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Case report

Non-lymphopenic pneumocystis pneumonia in low-dose methotrexate therapy: An exception to every rule

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ABSTRACT

Pneumocystis jiroveci associated pneumonia (PCP) is one of the most important opportunistic conditions affecting immunocompromised patients, especially those with rheumatic diseases, often associated with lymphopenia and high serum LDH levels. The risk of PCP correlates with immunomodulators' dosage given to control patient's underlying disease.

We present a case of a PCP involving a non-lymphopenic patient with psoriatic arthritis treated with low dose of methotrexate.

1. Introduction

Pneumocystis jirovecii, formally *P. carinii*, is an opportunistic fungus associated with severe acute and subacute infections, mostly pneumonia (PCP) affecting immunocompromised and, in rare cases, immunocompetent patients [1,2]. It can also be detected in the respiratory tract of healthy individuals, considered transiently natural reservoirs [3].

The nonspecific clinical features of PCP are challenging for early diagnosis, which could partly explain its high mortality rate [3]. Up to 15% of patients could have significant respiratory symptoms with a normal thoracic x-ray [4]. Since *P.jirovecii* cannot be cultured, PCP is definitely diagnosed through detection of cysts and/or trophozoites by colorimetric or immunofluorescent stains or even polymerase chain reaction (PCR) assays [3]. The serum levels of (1–3)- β-D-Glucan (BG) - a common cell wall constituent of most pathogenic fungi - is often used to confirm invasive fungal diseases (IFDs) and can differentiate *pneumocystis* colonization from PCP, when there are suitable clinical and radiological findings as well as positive staining or PCR [5].

In immunocompromised patients the incubation time has not been clearly defined. When it comes to rheumatic diseases, some authors estimate that previously colonized patients could develop PCP at least 4 weeks after the beginning of immunosuppressive therapy [6].

It is thought that pathogenic role of *Pneumocystis* stems from strains' reactivation (old exposure) or rapid proliferation (recent exposure) [6].

2. Case report

A 55-year old woman, previous smoker, with a 3-year history of remitted ACPA positive psoriatic arthritis (dactylitis of left foot's fifth finger and oligoarthritis of carpeal and metacarpophalangeal joints). Disease remission was achieved with methotrexate (MTX), whose dose was progressively reduced to 15mg/week. About 4 months later she went to see her rheumatologist for a routine consultation when she described a 2-week history of exertional dyspnoea, non-productive cough and high-grade fever (mainly 39 °C). At that time, she had normal blood tests run by her general practitioner. She denied rhinorrea, headache or odynophagia. There was no prior history of recent corticosteroids use, recurrent respiratory infections, sexual risk behaviour, recent travel or interaction with farm animals or pets. During consultation she was normotensive, febrile (37.8 °C) with shortness of breath easily noticed and persistent cough without intercostal retraction or abnormal auscultatory findings. Hypoxaemia was confirmed with arterial blood gas. No lymphadenopathies nor abnormal cutaneous signs were found. The patient was admitted for diagnostic investigation.

During admission, the patient presented a normal thoracic x-ray (Fig. 1A) and underwent a thoracic CT (Fig. 1B) which showed discrete upper lobe centrilobular ground-glass pattern with no pulmonary consolidation. Her blood analysis showed both normal serum leukocyte and lymphocyte counts (6500/μL and 1200/μL, respectively), high serum CRP levels (7.15mg/dl) as well as LDH levels of 360U/L.

A serologic test for HIV infection was performed which came

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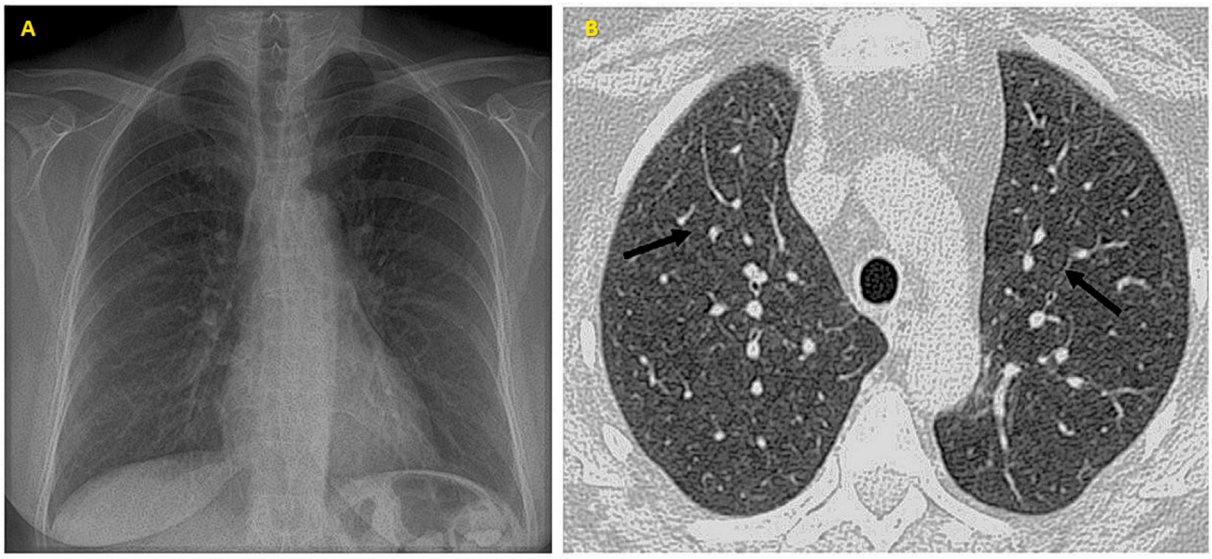

Fig. 1. (A) Patient's thoracic x-ray and CT scan (B) showing upper lobe centrilobular ground-glass pattern (arrows).

negative. Her blood cultures and direct microscopic examination of sputum came sterile, as well as negative serologic tests for *Haemophilus influenzae, Chlamydia pneumoniae* and *Mycoplasma pneumoniae*; the nasopharyngeal swab was negative for virus. Finally, a bronchoalveolar lavage (BAL) was performed and Grocott's methenamine silver (GMS) staining revealed a small amount of the cystic form of *P. jiroveci* along with positive PCR and elevated serum levels of BG (249 U/mL), which supported the diagnosis of PCP. The patient began standard dose of sulfamethoxazole-trimetoprim and later on discharged. About 2 weeks later she showed significant clinical improvements with normal blood tests, including low serum BG levels.

3. Discussion

Methotrexate (MTX) is a conventional disease modifying antirheumatic drug (DMARD) which represents one of the earliest therapeutic cornerstones in rheumatic diseases. Its anti-inflammatory and immunosuppressive actions include inhibition of immune cells' activation and proliferation (particularly T-cell lymphocytes) as well as decreased production of inflammatory cytokines (mainly IL-1 and IL-6) and cell adhesion molecules [7].

Most cases MTX-induced PCP have been associated with lymphopenia. Kane et al. were one of the first to propose low $CD4^+$ lymphocyte counts in patients receiving MTX therapy as another risk factor for PCP in HIV-negative patients. They also suggested that if cumulative MTX dosage were superior to 400mg it could predict the risk of infection [8], which was eventually seen in some published reports [9,10]. More recently, Akiyama et al. compared incidence of PCP in patients with rheumatoid arthritis treated with conventional DMARDs versus those treated with biologic therapy and found no consistent correlation between peripheral serum lymphocyte count and serum BG levels [11]. Our patient reports something similar. In fact, although she had a cumulative dosage of MTX that exceeded 400mg, she didn't have lymphopenia at the time of admission and still presented high serum BG levels during diagnostic workup, which reassured the diagnosis of PCP. We could speculate that she eventually had some transient lymphopenia in the 2-month period between her last blood test and the onset of her respiratory symptoms, but we can't also neglect the other immunomodulatory properties of MTX therapy, which aren't fully clarified.

On the other hand, there is recent intriguing data related to *P. jirovecii* genotype sequencing which leaves some important questions unanswered, for instance which strains are prone to colonize and which ones would most certain promote infection [12]. This is to our knowledge the first report of a non-lymphopenic PCP in a patient treated with low dose of methotrexate.

Disclosure of potential conflicts of interest

The authors have no conflicts of interest to disclose.

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