sciendo Internal Medicine 2023 vol. XX No. 3 - www.srmi.ro 83
10.2478/inmed-2023-0262

AN ATYPICAL CASE OF PULMONARY SARCOIDOSIS

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Rezumat
Sarcoidoza este o boală inflamatorie granulomatoasă, multisistemică, de etiologie incertă, mai des întâlnită în cadrul populației de sex feminin. Vârsta la debut este de obicei cuprinsă între 30 și 50 de ani, prezentând și un al doilea vârf al incidenței în perioada imediat post-menopauză.
Afectarea la nivelul sistemului respirator sau limfatic este prezentă în cca 90% dintre cazurile de sarcoidoză, fiind însă de cele mai multe ori de scurta durată și autolimitată, dar uneori boala se poate croniciza și mai rar poate progresa către fibroză pulmonară ireversibilă complicată cu hipertensiune pulmonară și mai apoi cord pulmonar cronic cu insuficiență cardio-respiratorie și exitus.
Prezentăm cazul unui pacient prezentând o forma rară, nodulară, de sarcoidoză, la care au fost identificate imagistic multiple calcificări, atât parenchimatoase, cât și limfatice, cel mai probabil cu o evoluție îndelungată a bolii în prealabil, dar cu funcție pulmonară complet conservată.
Cuvinte cheie: *sarcoidoză, forma nodulară, calcificări pulmonare.*

Abstract
Sarcoidosis is a multisystem, granulomatous, inflammatory disease, of uncertain aetiology, ubiquitous, much more common in the female population. The age at onset is usually between 30 and 50 years, also having a second peak of incidence in the immediate post-menopausal period. Respiratory system or lymphatic system involvement is present in about 90% of sarcoidosis cases, usually being short-lived and self-limiting, but sometimes the disease can become chronic and less often it can progress to irreversible pulmonary fibrosis, complicated with pulmonary hypertension followed by chronic pulmonary heart disease with cardio-respiratory failure and death.
We present the case of a patient presenting a rare, nodular form of sarcoidosis, in which multiple calcifications, both parenchymal and lymphatic, were identified by imaging, most likely with a long-term evolution of the disease beforehand, but with a completely preserved pulmonary function.
Keywords: *Sarcoidosis, nodular form, pulmonary calcifications.*

Internal Medicine

Clinical Cases

Introduction

Sarcoidosis is a multisystem, granulomatous, inflammatory disease, of uncertain aetiology, ubiquitous but with increased prevalence in populations of Scandinavian, Germanic, Irish origin, or Black people. The age at onset is usually between 30 and 50 years, an age range that includes approximately 70% of cases, also having a second peak of incidence in the immediate post-menopausal period, the pathology being also much more common in the female population[1].

Respiratory-like symptoms are found at the time of first presentation in approximately 30-53% of patients (cough 27-53%; dyspnoea 18-51%; chest pain 9-23%), but up to 50% of patients can be asymptomatic at the time of diagnosis[1].

Respiratory system or lymphatic system involvement is present in about 90% of sarcoidosis cases, usually being short-lived and self-limiting (60-70% of patients), but sometimes the disease can become chronic (20-30% of cases) and less often (10-15%) it can progress to irreversible pulmonary fibrosis, complicated with pulmonary hypertension followed by chronic pulmonary heart disease with cardio-respiratory failure and death, with a mortality rate in sarcoidosis being very low, at about 5%[2].

The pathogenetic mechanism in sarcoidosis is currently uncertain, but a combination of factors is suspected, such as genetic susceptibility (sarcoidosis is a polygenic disease, without a single responsible gene having been identified), environmental factors (patient's personal history of exposure to wood stoves, pollen, silicon, inorganic particles, insecticides, soil), infectious history (*Leptospira* spp., *Mycoplasma* spp., *Chlamydia pneumoniae*, *Mycobacterium* spp., *Borrelia burgdorferi*, *Pneumocystis jirovecii*, herpes simplex, hepatitis C virus), or autoimmunity, without being able to identify a single cause with certainty[3].

There is a possibility that sarcoidosis starts after exposure to a trigger environmental factor, in a genetically predisposed individual, triggering a systemic granulomatous-type inflammatory response[4].

Case presentation

The patient is a Caucasian male, aged 47, non-smoker, without history of occupational exposure to respiratory hazards, known with recently diagnosed right bundle branch block, without other significant pathologies. At the time of the first presentation, he accuses dull right lateral chest pain, worsened by deep breathing, and profound fatigability, symptoms with slow onset and progressive worsening.

The clinical examination is normal. The blood biochemistry, the respiratory functional tests

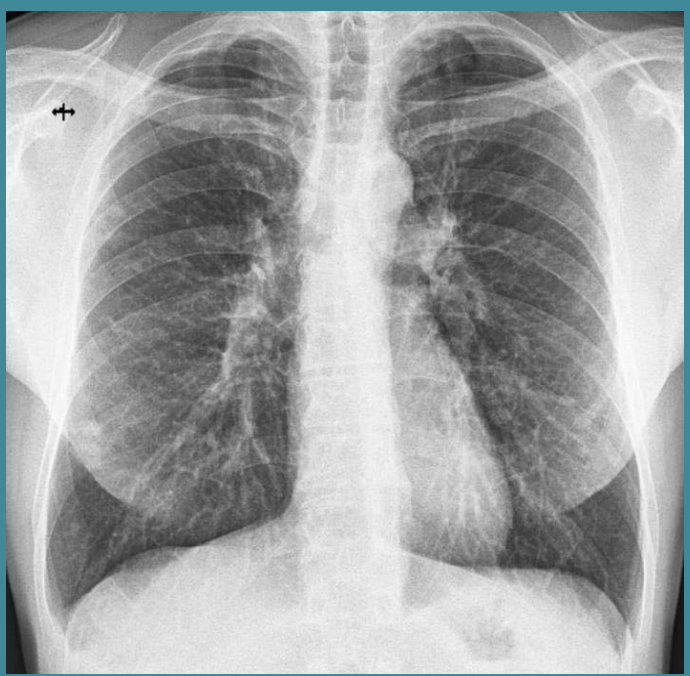

Figure 1. *Standard chest X-ray showing bilateral hilar enlargement and multiple diffusely disseminated nodular opacities, bilaterally*

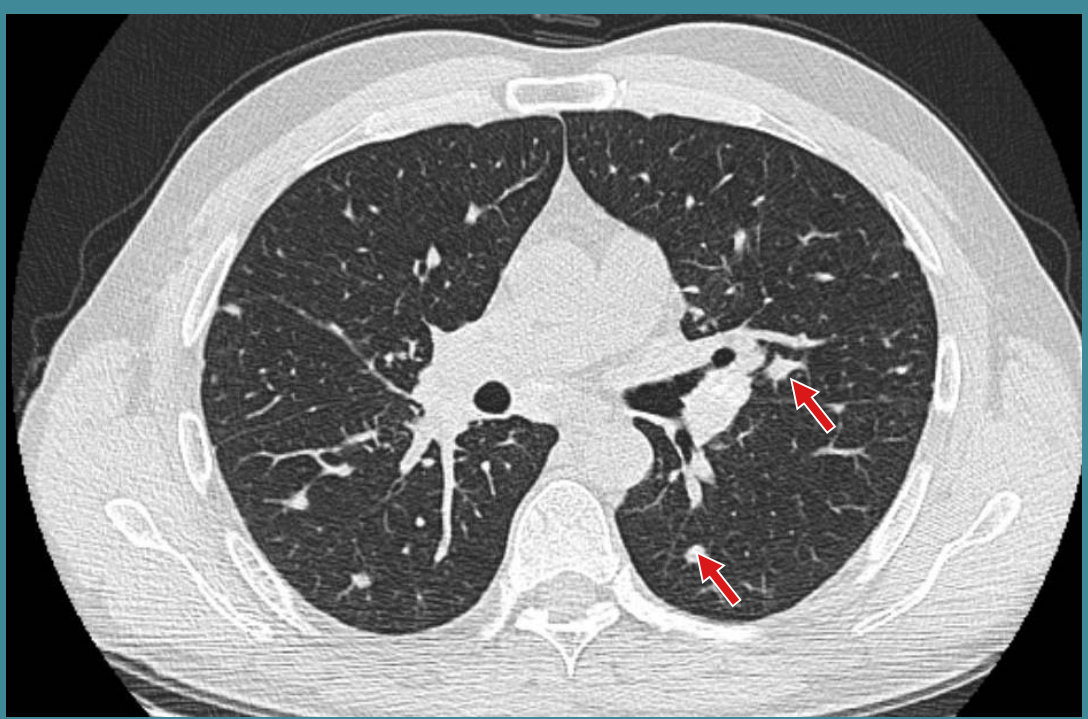

Figure 2. *Chest CT showing bilateral hilar enlargement through the presence of multiple hilar lymphadenopathies and multiple pulmonary nodules, of variable size, round-oval, disseminated in both pulmonary fields*

and the 6-minute walk test do not show pathological values. The serum ACE, the serum calcium and serum potassium are within normal limits. The abdominal ultrasound did not show any pathological change.

The simple chest X-ray, in postero-anterior view (Figure 1) reveals the presence of multiple nodular opacities, of low intensity, relatively well delimited and homogeneous, disseminated in both pulmonary fields, but also the slight increase in size of both pulmonary hila.

The chest CT without contrast agent (Figure 2) reveals the presence of multiple parenchymal nodules with a bilateral diffuse distribution, some of them with variable degrees of calcification (Figure 3), but none of them with cavities, the largest of which with a 11 mm diameter, as well as multiple mediastinal lymphadenopathies, some of them partially calcified (Figure 4).

At follow-up, a re-examination by chest CT without contrast agent, approximately 2 months later, identifies no changes of the radiological image, without significant changes in the number or the size of the nodules. The head CT and the abdominal CT do not find other lesions with similar characteristics.

The fibrobronchoscopy does not show pathological elements. The bronchioloalveolar lavage shows the presence of granulocytes in proportion of 42.6% (normal values 3%), 41.6% neutrophils, 55% macrophages and 2.4% lymphocytes, without other pathological elements. The endobronchial spur biopsy confirmed the diagnosis of sarcoidosis, following the identification of multiple giant sarcoid granulomas (Figure 5), some of them with peripheral hyalinization.

Systemic corticosteroid therapy with Methylprednisolone is initiated, originally in pulse therapy with a daily dose of 32 mg, with subsequent lowering of the doses every 21 days, until reaching the maintenance dose of 4 mg/day. Upon re-assessment, the patient reported an important increase of the quality of life via the significant reduction of the symptoms, with relatively few adverse effects related to the therapy (cortisone myopathy, recurrent oral candidiasis, anxious-depressive syndrome), which almost completely remitted once the cortisone doses were reduced to a minimum.

In terms of imaging, the patient was re-assessed via chest CT without contrast agent after 6 months of corticosteroid therapy and a regression in size of the bilateral nodular masses, with the persistence of the mediastinal and hilar lymphadenopathies being observed.

Material and methods

A search was performed in the PubMed, Google Scholar, Web of Science, Scopus and

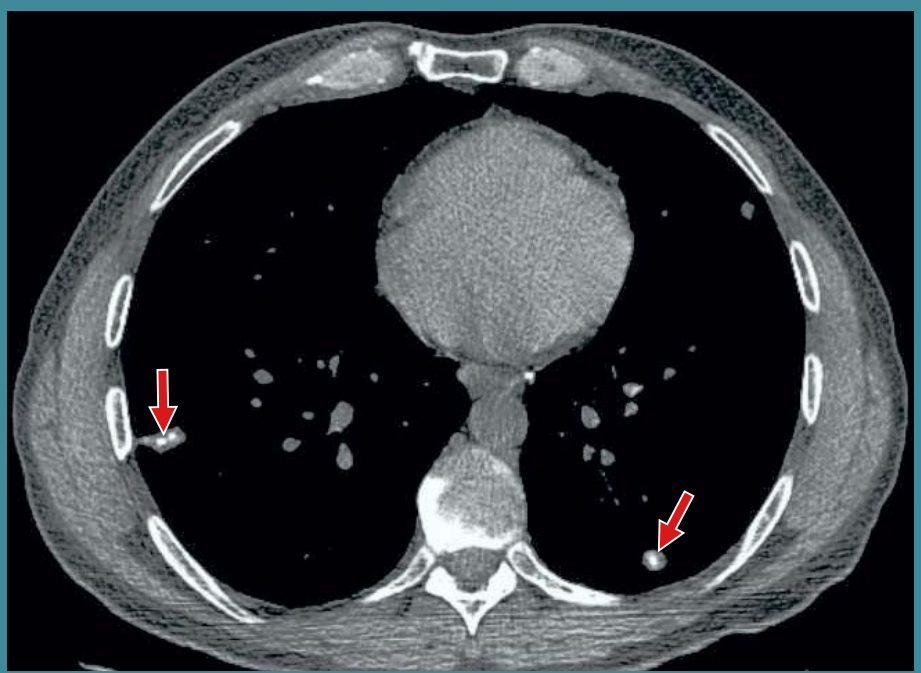

Figure 3. *Multiple pulmonary nodules, some of them partially calcified*

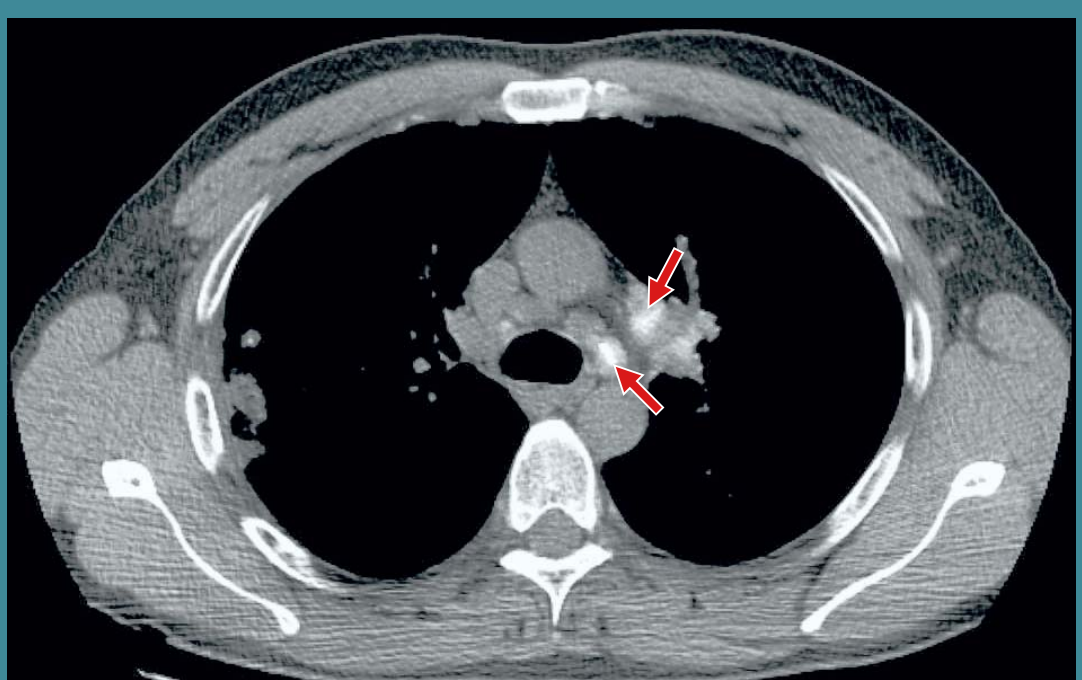

Figure 4. *Multiple mediastinal lymphadenopathies, some of them partially calcified*

UpToDate medical databases using the English terms “atypical sarcoidosis” and ”nodular sarcoidosis”, including only full, free-access articles published in the last 10 years (2013-2023). Thus, 9 case study articles [5.-13] were chosen, including a total of 11 patients, the key features of these patients being included in *Table 1*.

Discussions

The diagnosis of sarcoidosis requires 3 items: (a) clinical and radiological items consistent with this diagnosis (typical respiratory symptoms, nodular lesions in the pulmonary parenchyma and hilar lymph nodes), (b) exclusion of other pathologies that can manifest themselves in a similar manner, (c) a biopsy specimen that shows the presence of highly suggestive granulomas[(14)].

The nodular pattern is a rare form of manifestation of pulmonary sarcoidosis, affecting approximately 1.6-4% of patients. Similarly to the common form of sarcoidosis, it affects more frequently the Black race and the feminine gender. At the time of the first presentation, the patients frequently complain of non-specific symptoms, such as fever, fatigability, and unexplained weight loss, while the respiratory function is very rarely affected. On the standard chest X-ray, the nodules are between 1 and 5 cm in diameter and are usually located peripherally, with a high tropism for the upper lobes, with irregular and ill-defined borders, formed by the coalescence of several granulomas. Nodular sarcoidosis generally has a favourable prognosis, evolving towards total resorption under oral corticosteroid therapy[(5,6)].

The present patient does not fit into the classic picture of patients with sarcoidosis, being male and White, with minimal respiratory symptoms at the time of the diagnosis and with a radiological image that advocates rather for a neoplastic aetiology (multiple medium-sized nodules, without tendency of conglomeration and coalescence, without any tropism of distribution, well delimited from the surrounding healthy parenchyma, some of them partially calcified), this radiological aspect advocating rather the nodular form of sarcoidosis. The key difference between the previously presented literature cases and the present case is the presence of parenchymal or lymph node calcifications.

Due to the rarity of pulmonary calcifications in general and those induced by sarcoidosis in particular, such cases are few in the specialized medical literature. A thorough search performed in the PubMed, Google Scholar, Web of Science, Scopus and UpToDate databases using the English terms “calcified sarcoidosis” and “sarcoidosis calcification” identified 6 notable articles[(15-20)].

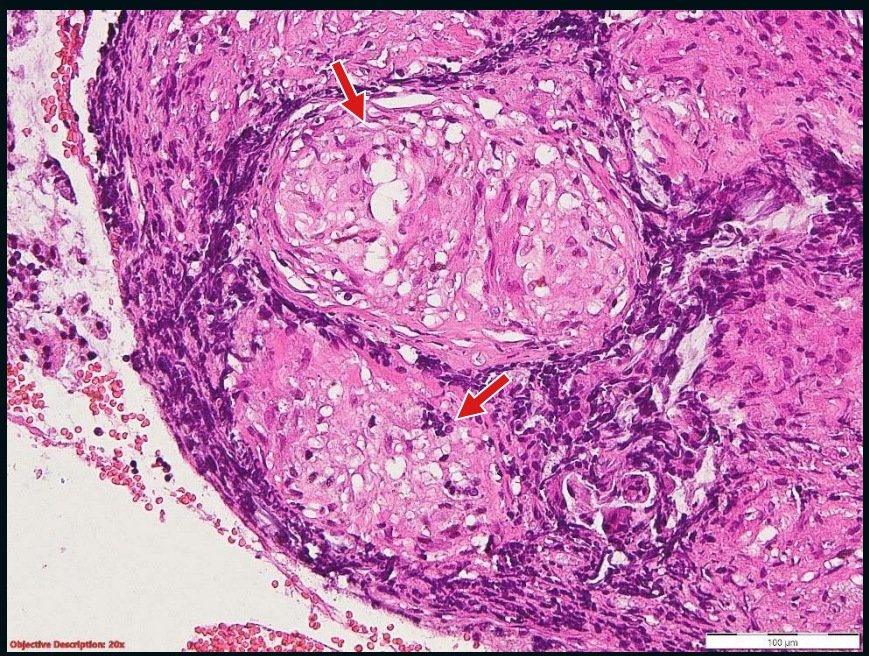

Figure 5. *Non-necrotizing, non-caseating sarcoid granuloma, Haematoxylin-Eosin staining, x20 magnification*

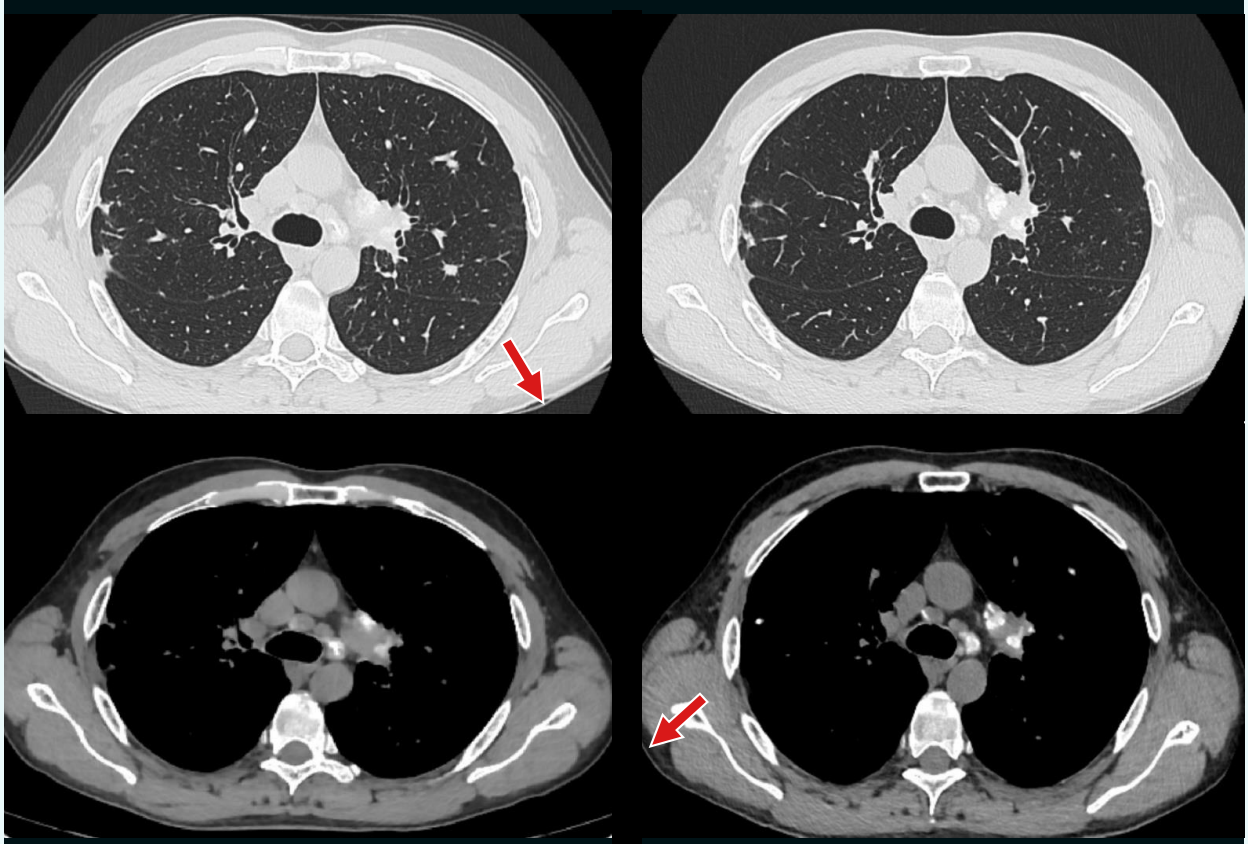

Figure 6. *The imaging evolution of the sarcoidosis after 6 months of corticoid therapy with Methylprednisolone (initial chest CT in the left half of the image; CT re-assessment in the right half of the image). The significant regression in size of the multiple bilateral pulmonary nodules, without a significant change of the hilar and mediastinal lymphadenopathies.*

Israel et al.[15] and *Scadding et al.*[16] meta-analyses[16] compiled a comprehensive case series of newly-discovered sarcoidosis and followed the clinical and imaging evolution of these patients for a minimum of 5 years from the time of the initial diagnosis. Of these patients, less than 5% developed calcification of lymph nodes or parenchyma during this interval, confirming the rarity of this form of sarcoidosis manifestation. During the consultation of the specialized literature, other case studies [18-19] were also identified, which present patients diagnosed incidentally with lymph node calcifications, after at least 7 years of disease evolution, excepting the case *Kunat et al* [20], where the female patient presented these calcifications at the time of diagnosis.

In sarcoidosis the calcification is generally localized inside the granuloma, very rarely alveolar or interstitial, thus generating a diffuse micronodular appearance on the standard chest X-ray[21]. The lymph node calcification depends on the duration of the evolution of the disease, with an incidence of approximately 3% at 3 years after the diagnosis and increasing up to 10% after 20 years of evolution, being considered a manifestation of the terminal stage of sarcoidosis.

It generally affects the hilar lymph nodes symmetrically and presents multiple types of distribution of calcium deposits (amorphous, egg-shell, popcorn, punctiform)[2, 22]. The presence of these lymphatic calcifications is frequently associated with more severe pulmonary forms, functionally quantified through altered values when tested by spirometry with DLCO[23]. The patient presents multiple central calcifications, both in the parenchyma nodules and the lymph nodes, which suggests a long-term evolution of the sarcoidosis, with late occurrence of the symptoms, with a totally preserved pulmonary function, and this hypothesis is supported by literature data [18-19] that identified a medium time range of 7 years between the time of the diagnosis and the time of the occurrence of the first calcifications. Because the patient does not have any previous thoracic imaging, we cannot exactly determine the time interval of indolent evolution of the sarcoidosis in this case.

Calcium metabolism anomalies are frequently found (approximately 10-17% of patients) in sarcoidosis and are represented mainly by hypercalcemia and hypercalciuria. The activated macrophages inside the granulomas are responsible for the expression of the enzyme 1alpha-hydroxylase, responsible for raising the blood level of calcitriol, thus leading to an excessive reabsorption of the calcium in the intestine and to a deposition of this calcium excess in all tissues. At the same time, altered levels of vitamin D and calcium

	Age	Gen-der	Race	Smoker status	Symptoms	Serum ACE	Number of nodules	Hilar lymphade-nopathy
Sweidan et al.	39	F	Afro-American	Yes	Chest pain	-	Solitary (RLL)	Bilateral
Taketa et al.	67	F	Asian	No	Asymptomatic	Normal	Solitary (RUL - spiculated)	Unilateral (right)
Senussi et al.	20	F	Afro-American	No	Chest pain	Normal	Multiple	None
Jafari et al.	31	M	Middle East	No	Bilateral oedema of the ankles	Increased	Multiple	Bilateral
Mulkaredd y et al.	39	M	Afro-American	Yes	Chest pain Cough Weight loss	-	Multiple nodules and 1 solitary mass	Unilateral (right)
Kong et al.	44	F	Afro-American	-	Dyspnoea	-	Solitary (RLL)	Bilateral
Shahzad et al. (Case 1)	32	F	Asian	No	Dyspnoea Dry cough Fever	Increased	Multiple	-
Shahzad et al. (Case 2)	43	F	Asian	No	Dyspnoea Dry cough Fever	Increased	Multiple (RUL and LUL)	Bilateral
Shahzad et al. (Case 3)	29	F	Asian	No	Cough Fever	Increased	Multiple	-
Lee et al.	64	F	-	Yes	Asymptomatic	Normal	Solitary (RUL)	Bilateral
Kelleher et al.	44	F	Afro-American	-	Dyspnoea Weight loss	-	Solitary (LLL)	Bilateral

Table 1. *A comparison between the main characteristics found in multiple cases of atypical nodular sarcoidosis, identified in the specialized literature*[18 - 26]

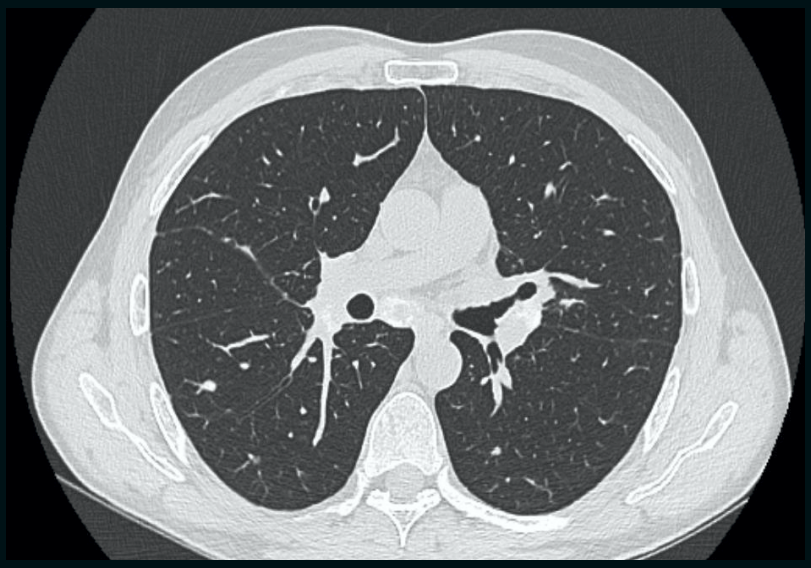

Figure 7. *Chest CT re-examination after 6 months: Multiple bilateral pulmonary nodules, regressing in size compared to the previous examination*

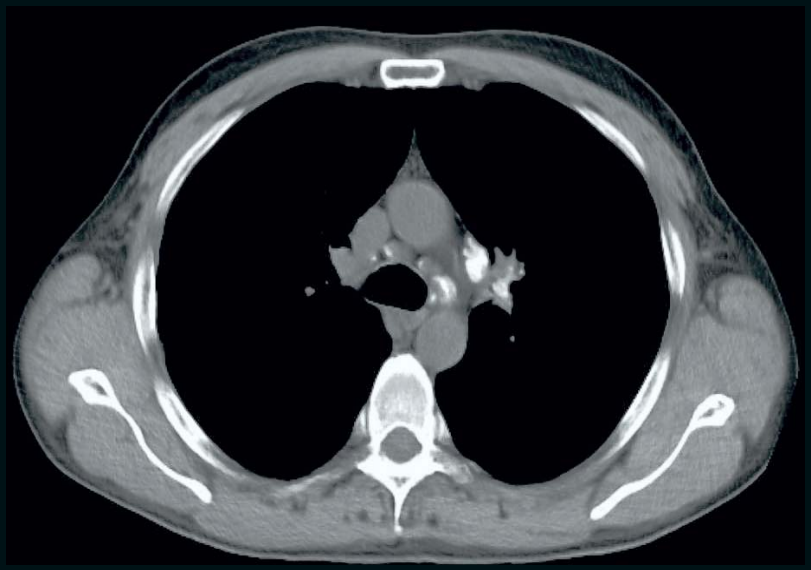

Figure 8. *Chest CT re-examination after 6 months: Multiple hilar and mediastinal bilateral lymphadenopathies, with stable size*

cause a suppression of the serum level of parathormone, with the massive excretion of excess serum calcium through the kidneys, causing hypercalciuria and urinary calcium pathology such as kidney and bladder lithiasis[24].

According to *Inui et al.*[25] and *Bell et al.*[26] there is a correlation between the genetic expression of 1alpha-hydroxylase in the alveolar macrophages, and thus between the severity of the calcium phosphate imbalance and the activity level of sarcoidosis itself, and therefore the severity of the disease, thus being able to explain the presence of a preserved lung function and a normal calcium phosphate balance in the presence of a significant nodular parenchymal involvement. In the present case, extensive tissue calcifications were identified in the absence of low serum levels of ACE, calcium and potassium, the patient presenting no other pathologies favouring the deposition of calcium salts in the tissues (chronic kidney disease, hyperparathyroidism, multiple myeloma, Paget disease, etc.).

The bronchoalveolar lavage in sarcoidosis is characterized by an increase in the lymphocyte fraction with an increased CD4/CD8 ratio and the presence of activated alveolar macrophages, frequently with normal values of neutrophils and eosinophils[27]. However, the patient's lavage fluid shows low values of lymphocytes, rich in granulocytic polymorphonucleocytes, with a significant increase in the number of neutrophils (13 x normal values) and a discreet increase in the number of eosinophils (2 x normal values), a totally different aspect compared to the classic picture of sarcoidosis. For technical reasons, the CD4/CD8 ratio could not be determined.

Because sarcoidosis is by definition a diagnosis of exclusion, other pathologies whose clinical and imaging manifestations can be difficult to differentiate from it must also be carefully considered[28].

In the presence of a radiological image with multiple nodular opacities, disseminated in both lung fields but with tropism for the apexes, the distinction between the nodular form of sarcoidosis and extensive pulmonary tuberculosis must be quickly made. In the present case, the Ziehl-Neelsen staining of the bronchial aspirate sample did not identify acid-alcohol-resistant bacilli, and the optical microscopy did not identify areas of coagulation necrosis with caseaton in the examined granulomas. The bacteriological examination also excluded any other infectious pathology, such as histoplasmosis or pneumocystosis. The negative history of exposure to occupational respiratory hazards excludes the most frequent pneumoconioses, asbestosis, silicosis, anthracosis and berylliosis.

The bronchoscopy examination did not identify foreign bodies in the tracheobronchial tree, which makes foreign body granulomatosis unlikely as the etiological factor of the parenchymal nodules.

Hypersensitivity pneumonitis in its chronic form can present few symptoms and a non-specific clinical picture, like that of the patient in question, but characterized by intensely positive non-specific serum inflammatory markers and lymphocytic predominance in the bronchoalveolar lavage, and computed tomographic images predominantly depicting ground-glass opacities, sometimes nodular opacities in the stagnant forms of disease.

Neoplastic pathology, both pulmonary and lymphatic, is another important differential diagnosis, in the present case this was rapidly excluded following the histopathological examination of the bronchoscopically-collected biopsy specimen. Nodular pulmonary

amyloidosis is another important differential diagnosis, with a clinical and imaging appearance almost identical to that of sarcoidosis, frequently accompanied by skin, kidney and heart lesions, and which was refuted by histopathological examination. Not lastly, Wegener's granulomatosis with polyangiitis was quickly ruled out by the lack of vasculitis involvement in the kidneys, skin and joints, the lack of non-specific inflammatory syndrome and the stable radiological image on follow-up.

Conclusions

As a particularity of the case, we note a patient with an unusual demographic profile for autoimmune pathologies, without increased serum levels of ACE, calcium, potassium, with a lavage fluid rich in granulocytes and relatively poor in lymphocytes, with few symptoms at the time of diagnosis, presenting a rare, nodular form of sarcoidosis, in which multiple calcifications, both parenchymal and lymphatic, were identified by imaging, most likely with a long-term evolution of the disease beforehand, but with a completely preserved pulmonary function.

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