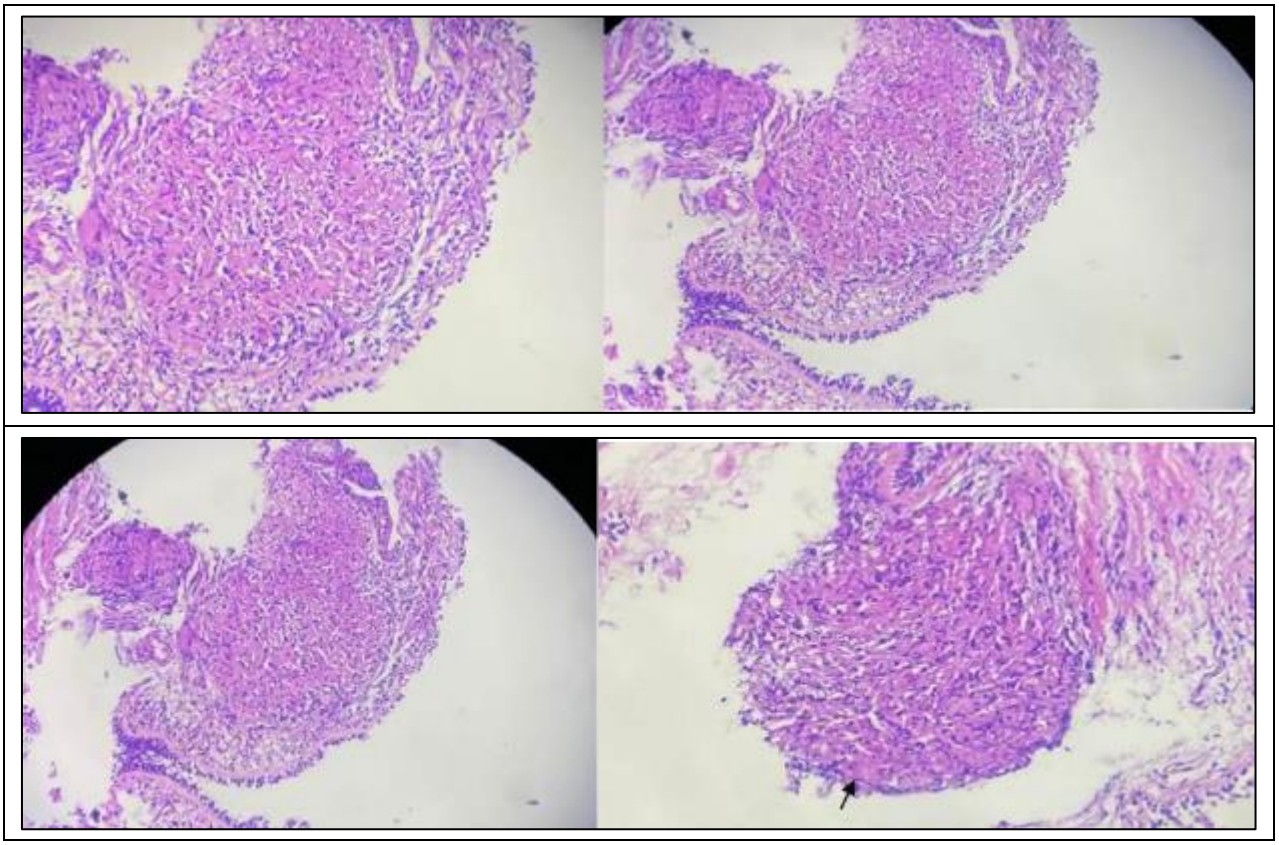

Figure 7 Histological sections under a microscope show a respiratory-type mucosa with a surface epithelium characterized by regular pseudostratified ciliated cells. There are areas of hyperplasia. The adjacent chorion is edematous with vascular congestion and an inflammatory infiltrate composed of epithelioid and giant-cell granulomas. These form variable-sized follicles, occasionally confluent, consisting of lymphocytes, epithelioid cells, and multinucleated giant cells, with some areas of fibrinoid necrosis (➔). There is no evidence of malignant tumor proliferation

2.2. Ocular involvement

The ophthalmological examination revealed sequelae from previous left anterior uveitis, such as granulomatous retrodescemet precipitates, pigment on the anterior crystalline lens, and iris synechiae. Fundoscopy showed no passage in the left eye, with visual acuity at 2/10. B-mode ultrasound further assessed the condition, showing physiological posterior vitreous detachment and a flat retina, indicating no vitreous inflammation (intermediate uveitis). However, due to the lack of fundoscopic passage, posterior uveitis could not be ruled out. The examination of the right eye was normal.

2.3. Neurological involvement

Given the neurological symptoms, a brain MRI with angiographic sequences was performed, which showed no abnormalities (fig.8). A lumbar puncture indicated an intracranial pressure of 12.5 mmHg, excluding intracranial hypertension. The cerebrospinal fluid appeared clear and suggested aseptic lymphocytic meningitis, characterized by hypoglycorrhachia and hyperproteinorrachia. Additionally, the angiotensin-converting enzyme (ACE) level was positive at 7, with a positive ACE ratio in blood and cerebrospinal fluid.

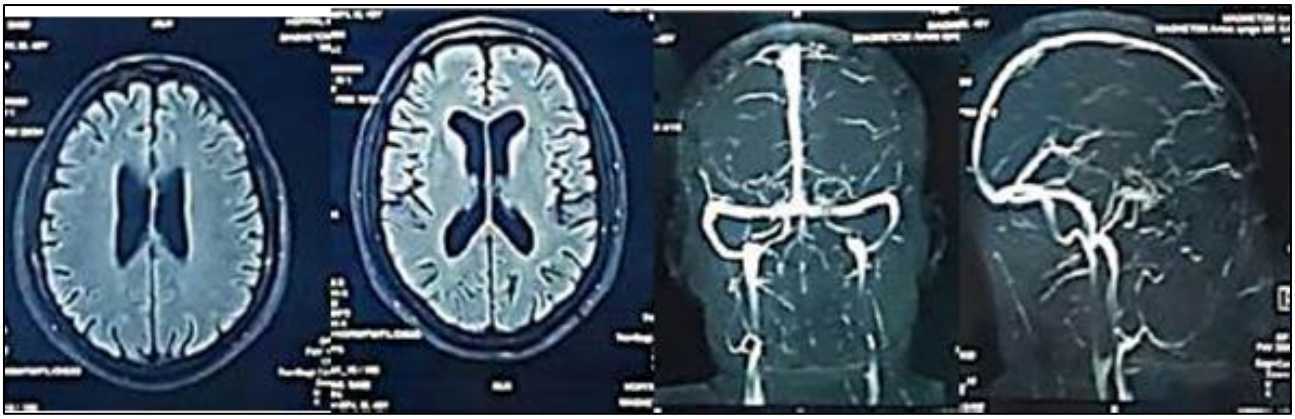

Figure 8 A brain MRI with angiographic sequences revealing no abnormalities

2.4. Involvement of exocrine glands and thyroid gland

The patient underwent a cervical ultrasound and facial CT scan, which revealed several findings. The sub- maxillary glands were slightly enlarged, normovascularized on Doppler, and exhibited a heterogeneous echostructure with poorly defined hypoechoic areas that were not vascularized on color Doppler. (fig.9) The superficial parotid lobe appeared normal in size but was heterogeneous, with poorly defined hypoechoic areas not vascularized by color Doppler. (fig.10) The thyroid was of normal size and contained nodules classified as EU-TIRADS III and II, with thyroid function tests returning normal results. Additionally, a polypoid lesion was observed in the right maxillary sinus. (fig.11) A biopsy of the accessory salivary glands, followed by an anatomical-pathological study, revealed non-specific subacute and chronic sialadenitis, Chisholm and Mason grade 2, with no evidence of malignancy.

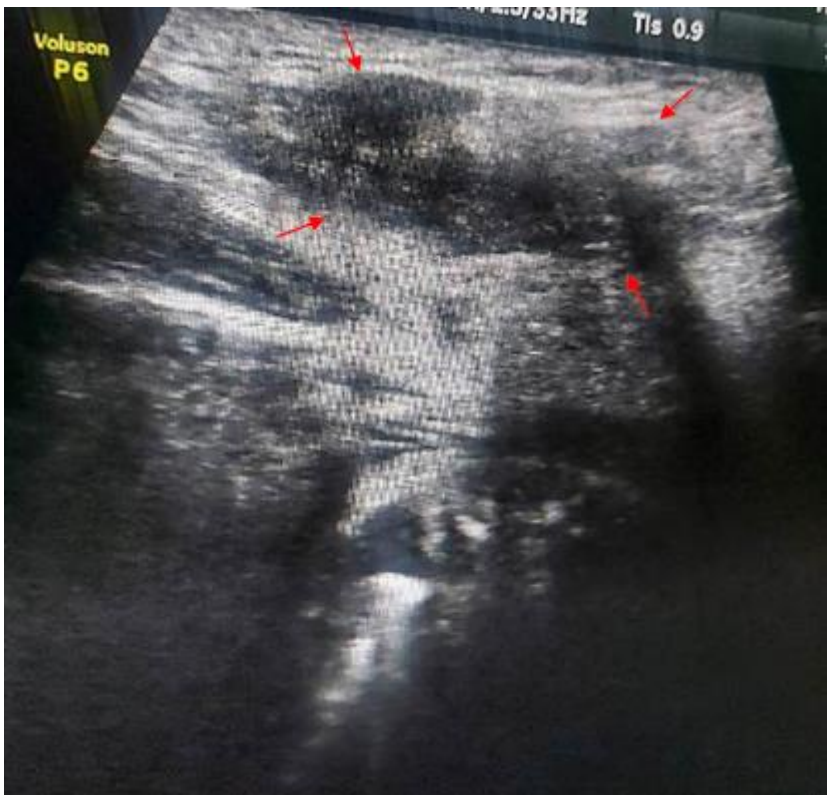

Figure 9 Heterogeneous ultrasound appearance of the submaxillary glands

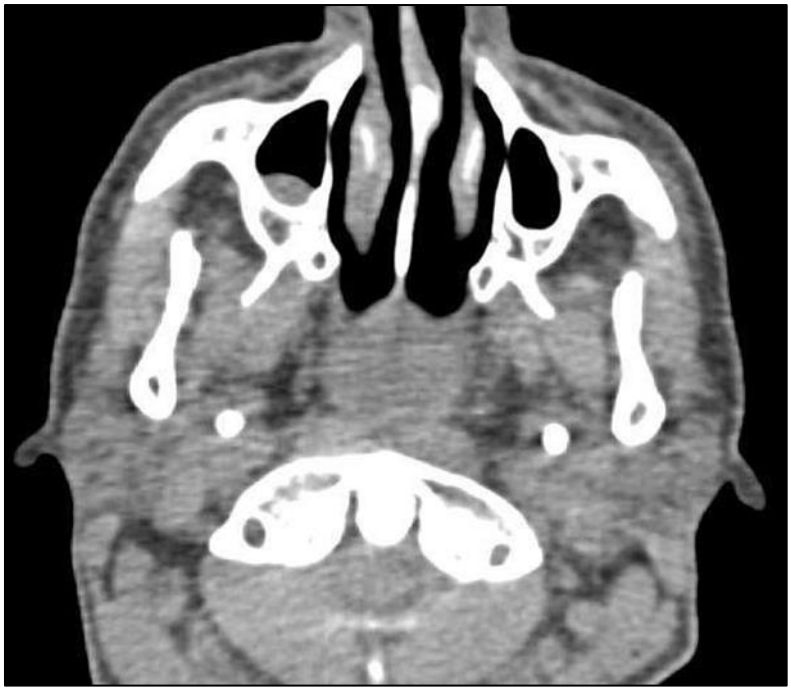

Figure10 Axial section of facial CT scan showing normal-sized parotid glands with spontaneously hypodense areas

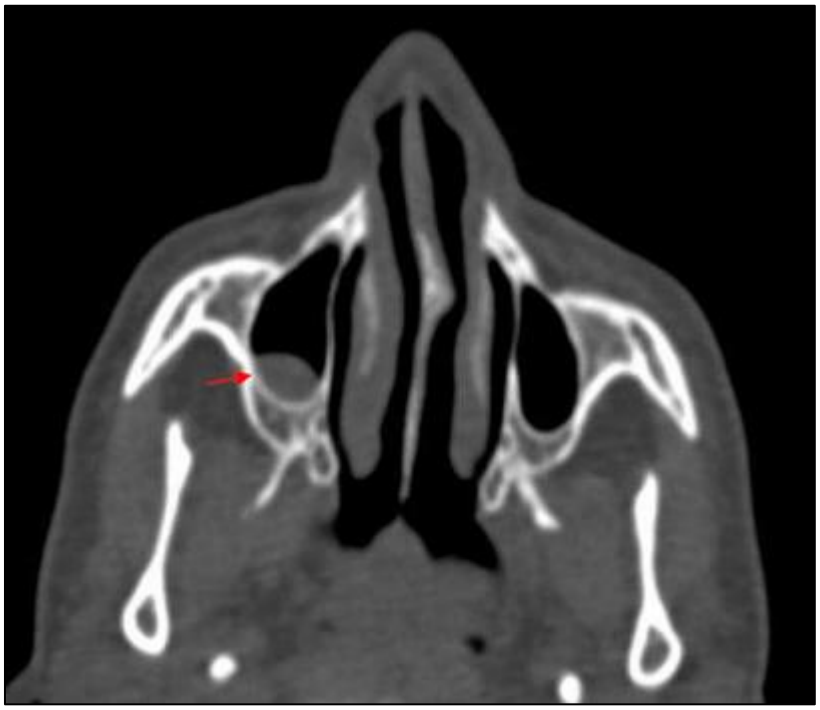

Figure 11 Scan section showing Polypoid opacification of the right maxillary sinus

2.5. Urogenital involvement

During his hospitalization, a testicular ultrasound was conducted, revealing hypotrophic, heterogeneous testes (fig.12-13) and diminished epididymides (fig.14-15), suggestive of sequelae from orchiepididymitis. Follow-up sperm analysis confirmed total azoospermia. Hormone levels, including FSH, LH, and testosterone, were all within the normal range.

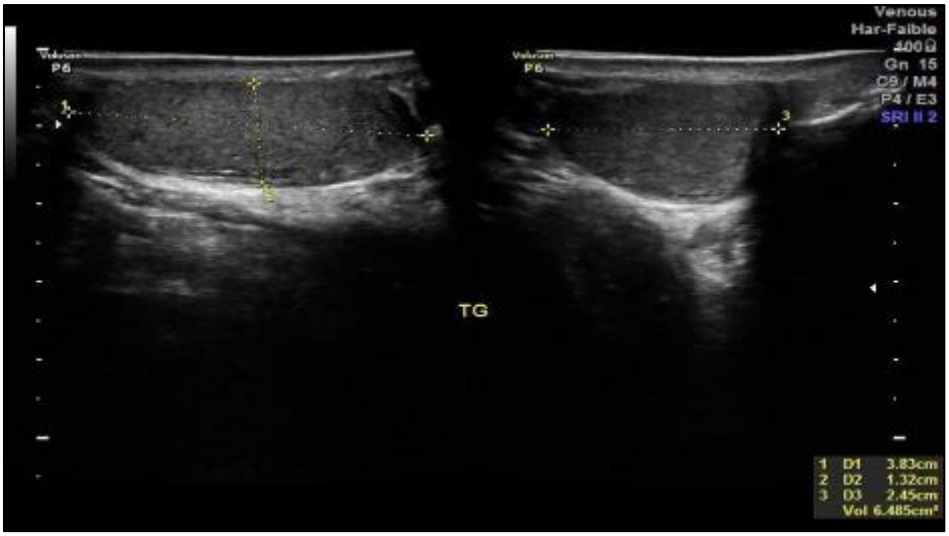

Figure 12 Ultrasound image of the left testicle with a volume of 6.48cm2

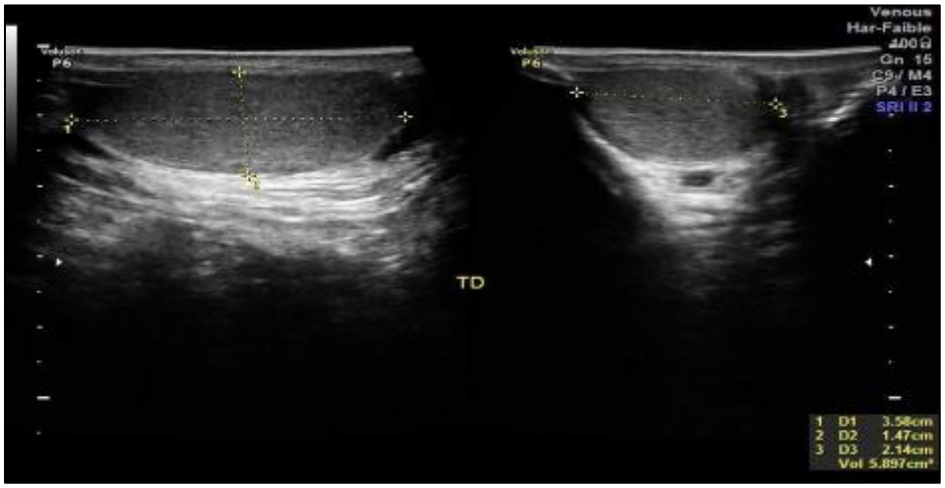

Figure 13 Ultrasound image of the right testicle with a volume of 5.89 cm2

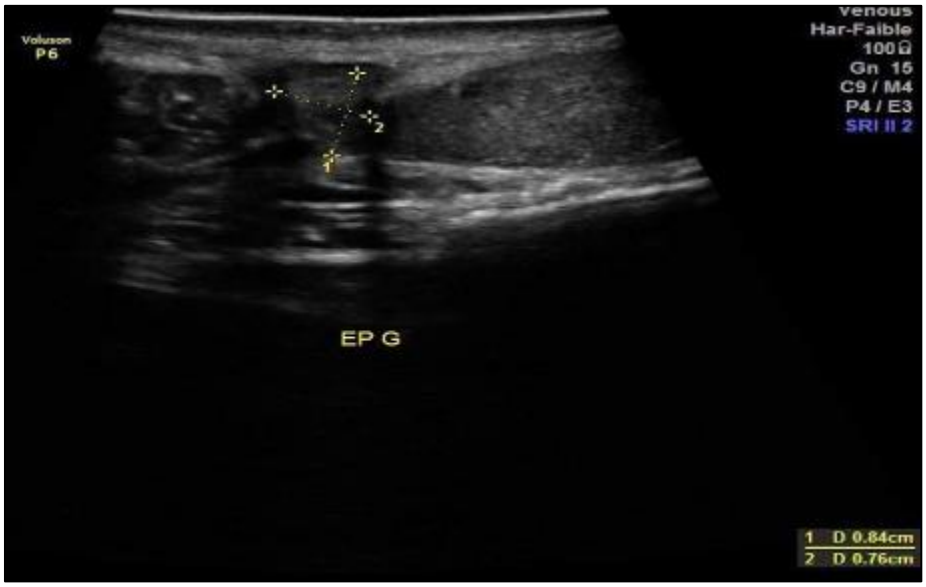

Figure 14 Ultrasound images of the left epididymis

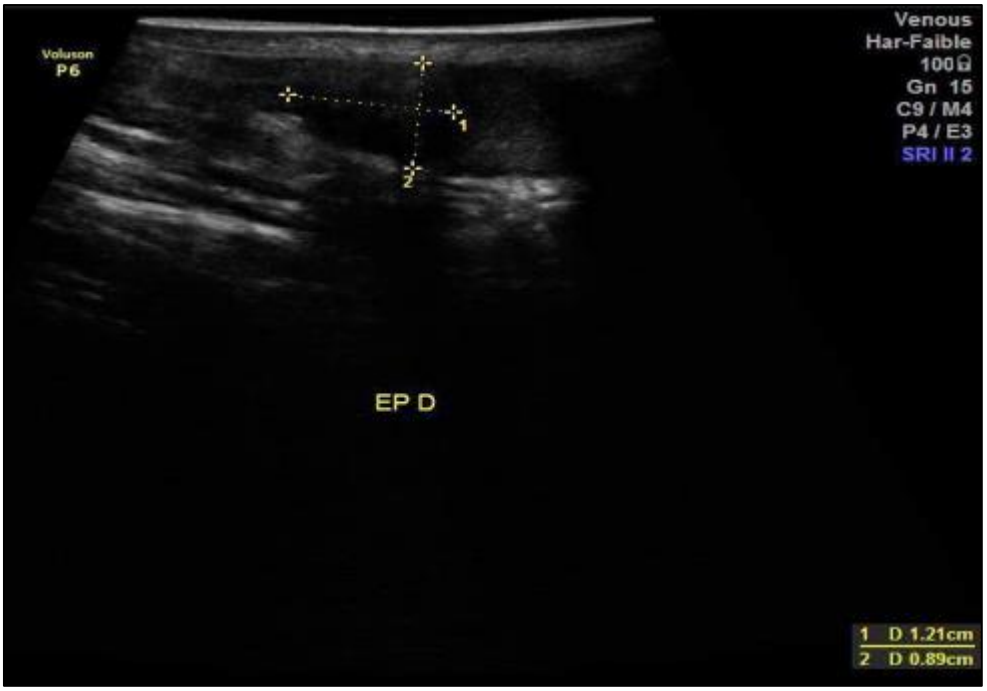

Figure 15 Ultrasound images of the right epididymis

3. Discussion:

Sarcoidosis is a systemic inflammatory disease of unknown cause, marked by the presence of non-caseating granulomas in various organs. First documented by Jonathan Hutchinson in 1877, the condition remains poorly understood. The combination of its elusive etiology and multisystem involvement complicates diagnosis and management. Sarcoidosis can range from asymptomatic cases to severe, life-threatening forms, affecting individuals of all ages and races. Due to these factors, its true global prevalence is unclear, as many cases go undiagnosed or are misdiagnosed, leading to delays in proper treatment [6]. As with our patient, the initial diagnosis led to treatment for pulmonary tuberculosis.

The lungs and intrathoracic lymph nodes are the most frequently affected sites in sarcoidosis, with over 90% of patients showing involvement. Beyond the lungs, other organs can be affected, with ocular sarcoidosis, particularly uveitis, being the second most common extrathoracic manifestation. Uveitis occurs in 25–60% of sarcoidosis cases, with approximately 30% of patients experiencing it at some point. If left undiagnosed or untreated, uveitis can lead to blindness and significantly impair quality of life [7]. Anterior uveitis is the most frequent type of uveitis, while posterior uveitis is crucial for visual prognosis. Uveitis can vary in severity, from mild anterior forms to severe bilateral panuveitis. Anterior uveitis is often granulomatous, chronic, and marked by large "mutton-fat" precipitates in the lower cornea, signaling active disease [8]. In our patient, ophthalmological involvement presented as unilateral sequelae of left- sided uveitis, characterized by granulomatous precipitates located behind Descemet's membrane.

CT scans are more sensitive than chest X-rays for detecting pulmonary abnormalities. Characteristic findings include bilateral micronodules in the upper lungs, distributed along thickened peribronchovascular axes and subpleural areas, creating a beaded appearance on the fissures. Staged bronchial biopsies have a 50-60% sensitivity for detecting epithelioid and giant cell granulomas, with better results when macroscopic mucosal abnormalities are present [9]. Focal fibrinoid necrosis was noted in 13 to 30% of cases in published series. Observations of granulomas resembling necrobiosis lipoidica have also been reported in cases of systemic sarcoidosis [10]. Our patient's CT scan shows subpleural and peribronchovascular micronodules along the scissures, creating a beaded appearance, and the bronchial biopsies revealed granulomas with focal fibrinoid necrosis.

Neurosarcoidosis often involves cranial nerves, with the facial nerve commonly affected, and may mimic conditions like Lyme disease. It can lead to neuroendocrine dysfunction (e.g., neurogenic diabetes insipidus), spinal cord issues, and chronic meningitis. Symptoms might include seizures, peripheral neuropathy, carpal tunnel syndrome, and muscle problems. Heerfordt syndrome, a rare manifestation, features facial nerve palsy, parotid gland enlargement, anterior uveitis, and fever. Seizures and cognitive changes can also occur, with the prognosis varying based on the type of seizure [11]. Angiotensin-converting enzyme (ACE) is produced by sarcoid granulomas and is found in various biological fluids.

Measuring ACE activity in cerebrospinal fluid (CSF) can assist in diagnosing neurosarcoidosis. However, elevated ACE levels in CSF are not specific to neurosarcoidosis and can also be seen in certain types of meningitis. Therefore, this test should be used in conjunction with other diagnostic tests to either rule out or confirm neurosarcoidosis [12]. In our patient's case, neurological involvement was indicated by aseptic lymphocytic meningitis and an increased level of angiotensin-converting enzyme (ACE) in the cerebrospinal fluid (CSF).

Infiltration of the exocrine glands (such as the parotid, lacrimal, and accessory labial glands) is common, but clinical manifestations (unilateral or bilateral parotitis with swollen and painful parotid glands) are reported in only 6% of patients [13]. Manifestations occur in 20%– 50% of individuals, with common involvement of the thyroid gland (5%) and parotid glands (5%–10%), often presenting as enlargement. Rare symptoms include hypothermia, adrenal suppression, and thyroid disorders. The condition can also affect the hypothalamic-pituitary axis, leading to issues like diabetes insipidus. Heerfordt's syndrome features fever, parotid enlargement, facial palsy, and anterior uveitis [14]. On ultrasound, sarcoidosis of the salivary glands may present as multiple solid hypoechoic areas within enlarged or normally-sized glands, or as diffuse low echogenicity. There may be increased parenchymal blood flow, and nodules can contain calcific foci indicating chronic inflammation. Additionally, multiple bilateral enlarged cervical lymph nodes may be observed .Heterogeneous appearances of the salivary glands on ultrasound may be associated with granulomatous infiltration, which can create a heterogeneous pattern due to the presence of granulomas within the glands [15]. The patient’s sub-maxillary glands were mildly enlarged with a heterogeneous structure and non-vascularized hypoechoic areas. The superficial parotid lobe, although normal in size, also exhibited a heterogeneous appearance with poorly defined, non-vascularized hypoechoic areas.

Azoospermia affects about 10% of infertile men and 1% of the general male population. The evaluation of azoospermia should be categorized into pre-testicular (hypothalamic-pituitary dysfunction), testicular (testicular failure), and post-testicular (obstruction or ejaculatory dysfunction) issues. Testicular failure and obstruction are the most common causes. Although literature on genitourinary sarcoidosis is limited, it has been suggested that men with sarcoidosis consider semen analysis and sperm banking due to the disease’s unpredictable nature [16]. Testicular dysfunction causing by urogenital sarcoidosis is very rare. Only about 60 cases have been reported in the literature. It is usually characterized by epididymis and testis involvement [17].

H. Gindre et al. explored the manifestations of sarcoidosis affecting the urogenital system in men through three distinct clinical cases. The first case involves a patient with azoospermia, revealing granulomatous infiltration in the testicles and impaired testicular function. The second case features a patient with erectile dysfunction and a scrotal mass, where ultrasound highlighted sarcoid involvement of the urogenital glands. The third case describes a patient with granulomatous prostatitis and urinary disorders, confirmed by histological examination showing granulomas in the prostate. These cases emphasize the diverse clinical manifestations of urogenital sarcoidosis and the importance of a comprehensive diagnosis using clinical examinations, imaging, and histological analyses for effective management [18]. In our patient's case, infertility due to total azoospermia was the first symptom of sarcoidosis to appear. The testicular ultrasound revealed hypotrophic, heterogeneous testes, indicative of sequelae from orchiepididymitis. The initial ultrasound, however, was normal.

S. Haddad et al. described a 50-year-old woman with sarcoidosis initially detected through an eyelid mass. Along with the mass, she experienced general symptoms like fatigue and weight loss. Diagnostic tests and imaging revealed bilateral hilar lymphadenopathy and granulomas in the excised eyelid tissue. Elevated angiotensin-converting enzyme levels supported the diagnosis. The case emphasizes the significance of ocular symptoms as potential early indicators of sarcoidosis and the need for prompt diagnosis and treatment [19].

Ouchkat et al. reported a case involving a 25-year-old patient who was admitted with daytime drowsiness and a month-long fever, along with parotid gland enlargement. Although brain MRI, EEG, and cerebrospinal fluid analysis showed no abnormalities, cervical ultrasound revealed inflammatory lymphadenopathy. Additional tests, including a thoracic CT scan, hormonal evaluation of the hypothalamic-pituitary axis, and a biopsy of the accessory salivary glands, led to a diagnosis of sarcoidosis [20].

4. Conclusion

Reviewing both the literature and our case, we highlight that diagnosing sarcoidosis presents a significant challenge due to its diverse symptoms, which can mimic various other conditions, and the lack of specific diagnostic tests. This symptom variability often leads to delays in diagnosis and complicates the clinical picture. Additionally, in regions where tuberculosis is endemic, there is a risk of confusing sarcoidosis with tuberculosis, further complicating the diagnostic process. Sarcoidosis can affect multiple organ systems, including rare urogenital involvement, which is often

overlooked. Clinicians must maintain a high level of suspicion and include sarcoidosis, especially with urogenital manifestations, in their differential diagnosis to avoid misdiagnosis and ensure timely treatment. Our case underscores the importance of a comprehensive diagnostic approach, involving detailed clinical assessment, imaging studies, and targeted biopsies, to accurately identify sarcoidosis and recognize its rare urogenital involvement, while also distinguishing it from other conditions like tuberculosis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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