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Therapeutic challenges in a case of sarcoidosis

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Abstract

English:

Sarcoidosis is a chronic systemic inflammatory disease with unknown etiology, whose diagnosis is based on suggestive symptoms/imaging, histopathological examination with non-caseous granuloma, and exclusion of other etiologies. Corticosteroid therapy is the treatment of choice for moderate/severe forms, but medication intolerance or unfavorable evolution may require immunomodulatory therapy. A 40-year-old patient known with poly-allergy was hospitalized for resting dyspnoea, dry cough, night sweats, and itching. Objective examination identifies roughened breathing, wheezing and SpO_2 = 98%. Spirometry shows a medium mixed ventilatory dysfunction. Computed tomography (CT) describes multiple mediastinal lymphadenopathies and inhomogeneous hepatomegaly. Osteomedullary biopsy refutes the suspicion of lymphoma. Bronchoscopy detects bronchial hypervascularization. Due to the suggestive imaging context, a transbronchial biopsy was performed (EBUS-TBNA) from the mediastinal lymphadenopathy. Histopathological examination suggested sarcoidosis: granulomas with epithelioid histiocytes, without caseous necrosis, associated with Langerhans cells and lymphocytes. We initiated corticosteroid therapy, but the patient had an allergic reaction that required the interruption of treatment and administration of methotrexate. After eight months, the clinical and imaging aspect worsened, and we replaced the treatment with cyclophosphamide. However, side effects occurred after a few months, it was replaced with azathioprine. The patient's condition deteriorates significantly with desaturation. We requested a consultation with the 'Sarcoidosis Center' in Rotterdam, which recommended treatment with anti-TNF-α or human immunoglobulin. The patient shows a slightly favorable evolution under human immunoglobulin. The poly-allergy and drug intolerance, including corticosteroid therapy, led to the initiation of immunomodulatory therapy for a young patient with moderate/severe sarcoidosis. The choice of medication was difficult due to the side effects.

Keywords

sarcoidosis • drug poly-allergy • immunomodulator therapy • human immunoglobulin

Provocări terapeutice la un caz de sarcoidoză

Rezumat

Romanian:

Sarcoidoza este o boală inflamatorie cronică sistemică de etiologie neprecizată a cărei diagnostic se bazează pe simptomatologie, imagistică sugestivă, examen histopatologic cu inflamație granulomatoasă non-cazeoasă și excluderea altor etiologii. Corticoterapia reprezintă tratamentul de elecție în formele medii/severe, însă intoleranța medicației sau lipsa evoluției favorabile necesită terapie imunomodulatoare. Pacientă în vârstă de 40 ani, cunoscută cu polialergie medicamentoasă se internează pentru dispnee de repaus, tuse seacă, transpirații nocturne și prurit. Examenul obiectiv identifică respirație înăsprită, raluri sibilante, SpO_2 = 98%. Spirometria arată o disfuncție ventilatorie mixtă formă moderată. Examinarea CT (tomografie computerizată) descrie multiple adenopatii mediastinale și hepatomegalie inomogenă. Biopsia osteomedulară infirmă suspiciunea de limfom. Bronhoscopia decelează hipervascularizație bronșică. Datorită contextului imagistic sugestiv, s-a efectuat o biopsie transbronșică (EBUS-TBNA) din adenopatia mediastinală. Examenul histopatologic a fost sugestiv pentru sarcoidoză: granuloame cu histiocite epitelioide, fără necroză cazeoasă, asociate cu celule Langhans și limfocite. S-a inițiat corticoterapie, însă pacienta prezintă reacții alergice, necesitând întreruperea tratamentului și administrarea de metotrexat. După opt luni aspectul clinico-imagistic se agravează iar tratamentul se înlocuiește cu ciclofosfamidă. După câteva luni apar efecte adverse, motiv de înlocuire cu azatioprină. Starea pacientei se degradează semnificativ cu desaturări importante. S-a solicitat consult în "Centrul de Sarcoidoză" din Rotterdam care a recomandat tratament cu anti-TNF-α sau imunoglobulină umană. Pacienta prezintă o evoluție ușor favorabilă sub tratamentul cu imunoglobulină umană. Polialergia și intoleranța medicamentoasă inclusiv la corticoterapie a făcut necesară inițierea terapiei imunodulatoare la o pacientă tânără cu formă medie/severă de sarcoidoză. Alegerea medicației a fost dificilă datorită efectelor adverse.

Cuvinte-cheie

sarcoidoză • polialergie medicamentoasă • imunomodulatoare • imunoglobulină umană

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Introduction

Sarcoidosis is a chronic systemic inflammatory disease and it most often affects the lungs and intrathoracic lymph nodes (90%), but the lesions can occur in any other organ, associated or not with lung damage [1]. The etiology is unknown but multiple genetic and environmental risk factors are recognized which are capable of initiating immunological reactions with multi-organ damage.

The clinical manifestations are varied, evolving from asymptomatic forms to acute/subacute forms (Löfgren or Heerfordt syndrome) or chronic with possible extrapulmonary damage: peripheral and deep lymphadenopathy, pulmonary interstitial damage (with ventilatory and gas transfer dysfunctions), ocular sarcoidosis (uveitis, glaucoma and blindness), cardiovascular sarcoidosis (myocarditis, arrhythmias and vasculitis), sarcoidosis in the central nervous system (CNS; central or peripheral neuropathy and meningitis), cutaneous sarcoidosis (sarcoids and lupus pernio) [2–7].

An aberrant immune response caused by an unknown antigen is thought to exist in people having a genetic predisposition, moreover, an excess of T cell mediated reactions. Sarcoidosis associates with the increase of CD4+ T lymphocytes, increase in CD4/CD8 ratio (visible in the bronchoalveolar lavage) and increase of proinflammatory cytokines (IFN-γ, IL-2, IL-12 and TNF-α) [8,9].

Further, an exaggerated/denatured B cellular response with immunoglobulin hyperproduction is associated with the presence of elevated levels of HLA class I and elevated serum angiotensin-convertase-enzyme (ACE) [10].

According to the first guide developed by the American Thoracic Society (ATS), the diagnosis and treatment of sarcoidosis is not yet fully standardized but is based on targeted recommendations: suggestive symptoms according to organic damage, histopathological confirmation of non-necrotic granulomatous inflammation and exclusion of other causes of the disease [11].

Currently, mediastinal lymph node biopsy by mediastinoscopy is not recommended (invasive investigation with complications, 98% yield), it is favorable to perform endobronchial ultrasound (EBUS) with transbronchial needle aspiration (TBNA) (less invasive, cheaper, accessible, with 87% yield) [12,13].

Sarcoidosis granuloma has an appearance of immune cell agglomeration without central caseous necrosis, with central aggregates of epithelioid histiocytes, multinucleated cells (smaller and with fewer nuclei than those of tuberculosis) and T lymphocytes [14].

The World Association for Sarcoidosis and Other Granulomatous Disorders (WASOG) recommends corticosteroid therapy as first line treatment, but the occurrence of adverse effects, drug intolerance or development of corticosteroid resistance may induce the use of immunomodulatory preparations [15].

Case report

We present the case of a 40-year-old female patient, former smoker (six packs-year), who was admitted to the Pulmonology Clinic accusing dyspnoea, dry cough, wheezing, night sweats and itching. Medical history included a drug poly-allergy. The physical examination revealed a cervical lymphadenopathy (2 cm × 3 cm, mobile, soft, painless), difficult breathing, wheezing and diffuse crackles, rest SpO_2 = 98% in the ambient air. Chest radiography revealed an enlarged mediastinum with bilateral paratracheal and hilar lymphadenopathy (Figure 1). Respiratory function tests showed a medium mixed ventilatory dysfunction [forced vital capacity (FVC): 45%, forced expiratory volume in one second (FEV1): 57%]. The Koch bacillus was absent on direct microscopy examination and later on sputum culture. We do not identify pathological changes in the complete blood count, coagulation tests, or hepatic and renal function tests.

Bronchoscopy revealed an aspect of bronchial hypervascularization with modest secretions and rare Gram-positive cocci were isolated from the bronchial aspirate. Koch bacillus was negative on microscopy and culture from bronchial aspirate.



Figure 1. Chest radiography – enlarged mediastinum with bilateral paratracheal and hilar lymphadenopathy.

Computed tomography (CT) examination described multiple paratracheal, subcarinal, and hilar lymphadenopathy and inhomogeneous hepatomegaly (Figure 2). Osteomedullary biopsy excluded the diagnosis of lymphoma. The level of ACE was slightly increased (58.6 U/L). Immunological determinations performed to identify a systemic inflammatory disease were negative (Table 1). The patient refused surgical excision biopsy of cervical lymphadenopathy. Short-term antibiotic treatment and inhaled corticosteroid therapy associated with long-acting beta-agonist (ICS + LABA) were initiated for the present symptomatology and the investigations were continued.

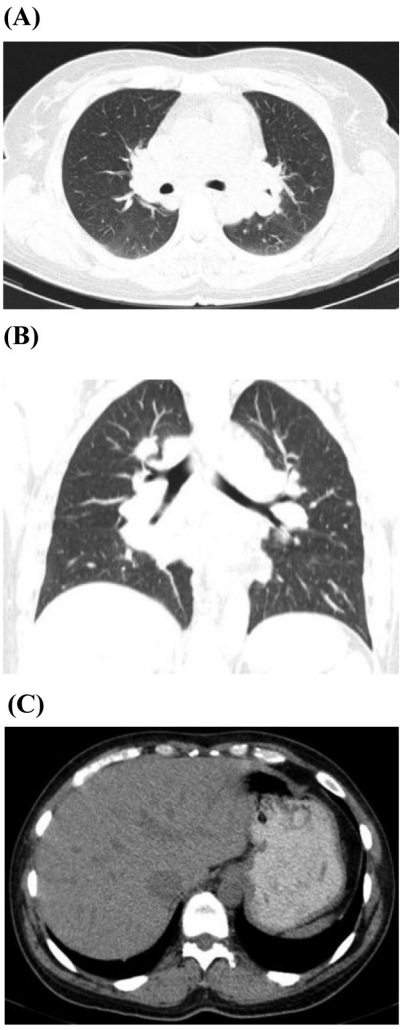


Figure 2. Thoraco-abdominal CT – multiple paratracheal, subcarinal, and hilar lymphadenopathy associated with diffuse interstitiale fibrosis (**A**, **B**). Inhomogeneous hepatomegaly (**C**).

We recommended EBUS-TBNA to exclude malignancies or tuberculosis and for the histopathological confirmation of suspected sarcoidosis. Histopathological examination revealed the presence of multiple non-necrotic epithelioid granulomas associated with lymphocyte agglomeration, very suggestive for sarcoidosis.

The patient was readmitted to the hospital to introduce systemic corticotherapy (the most common treatment for symptomatic sarcoidosis with decreased respiratory function). However, she had a severe allergic reaction after oral corticosteroid administration with skin rash, tachycardia, and suffocation; it was necessary to discontinue the treatment. She started the new treatment with Methotrexate (20 mg/week) associated with well-tolerated ICS + LABA. The evolution was initially favorable for eight months. The symptoms returned insidiously, and the reassessment found worsening dyspnoea, SpO_2 = 94%, an increase in mediastinal lymphadenopathy, interstitial opacities with fibrotic aspect and bilateral pelvic lymphadenopathy (Figure 3). The gynecological examination did not find any particular pathology. Another lymph node biopsy was recommended, but the patient refused. We decided on CT monitoring. The persisting symptoms and the progression of the disease required the replacement of treatment with cyclophosphamide 200 mg iv/month.

After five months of slightly favorable evolution under cyclophosphamide, the patient complains of nausea, vomiting, and pruritus. Total IgE 34.8 IU/mL and allergic testes (allergen mix panel) were within normal limits. The CT examination reveals the persistence of mediastinal lymphadenopathy associated with diffuse interstitial fibrosis and the disappearance of pelvic lymphadenopathy (Figure 4). Cyclophosphamide was replaced with azathioprine 50 mg 1 tab/day.

After a year, we attempted to reintroduce cyclophosphamide, but the patient developed an allergic reaction with facial

Table 1. Immunological determinations performed to identify a systemic inflammatory disease with negative results.

Analyse	Result	Biological reference range
Anti-nuclear anti-ds DPN antibodies (SLE-latex agglutination)	Negative	Negative
ASLO-Latex	Negative	<200 UI/mL Negative/>200 UI/mL Positive
Rheumatoid factor - Latex	Negative	<8 UI/mL Negative/>8 UI/mL Positive
Procalcitonin	Negative	<0.5 ng/mL Negative/>0.5 ng/mL Positive

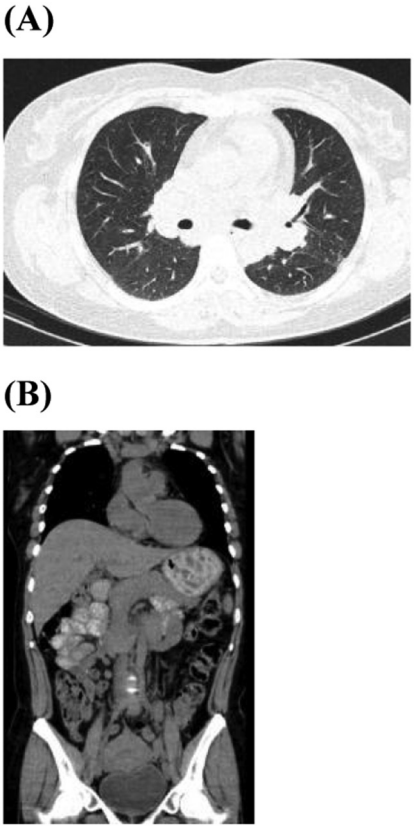


Figure 3. Thoraco-abdominal CT – increased mediastinal lymphadenopathy, interstitial opacities (fibrotic aspect) (**A**). Bilateral pelvic lymphadenopathy (**B**).

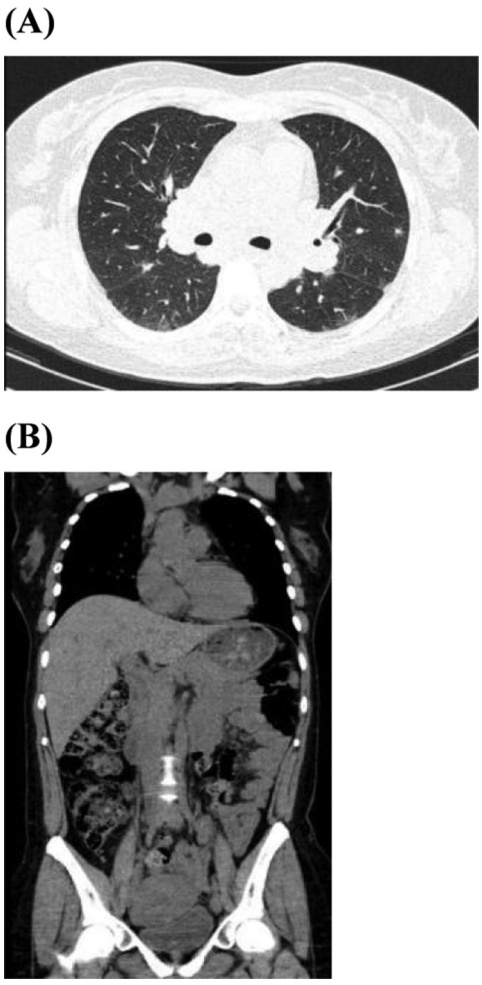


Figure 4. Thoraco-abdominal CT – persistence of mediastinal lymphadenopathy, diffuse interstitial fibrosis (**A**). Disappearance of pelvic lymphadenopathy (**B**).

erythema and angioedema. The administration was stopped immediately with the recommendation of not to be introduced ever.

In December 2018, the patient's condition deteriorated with worsening dyspnoea, significant desaturation (SpO_2 = 90% at rest, 87% on exertion) and tachycardia.

We requested consultation from the WASOG and the Center of Excellence in Rotterdam (Erasmus University Medical Center, Rotterdam, Netherlands). They recommended the initiation of anti-TNF-α therapy. Immunomodulator medication was not available and it was replaced with human immunoglobulin (Intratect 600g at three months, three vials of 100g iv. on two consecutive days), along with continued oxygen therapy (2–4 L/min 16–18 h/day) + ICS + LABA, superinfection prevention with influenza vaccination. At the subsequent controls, the symptomatology was slightly improved but with almost identical imaging findings (Figure 5).

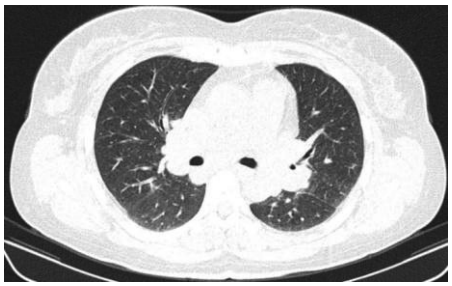


Figure 5. Thoracic CT 2019 – bilateral hilar and mediastinal adenopathy, diffuse interstitial fibrosis.

In Romania, the treatment of sarcoidosis with anti-TNF-α is challenging to access. Human immunoglobulin was administered in the Rheumatology Clinic. The administration was sometimes intermittent, especially in the current period of SARS-CoV-2 virus pandemic. The patient currently had stationary imaging with a symptomatic improvement and increased quality of life. Multidisciplinary re-evaluation

(pulmonology, cardiology, and rheumatology) is indicated with consideration for anti-TNF-α medication administration.

Discussions

Sarcoidosis in 85–95% of cases is characterized by mediastino-pulmonary lymphadenopathy, of which 50% are associated with extrathoracic localizations. Isolated extrapulmonary localizations (5–10%) without respiratory involvement are also possible [16]. Our patient had mediastinal, cervical and pelvic lymphadenopathy, interstitial pulmonary infiltrates and hepatomegaly. In evolution, the bilateral hilar and paratracheal lymphadenopathy can associate parenchymal infiltrates and diffuse fibrosis [17–19].

Sarcoidosis is characterized by well delimited micronodular opacities with perilymphatic, perilobular, septal, and subpleural localization. Atypical lesions are also possible in 25–30% of cases: isolated or unilateral lymphadenopathy, solitary lung nodules, 'ground glass' opacity, fibrocystic lesions, atelectasis, pleural effusion or 'honeycomb' pattern [19]. Our patient had both typical and atypical lesions.

Respiratory function tests express restrictive or mixed ventilatory dysfunction in the advanced stages with decreased DLCO (diffusing capacity for carbon monoxide). Initially, we can find obstructive dysfunction due to compression of the airways by lymph nodes or granulomas [1].

Elevated serum levels of ACE have a sensitivity of 40% in sarcoidosis, with low specificity being possible in 15% false positive reactions [11]. In our patient, ACE had slightly elevated values at repeated determinations.

EBUS-TBNA of the mediastinal/hilar lymph nodes was crucial for confirmation of the disease (according to the ATS 2020 indication) [20]. It allowed the differential diagnosis with other granulomatous diseases with micronodular images: tuberculosis or atypical mycobacteriosis, fungal infections (Aspergillosis, Cryptococcosis, Blastomycosis), histoplasmosis, Wegener's granulomatosis, carcinomatosis, foreign body granuloma [21].

Treatment is indicated in symptomatic patients with decreased lung function and radiological progression. In patients with predominantly pulmonary manifestations, corticosteroid therapy is effective in 50–90%, and its interruption leads to reactivation in 20–74% of cases [22]. Unfortunately, our patient developed unusual and severe reactions to systemic corticosteroid therapy.

The immediate hypersensitivity reaction to corticosteroid therapy is a rare entity with an unknown mechanism that may manifest as anaphylaxis, urticaria, and angioedema. It occurs more frequently with methylprednisolone and very rarely with inhaled fluticasone treatment [23].

Methotrexate is an alternative to patients with contraindication or refusal, side effects, intolerance, or corticoid resistance. Efficacy is superior to corticosteroids and has rare side effects [24]. Azothioprine's therapeutic indications are similar to methotrexate but associated with a higher rate of secondary infections [25].

Due to high toxicity, cyclophosphamide is used only for refractory sarcoidosis (especially cardiac or neurosarcoidosis) [26]. In the literature are described cases of delayed type allergic reaction after cyclophosphamide. The clinical manifestations are often interpreted as exacerbations of the underlying disease [27].

Biological agents (anti-TNF-α– e.g., adalimumab, infliximab) represent third-line therapy in sarcoidosis. They are effective in refractory cases for immunosuppressive therapy and have a well-proven safety profile. The role of TNF-α was recognised in the formation and maintenance of granulomas, which justifies the therapeutic indication in the refractory phases to the common treatment of sarcoidosis [28,29].

Conclusions

Sarcoidosis can be diagnosed later in the middle/advanced stages of the disease with a progressive evolution that is not responsive to treatment. EBUS-TBNA allowed the histopathological diagnosis of mediastino-pulmonary sarcoidosis. Treatment for sarcoidosis is an ongoing challenge, especially in the context of the combination of poly-allergy and drug intolerance or lack of therapeutic response. In this case, immunomodulator therapy may be helpful. In severe forms of the disease, a favorable evolution is associated with the relief of symptoms even in the absence of radiological/functional regression of fibrosis.

Ethical approval

The patient's consent was obtained before the publication of this article.

Conflicts of interest

None.

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