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Pneumologia

Combination with reserved prognosis: TB- rheumatoid arthritis

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Abstract

English:

As shown in a Spanish study, patients with rheumatoid arthritis (PAR) have a 4-fold increased risk of developing TB (tuberculosis) compared to the general population. Abruptly stopping anti-TNF (tumor necrosis factor α) agents after the development of TB could cause a paradoxical response leading to severe complications and death. We present the case of a 54 years old female patient with seropositive PAR since 2012 in treatment with biological therapy, which was diagnosed 10 years after the start of immunosuppressive treatment with miliary TB. She has had an unfavorable prognosis, dying after one month from the initiation of antituberculosis treatment due to septic shock. Therefore, it is very important to evaluate the bacillary status before initiating any immunosuppressive treatment.

Keywords

tuberculosis • rheumatoid arthritis • immunosuppressive treatment

Asociere cu prognostic rezervat: TB-poliartrita reumatoida

Rezumat

Romanian:

Asa cum evidentiaza un studiu din Spania, pacientii cu poliartrita reumatoida prezinta un risc de 4 ori mai mare de a dezvolta tuberculoza comparativ cu populatia generala. Oprirea brusca a terapiei cu agenti anti factor necrozant tumoral α dupa dezvoltarea tuberculozei, poate cauza un raspuns paradoxal, determinand complicatii severe, chiar deces. Prezentam cazul unei paciente in varsta de 54 de ani cu poliartrita reumatoida seropozitiva din 2012, in tratament cu terapie biologica, care a fost diagnosticata dupa 10 ani de la initierea tratamentului imunosupresor cu tuberculoza- forma miliara. Aceasta a prezentat un prognostic nefavorabil, cu deces dupa o luna de la initierea tratamentului antituberculos din cauza socului septic. Prin urmare, este foarte importanta evaluarea statusului bacilar inaintea initierii tratamentului imunosupresor.

Cuvinte-cheie

tuberculoza • poliartrita reumatoida • tratament imunosupresor

Introduction

Mycobacterium tuberculosis remains one of the major pathogens infecting approximately one-third of the population and is responsible for nearly 2 million deaths annually. It is known that rheumatological pathologies such as rheumatoid arthritis can be associated with an increased risk of association with tuberculosis, but it remains unknown what proportion of this risk comes from the immunologic disease itself and what proportion from immunosuppressive therapy. The latent form of tuberculosis can become active (about 10 per cent of the time) and a reactivated TB case can be fatal. Therefore, the patients with PAR should be screened for TB regularly. There are recommended test for TB like tuberculin skin test,

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interferon gamma release assay, sputum analysis and chest X-ray. (1) In the specialized literature, a lot of opportunistic and non-opportunistic infections are described in patients with PAR who follow treatment with the "anchor drugs" (methotrexate, azathioprine, cyclophosphamide, corticosteroids). An increased risk of developing active tuberculosis has been shown in patients with PAR receiving a mean prednisone dosage/day/year. With the introduction of biological therapy - inhibitors of TNFα in PAR, otherwise very effective, the development of tuberculosis was observed, TNFα representing a factor with a crucial role in the host's immune response (2). The production of TNFα by alveolar macrophages is essential in tuberculous granuloma formation, cytokine production, leukocyte recruitment and destruction of pathogens, in this case Mycobacterium tuberculosis. Anti-TNFα agents proved to determine a good control of the symptoms and the lowering or arrest of the disease progression. However, it has been recognized that the anti- TNFα agents associate an increased risk of reactivation of latent tuberculosis infection (LTBI). A rare fatal presentation of mycobacterial infection, miliary TB, can occur in patients under immunosuppressive treatment especially when anti-TNFα agents are combine with other non-biological therapy (3).

Case report

A 54 years old female, former smoker weaned for 15 years, with professional exposure, diagnosed in 2012 with rheumatoid arthritis, initially treated with Methotrexate and corticotherapy, then with Leflunomide and Adalimumab interrupted in June 2022 due to impaired renal function when she also performed in another medical center a CT scan (computed tomography) which highlighted multiple centrilobular "ground-glass" micronodules, disseminated in both lung areas, suggestive of pulmonary tuberculosis-miliary form (Figure 1) has been admitted in our Institute for dyspnea at moderate-low exertion, cough with mucous sputum, loss of appetite, weight loss and fatigue. She was also known with hepatitis C and high blood pressure. In addition, in the other medical center, infective endocarditis was suspected following a prolonged febrile syndrome and an echocardiography with an image suggestive for vegetation on mitral valve, for which the patient has undergone antibiotic treatment with Vancomycin. We mention that we did not have medical documents to establish whether the patient underwent treatment for hepatitis C.

On clinical examination, the following were observed: affected general condition, hemodynamically and respiratory stable, overweight, epigastric pain and right upper quadrant and vomiting.

The paraclinical investigations: the results from blood sample highlight nitrogen retention syndrome (increased creatinine=2.55mg/dL), low estimated glomerular filtration rate (22mL/min/1.73m$^{2)}$, mild microcytic hypochromic anemia (Hb=11.7g/dL), hyposideremia and *anti-HCV antibodies-positive.*

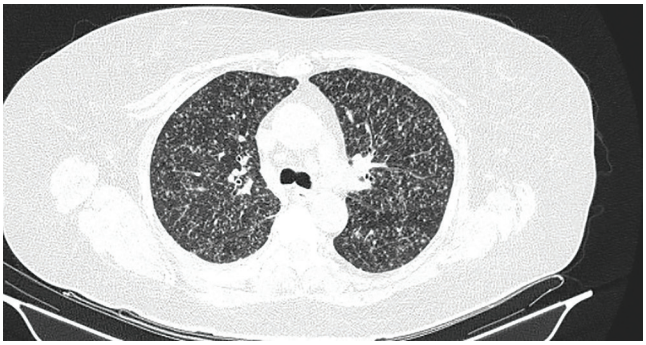
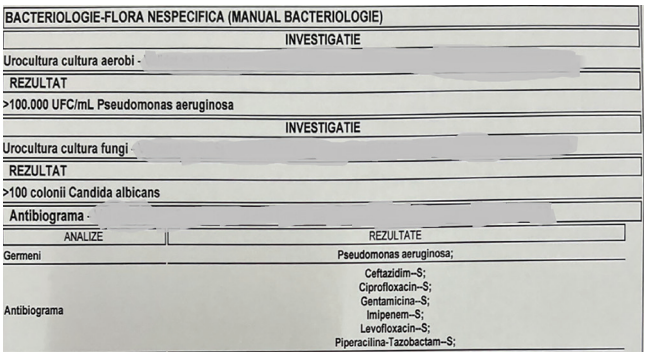


Figure 1. Computed tomography: multiple centrilobular "ground--glass" micronodules, disseminated in both lung areas, suggestive of pulmonary tuberculosis-miliary form.

The ECG tracing (electrocardiogram) showed sinus tachycardia and DI, aVL, V3-V6 T wave inversion. The transthoracic echocardiography showed signs of heart failure with moderate left ventricular systolic dysfunction, signs of ischemic heart disease, moderate mitral regurgitation and no direct or indirect signs of infective endocarditis were observed. Fibrobronchoscopy with bronchial aspirate was also performed for Mycobacterium tuberculosis bacteriology and GeneXpert test result was Mtb complex detected medium, drug-sensitive tuberculosis. Abdominal ultrasound showed an embedded stone in the gallbladder infundibulum.

The clinical and paraclinical investigations led to some diagnoses namely pulmonary tuberculosis-miliary form-Mtb complex detected medium, seropositive rheumatoid arthritis, high blood pressure, heart failure with moderate left ventricular systolic dysfunction, ischemic heart disease, moderate mitral regurgitation, hepatitis C was confirmed, cholelithiasis, chronic kidney disease and microcytic hypochromic anemia. *The evolution* was unfavorable, the patient did not tolerate the antituberculosis treatment for 3 weeks (Isoniazid-200mg, Rifampin-300mg, Pyrazinamide-1000mg, Ethambutol-800mg) presenting multiple adverse reactions during hospitalization, including enterocolitis with Clostridium difficile and drug-induced toxic hepatitis (the highest values of transaminases (TGO=372U/L, TGP=803U/L), but they decreased after stopping antituberculosis treatment). For the enterocolitis with Clostridium Difficile, Vancomycin 2.5mL every 6 hours, oral administration and Metronidazole 500mg, 1 bottle every 12 hours have been used for 10 days. The anemic syndrome persisted for which the patient received three blood transfusions (the lowest value of hemoglobin was 7 g/dL, which increased to 11g/dL after red blood cell transfusion). She also contacted a urinary infection with



BACTERIOLOGIE-FLORA NESPECIFICA (MANUAL BACTERIOLOGIE)

INVESTIGATIE

Urocultura cultura aerobi -

REZULTAT

>100.000 UFC/mL Pseudomonas aeruginosa

INVESTIGATIE

Urocultura cultura fungi -

REZULTAT

>100 colonii Candida albicans

Antibiograma -

ANALIZE	REZULTATE
Germeni	Pseudomonas aeruginosa;
Antibiograma	Ceftazidim–S; Ciprofloxacin–S; Gentamicina–S; Imipenem–S; Levofloxacin–S; Piperacilina-Tazobactam–S;

Figure 2. Antibiogram for Pseudomonas aeruginosa.

Pseudomonas aeruginosa and Candida albicans which were treated according to the antibiogram with Levofloxacin 500mg, once a day, orally and Fluconazole 150mg, once a day orally, both for 5 days. (Figure 2) But after 2 months from admission, the patient's condition suddenly deteriorated with severe metabolic acidosis (pH=6.7) and hyperlactacidemia (lactic acid=7.7mmol/L), a fact that has concurred with the moment when a computer tomography was performed. Later, the result of the computer tomography revealed bilateral pleural effusion, more on the right side, which associated pulmonary consolidation that almost entirely involved the right lower lobe. Unfortunately, the patient subsequently suffered an unsustainable cardio-respiratory arrest and death.

Discussions

Canadian researchers have shown through case-control studies a modestly increased risk of tuberculosis in patients receiving methotrexate and the rate of development of tuberculosis in people with rheumatologic pathology who are treated with either methotrexate or biological therapy is generally higher than in the general population. Other studies based on the development rate of tuberculosis in countries such as Spain, South Africa and Canada have shown that this rate is higher in patients who were prescribed methotrexate associated with corticosteroids or other immunosuppressants. The patient in the case report, at the initiation of treatment for rheumatoid arthritis received the combination with corticosteroids (4). Leflunomide can increase the susceptibility of tuberculosis reactivation, as it has an anti-inflammatory and immunomodulatory role. *Hočevar et al*. presents in "Leflunomide-associated tuberculosis?" 5 cases that developed tuberculosis during treatment with leflunomide. In 4 out of 5 cases, leflunomide was the only drug belonging to non-biological therapy (DMARDs- disease-modifying antirheumatic drugs), used at the time of symptomatology suggestive of tuberculosis and in 3 of the cases it was combined with corticosteroid therapy and in 1 case with methotrexate. In the case of patients who received the combination, the contribution of both drugs to the occurrence of tuberculosis cannot be excluded. Also, at the patient in the case report, methotrexate was replaced with leflunomide due to adverse gastrointestinal reactions, and when tuberculosis was diagnosed, she was treated with leflunomide (5). It is considered that any patient with rheumatoid arthritis should be tested for both latent tuberculosis infection and active disease, even if they are not receiving treatment with any DMARDs. This fact is recommended, because patients with rheumatoid arthritis have a 4 times higher risk of developing tuberculosis compared to the general population. Experts recommend tests for tuberculosis annually, which involves the patient's medical history, Mantoux test, chest X-ray and objective clinical examination (6) (7). The presented patient who also received anti-TNFα treatment (Hyrimoz-adalimumab) was diagnosed with miliary pulmonary tuberculosis. This is considered a rare and at the same time fatal form of tuberculous infection that can occur in the presence of the host's immunity under the prescription of immunosuppressive agents (8). In the literature, a series of cases of pulmonary tuberculosis have been documented in patients receiving anti-TNFα therapy, such as etanercept, infliximab and adalimumab. The risk proved to be higher in the case of infliximab and adalimumab compared to etanercept. It is considered a fact that most cases are due to the reactivation of latent tuberculosis infection and several studies have demonstrated that pevention of latent tuberculosis infection before or during anti-TNFα therapy reduces the risk of reactivation, but also the risk of critical forms of active tuberculosis (9).

Case particularity

The patient presented above has had an unfavorable evolution despite the treatment administered, a fact supported by the data mentioned in the discussions. She was in biological treatment for PAR with Adalimumab, a context that greatly contributed to the risk of developing tuberculosis. In addition, the miliary form of tuberculosis determined the unfavorable evolution too (10).

Conclusions

In conclusion, pulmonary tuberculosis associated with rheumatoid arthritis can present atypical manifestations that can lead to an incorrect or delayed diagnosis with unfavorable evolution. Thus, it is very important to evaluate the bacillary status before initiating any immunosuppressive treatment.

Funding

None

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from the family of the subject involved in the study.

Data Availability Statement

Data used to support the presented case report are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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