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Diagnostic challenges of a rare disease with an unusual presentation

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Abstract

English:

Sarcoidosis is a chronic systemic granulomatous disease that can show overlapping clinical features with various rheumatological entities. Even though it can be more commonly associated with Sjögren syndrome and systemic lupus erythematosus, only on rare occasions, it can concomitantly occur with rheumatoid arthritis. While lacking a gold standard diagnostic tool, sarcoidosis remains an exclusion diagnosis. Moreover, an atypical presentation of a rare disease on the background of another systemic disease can be challenging, even for an experienced physician. We present a rare case of a patient with a long-standing history of rheumatoid arthritis treated with methotrexate who developed sarcoidosis with an unusual presentation and possible cardiac involvement.

Keywords

sarcoidosis • rheumatoid arthritis • overlap • autoimmune

Provocări ale diagnosticului într-o boală rară cu prezentare neobișnuită

Rezumat

Romanian:

Sarcoidoza este o patologie granulomatoasă sistemică cronică ce poate prezenta caractere clinice ce se suprapun cu diferite entități reumatologice. Deși se poate asocia mai des cu sindromul Sjögren și lupusul eritematos sistemic, apariția concomitentă cu artrita reumatoidă este foarte rară. În lipsa unui standard de aur pentru diagnostic, sarcoidoza rămâne un diagnostic de excludere. Mai mult, o prezentare atipică a unei boli rare ce se suprapune unei boli sistemice poate fi o provocare chiar pentru un clinician cu experiență. Prezentăm un caz rar al unui pacient cu un istoric îndelungat de artrită reumatoidă în tratament cu metotrexat, care a dezvoltat sarcoidoză, cu o prezentare neobișnuită și posibilă afectare cardiacă.

Cuvinte-cheie

sarcoidoză • artrită reumatoidă • suprapunere • autoimun

Introduction

Sarcoidosis is a systemic granulomatous disease that most commonly affects the mediastinal lymph nodes, lungs, skin, eyes, liver and rarely the heart and nervous system. It is determined by an abnormal T lymphocyte and macrophage activation (1). The aetiology and pathogenesis of sarcoidosis are not entirely understood, although early and more recent studies suggest a cellular immune response triggered by an infectious, occupational or environmental agent in genetically susceptible individuals (2,3). Sarcoidosis is a great imitator, showing overlapping clinical features with various rheumatological diseases. Rheumatoid

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arthritis (RA) is a primary connective tissue disorder that causes chronic inflammation manifested by erosive synovitis and extra-articular involvement. Despite the fact that sarcoidosis can coexist with rheumatological diseases such as Sjögren syndrome (4) and systemic lupus erythematosus (5), it has rarely been reported to occur alongside RA.

We present a rare case of sarcoidosis with an unusual presentation in a patient with a long history of RA taking an immunosuppressive medication with shown efficacy in sarcoidosis.

Case presentation

A 67-year-old non-smoking woman presented with a 1-month history of dry cough, dyspnoea and fatigue; 3 days of 38˚ fever at the onset; and heart palpitations.

The patient has a 15-year history of seropositive RA treated with 15 mg of methotrexate weekly, a 5-year history of rare episodes of paroxysmal atrial fibrillation; autoimmune thyroiditis with hypothyroidism, compensated with L thyroxine; osteoporosis; and obesity.

The physical examination revealed no significant abnormalities except mild hand and foot deformities, tenderness on joint palpation and morning stiffness.

The chest radiography performed at baseline was interpreted as pneumonia, and she received two courses of empirical antibiotics for 15 days with a slight improvement in her symptoms, emphasising a right-sided enlarged hilum and a consolidation area in the right middle lung field at the repeated chest radiography (Figure 1).

The chest high-resolution computer tomography (HRCT) revealed a solid mass in the right hilum with compression over the B4, B7 and B8 bronchi; a consolidation area in the middle lobe; a 2.3-cm-diameter subcarinal lymph node; multiple pulmonary nodules of about 6 mm in size with random distribution, some of them with a ground glass halo; and no signs of adenopathy in the left hilum (Figures 2A and 2B).

Based on her clinical presentation and imaging data, it was deemed necessary to consider a differential diagnosis list of entities comprising lymphoma, bronchopulmonary carcinoma, granulomatous infection, carcinoid tumour and lung metastases. Considering the high likelihood of a malignancy, a bronchoscopy was imperative. The endoscopic examination revealed no changes on the left side, while on the right side, the medium lobar and the B4 bronchi were narrowed, with signs of mucosal hypertrophy and a concentrically narrowed lumen that impeded the bronchoscope passage in the B7 bronchus. A brush biopsy, transbronchial biopsy and bronchial aspirate were performed, with unrevealing histopathological results. The bronchial aspirate did not show any signs of nonspecific infection. Moreover, it tested negative for acid-fast bacilli and XpertMBT.

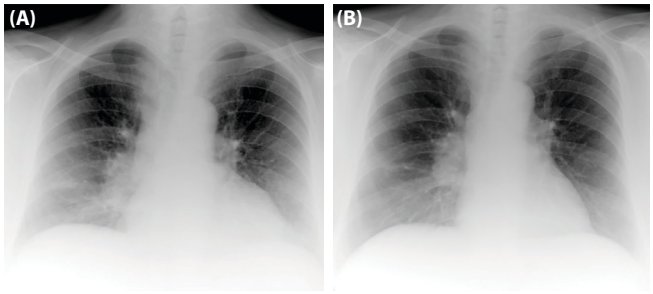


Figure 1. (A) PA chest radiography at the onset of lung symptoms, with right-sided parahilar infiltration and a lower zone linear opacity, interpreted as pneumonia. (B) PA chest radiography performed after 15 days of antibiotic treatment showed an enlarged hilum with a cyclic contour on the right side and a consolidation area in the right middle lung field. PA, posteroanterior.

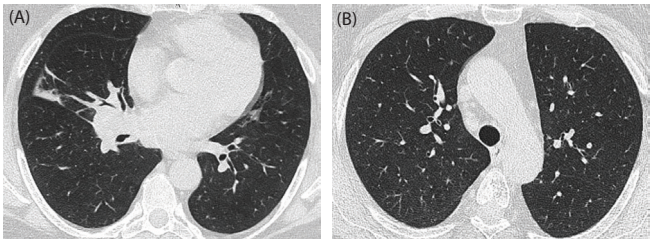


Figure 2. (A,B) – Axial images of chest HRCT at baseline showing a solid mass in the right hilum with compression over the B4, B7 and B8 bronchi; a consolidation area in the middle lobe; a 2.3-cm-diameter subcarinal lymph node; multiple pulmonary nodules of about 6 mm in size with random distribution, some of them with a ground glass halo; and no signs of adenopathy in the left hilum. HRCT, high-resolution computer tomography.

A contrast chest CT performed 3 months after the initial computer tomography revealed a progression of the initial lesions (Figures 3A and 3B). Thus, a video-assisted thoracoscopic (VATS) lung biopsy was recommended. During the biopsy procedure, a hilar lymph node and a lung specimen were obtained.

Due to more frequent palpitations accompanied by syncopal episodes shortly after the surgical procedure, she was referred to a cardiologist. A Holter ECG found tachycardia-bradycardia syndrome, sick sinus syndrome, episodes of sinoatrial block with 4-s pauses and paroxysmal atrial fibrillation. It is worth mentioning that none of these changes were present in a previous Holter ECG performed a year ago (Figure 4).

The echocardiography showed a left ventricular diastolic dysfunction and 40 mmHg systolic pressure of the pulmonary artery. A cardiac MRI with gadolinium was recommended, but due to financial considerations, it was not performed, so a pacemaker was implanted.

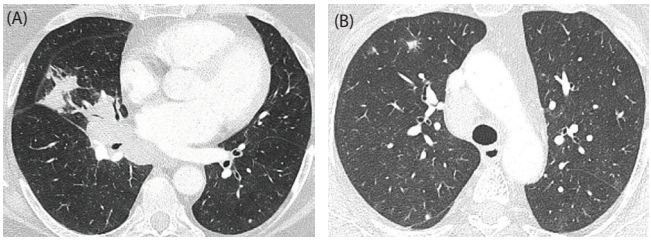
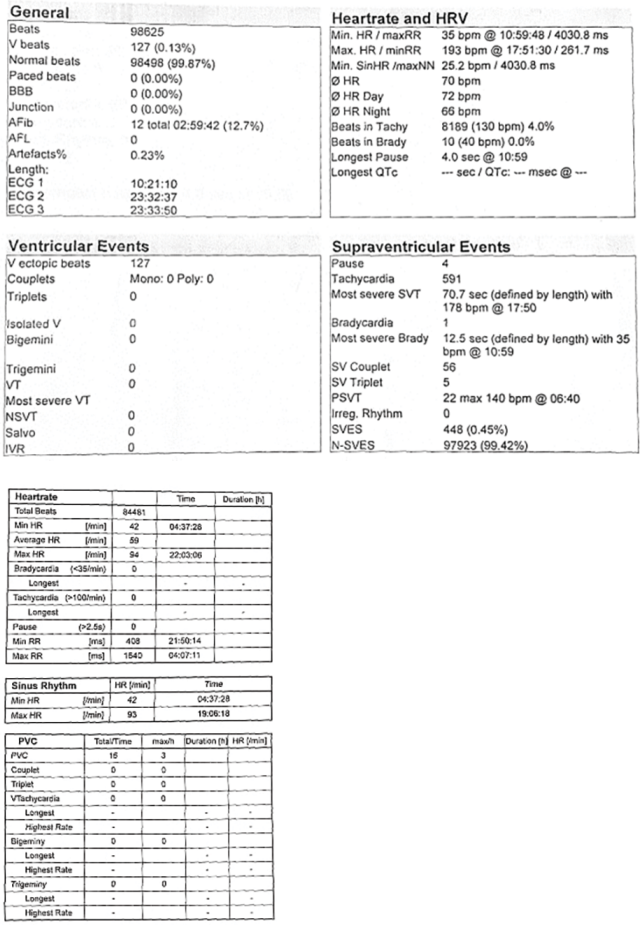


Figure 3. (A,B) – Contrast chest HRCT performed 3 months after the initial CT revealed progression of the initial lesions with an increasing number and size of lymph nodes in the mediastinum: paratracheal lymph nodes till 30 mm and mediastinal lymph nodes till 36 mm, with no contrast accumulation in the pathological areas. The right hilum is significantly enlarged, with the solid mass narrowing the previously mentioned lobar bronchi. The spiculated margin consolidation area in the medium lobe has increased in size. On image B, there are multiple nodules in the lung parenchyma of 13 mm in diameter with a ground glass halo. CT, computer tomography; HRCT, high-resolution computer tomography.



General

Beats	98625
V beats	127 (0.13%)
Normal beats	98498 (99.87%)
Paced beats	0 (0.00%)
BBB	0 (0.00%)
Junction	0 (0.00%)
AFib	12 total 02:59:42 (12.7%)
AFL	0
Artefacts%	0.23%
Length:	
ECG 1	10:21:10
ECG 2	23:32:37
ECG 3	23:33:50

Heartrate and HRV

Min. HR / maxRR	35 bpm @ 10:59:48 / 4030.8 ms
Max. HR / minRR	193 bpm @ 17:51:30 / 261.7 ms
Min. SinHR /maxNN	25.2 bpm / 4030.8 ms
Ø HR	70 bpm
Ø HR Day	72 bpm
Ø HR Night	66 bpm
Beats in Tachy	8189 (130 bpm) 4.0%
Beats in Brady	10 (40 bpm) 0.0%
Longest Pause	4.0 sec @ 10:59
Longest QTc	--- sec / QTc: --- msec @ ---

Ventricular Events

V ectopic beats	127
Couplets	Mono: 0 Poly: 0
Triplets	0
Isolated V	0
Bigemini	0
Trigemini	0
VT	0
Most severe VT	
NSVT	0
Salvo	0
IVR	0

Supraventricular Events

Pause	4
Tachycardia	591
Most severe SVT	70.7 sec (defined by length) with 178 bpm @ 17:50
Bradycardia	1
Most severe Brady	12.5 sec (defined by length) with 35 bpm @ 10:59
SV Couplet	56
SV Triplet	5
PSVT	22 max 140 bpm @ 06:40
Irreg. Rhythm	0
SVES	448 (0.45%)
N-SVES	97923 (99.42%)

Heartrate

			Time	Duration [h]
Total Beats		84481		
Min HR	[/min]	42	04:37:28	
Average HR	[/min]	59		
Max HR	[/min]	94	22:03:06	
Bradycardia	(<35/min)	0		
Longest			-	-
Tachycardia	(>100/min)	0		
Longest			-	-
Pause	(>2.5s)	0		
Min RR	[ms]	408	21:50:14	
Max RR	[ms]	1540	04:07:11	

Sinus Rhythm		HR [/min]	Time
Min HR	[/min]	42	04:37:28
Max HR	[/min]	93	19:06:18

PVC	Total/Time	max/h	Duration [h]	HR [/min]
PVC	16	3		
Couplet	0	0		
Triplet	0	0		
VTachycardia	0	0		
Longest	-		-	-
Highest Rate	-		-	-
Bigeminy	0	0		
Longest	-		-	-
Highest Rate	-		-	-
Trigeminy	0	0		
Longest	-		-	-
Highest Rate	-		-	-

Figure 4. Holter ECG results. On the upper panel, Holter ECG results on the occasion of syncopal episodes documented a tachycardia-bradycardia syndrome, sick sinus syndrome, episodes of sinoatrial block with 4-s pauses and paroxysmal atrial fibrillation. On the lower panel, Holter ECG results from 1 year prior to syncopal episodes show the absence of these cardiac rhythm abnormalities.

While the patient was in the cardiology service, we had the histopathological results of the lung biopsy, which highlighted sarcoid granulomas with lymphocytic infiltration in the lung tissue and the lymph node (Figure 5). The immunohistochemical staining ruled out lymphoma, while the Ziehl–Nielson coloration was negative for acid-fast bacilli.

A month after the VATS biopsy, a low-grade fever for about a week, dry cough and MRC2 dyspnoea reoccurred. There was no skin discoloration, but on palpation, she presented subcutaneous nodules over the thighs and arms, which the patients noticed for about a month, and no peripheral lymph nodes. Lung auscultation was normal, with an oxygen saturation (SaO_2) of 99%.

Laboratory findings indicated an inflammatory syndrome with a six-fold increase in C reactive protein, a 1.5-fold increase in alkaline phosphatase, normal transaminases and slightly elevated serum and urine calcium levels. A Quantiferon test was negative (Table 1). Lung function showed a mild restriction and a moderately reduced DLCO.

Considering the long-standing history of RA with only mild deformities of the hands, a reassessment by a rheumatologist was imposed. The patient was recommended a 2-week withdrawal of methotrexate while waiting for the laboratory results (Table 1): the rheumatoid factor showed an eight-fold increase, anti-CCP showed a five-fold increase and ANA, Anti-DNAds, Anti-SSA, Anti-SSB, ANCA-MPO and ANCA – PR3 were negative, while the hand radiography emphasised periarticular osteoporosis; Ist metacarpophalangeal joint dislocation, with intraarticular space narrowing; and small cystic opacities (Figure 6).

The temporary methotrexate withdrawal resulted in the worsening of joint pain and morning stiffness. Thus, based on clinical, radiological and serological markers, she was confirmed to have low-activity seropositive RA.

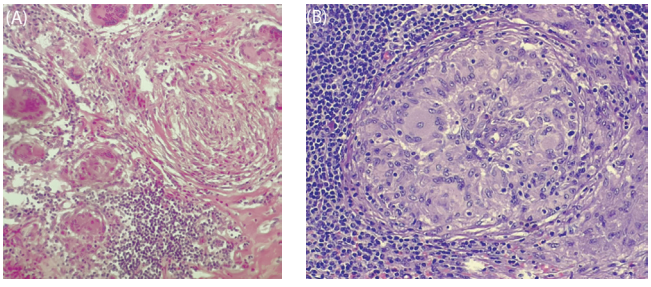


Figure 5. Histopathological aspect. (A) Lung specimen showing noncaseating epithelioid granulomas with Langhans giant cells. (B) Lymph node specimen showing a noncaseating epithelioid granuloma containing multiple Langhans giant cells.

Finally, the patient was diagnosed with pulmonary sarcoidosis with skin involvement, calcium metabolism alteration and probably cardiac sarcoidosis with concomitant

Table 1. Laboratory findings and lung function

Laboratory test		**Serology for collagen diseases**	
Complete blood count	Normal	Rheumatoid factor	64 (0–8 IU/mL)
Angiotensin-converting enzyme	12 (12–68 U/L)	Anti-CCP	106 (0–20 IU/mL)
C reactive protein	36 (0–6 mg/L)	ANA	Negative
Alkaline phosphatase	306 (0–240 U/L)	Anti-DNAds	Negative
ALAT	15 (0–42 U/L)	Anti-SSA	Negative
ASAT	15 (0–37) U/L	Anti-SSB	Negative
Serum calcium	3.01 (2.07–2.57 mmol/L)	ANCA-MPO	Negative
Urinary calcium	7.8 (2.25–7.5 mmol/L)	ANCA – PR3	Negative
Quantiferon test	Negative	LE cells	Negative
Lung function	FVC – 82%, FEV1 – 94%, FEV1/FVC – 92%, RV – 128%, TLC – 96%, DLCO – 57%		

ALAT, Alanine Aminotransferase; ASAT, Aspartat Aminotransferase; Anti-CCP, Anti–cyclic citrullinated peptide; ANA, Antinuclear antibodies; Anti-DNA ds, Anti-double-stranded deoxyribonucleic acid antibodies; Anti-SSA, anti–Sjögren's-syndrome-related antigen A; Anti-SSB, anti–Sjögren's-syndrome-related antigen B; ANCA-MPO, myeloperoxidase anti-neutrophil cytoplasmic antibodies; ANCA-PR3, proteinase 3 anti-neutrophil cytoplasmic antibodies; LE cells, lupus erythematosus cells; FVC, Forced Vital Capacity; FEV1, Forced expiratory volume in the first second; FEV1/FVC, Tiffeneau index; RV, Residual volume; TLC, Total Lung Capacity; DLCO, diffusing capacity of the lungs for carbon monoxide.



Figure 6. Direct hand radiography showing periarticular osteoporosis, Ist metacarpophalangeal joint dislocation, intraarticular space narrowing and small cystic opacities.

low-activity seropositive RA and was assigned 20 mg of methylprednisolone a day with a weekly administration of 15 mg of methotrexate. During her follow-up period, she did not show any new syncope episodes, the HRCT at 6 months demonstrated a complete resolution of the lung lesions (Figures 7A and 7B), and the lung function showed slightly improved static and dynamic volumes, while gas diffusion remained stable (FVC – 97% FEV1 – 95%, FEV1/FVC – 82%, RV – 160%, TLC – 113 %, DLCO – 59.3%).

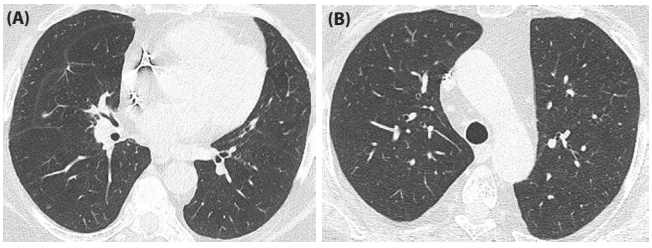


Figure 7. (A,B) Chest HRCT after 6 months of methylprednisolone showing a significant reduction of hilar adenopathy on the right, the consolidation area disappeared, and there were no signs of nodular opacities all over the lung fields. HRCT, high-resolution computer tomography.

Discussions

Sarcoidosis is a granulomatous inflammatory disease of unknown cause. Historically, it has been considered that an antigen drives an exaggerated inflammatory response in sarcoidosis, although there is not enough evidence supporting this hypothesis (6). More recent studies describe the role of self-antigens suggesting the autoimmune feature of sarcoidosis (7). Nevertheless, the clinical presentation of sarcoidosis hardly resembles an autoimmune disease, although some symptoms such as erythema nodosum, arthralgia and fatigue may imitate rheumatological diseases (8,9). Previously, the co-occurrence of sarcoidosis with autoimmune disorders has been reported, particularly autoimmune thyroiditis, Sjögren syndrome and ankylosing spondylitis (4,10,11), whereas the association with RA is a rare finding.

Both RA and sarcoidosis involve the musculoskeletal system, with RA typically affecting the wrist and metacarpophalangeal and proximal interphalangeal joints. By contrast, sarcoidosis can demonstrate either self-limiting polyarthritis in its acute form or unilateral or bilateral ankle, knee and wrist joints seen more rarely in chronic evolution, which can progress to joint deformity (12). Both diseases can cause destructive erosive changes, periarticular osteoporosis and joint space narrowing on X-ray (13). Despite the long history of RA diagnosis in our patient, judging only by minimal hand deformity on inspection, it seemed unlikely that we could confirm this diagnosis. Nonetheless, the recurrence of joint pain and morning stiffness after methotrexate withdrawal, the typical changes seen on direct X-ray and the serological markers (significantly elevated rheumatoid factor and anti-CCP), all indicated RA with minimal activity.

Despite the shared clinical signs, sarcoidosis and RA are two distinct diseases, even in their genetic background. While RA is associated with HLA-DR4 (14), in sarcoidosis patients, HLA-DR5 is more commonly found, and HLA-B8 in acute forms of sarcoidosis is associated with self-limiting disease (15). A test that will identify the presence of both alleles in a single patient will prove the coexistence of two diseases.

Since it lacks a pathognomonic diagnostic test, sarcoidosis is typically considered an exclusion diagnosis, even in biopsy-supported cases. Since our patient was immunosuppressed for a significant amount of time and lived in a TB-endemic area, tuberculous infection was to be considered (16). However, we did not find signs of active or latent tuberculosis in our patient. Another diagnostic pitfall was the atypical appearance of lung lesions with unilateral involvement with bronchial compression, commonly seen in malignancies and lymphoma, and extremely rare in sarcoidosis. An earlier study on a cohort of 2500 sarcoidosis patients reported only 18 cases that demonstrated bronchial stenosis (17), with a similar incidence in a more recent publication (18). It is worth mentioning about the so-called tumour-related sarcoid reaction, which can be found either at the tumour primary site in the draining lymph nodes of a solid tumour or in distant sites (mostly the spleen, liver or bone marrow) (19). We ruled out the malignant origin of the disease based on the morpho-pathological aspect and immunohistochemical staining of the biopsy samples.

Moreover, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis should be on the list of alternative causes of granulomatous disease of inflammatory origin. In addition, non-caseating granulomas are also a possible symptom of inflammatory bowel disease, notably Crohn's disease (20). The negative ANCA results, absence of eosinophils in the bronchoalveolar lavage and in the complete blood count and the lack of gastrointestinal symptoms in our patient make these entities a less probable diagnosis. Therefore, cases with atypical presentation need a comprehensive approach and only a careful serological, microbiological and histologic examination with added immunohistochemical staining can help clarify the diagnosis.

About 5% of patients with sarcoidosis have clinical symptoms, while imaging and autopsy studies indicate that roughly 25% of patients with extracardiac sarcoidosis appear to have clinically silent myocardial involvement (21). Most commonly affected is the left ventricular free wall, followed by the basal segment of the ventricular septum, the right ventricular free walls and, less frequently, the atrial walls (22). It may be a cause of severe cardiac failure, but its feature is conduction anomalies and tachyarrhythmias, notably ventricular arrhythmia and less frequently atrial arrhythmia (23). Because this complication can arise in any patient with sarcoidosis, complaints of dizziness, episodes of syncope, palpitations or ECG abnormalities should prompt a cardiac assessment. We can only speculate that our patient had another rare manifestation like cardiac sarcoidosis, based on the clinical condition, which worsened significantly in the year of diagnosis with many cardiac events on the Holter ECG that were not present on the Holter ECG a year before. A more accurate investigation into cardiac sarcoidosis diagnosis with gadolinium cardiac MRI is lacking, which, unfortunately, was impossible to perform due to the patient's financial condition. Moreover, the addition of corticosteroid to the treatment temporally coincided with the implantable cardioverter defibrillator insertion, which could be a bias in supporting cardiac sarcoidosis as a potential diagnosis in this case.

Despite differences in the genetic background, studies have highlighted that sarcoidosis and autoimmune diseases such as RA, psoriasis and inflammatory bowel diseases share Th1 as a pattern of inflammation and also Th17 cells, which play a pro-inflammatory role (24,25). In such a way, excessive Th1 cytokine secretion, found in both entities, can trigger either Th17 synovial tissue infiltration, as seen in RA, or granuloma formation, as seen in sarcoidosis. Contrary to this opinion, Judson et al. (5) suggested that autoimmune disorders themselves have a potential to induce a granulomatous inflammation, having the highest confidence of this affirmation when there is a single organ involved in sarcoidosis. Therefore, since our patient showed granulomas both in the lung and the lymph nodes, as well as altered calcium metabolism, it proves the systemic nature of sarcoidosis, and not a local sarcoid reaction.

Although methotrexate is a drug used as a steroid-sparing agent for sarcoidosis, as a second-line immunosuppressant, it tends to offer a lower response (26), thus explaining the possibility of the disease to occur in a patient receiving one of sarcoidosis treatment options.

Conclusions

Sarcoidosis is a great mimicker, and diagnosing it can be challenging. While sarcoidosis is an exclusion diagnosis, an unusual presentation of a rare disease with an infrequent association, such as RA, urges a comprehensive assessment by an experienced multidisciplinary team using various diagnostic tools.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Informed consent statement

Informed consent was obtained from the involved subject.

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