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Methotrexate-Induced *Pneumocystis jirovecii* Pneumonia in a Patient with Rheumatoid Arthritis: A Case Report

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Abstract

Pneumocystis jirovecii Pneumonia (PJP) is an emerging threat to immunocompromised patients, such as those receiving immunosuppressive therapeutics for autoimmune and inflammatory disorders. Though uncommon, PJP complicating low-dose methotrexate therapy can occur due to the risk of myelosuppression.

Here we present a case of PJP in a 57-year-old man with Rheumatoid Arthritis (RA) treated with low-dose methotrexate and prednisolone for 11 years. Two years prior to hospital admission, he discontinued attendance at follow-up appointments and had been taking medications without surveillance. His symptoms consisted of fever, cough and dyspnea; with wide spread alveolar opacities and micronodules on chest radiograph, hypoxia, and severe pancytopenia. A severe folate deficiency was notable. Despite slight initial improvement, patient's respiratory status progressively declined following immune reconstitution. The diagnosis was confirmed by bronchoalveolar lavage on the eleventh day after admission. The patient fully recovered under treatment with Trimethoprim-Sulfamethoxazole (TMP-SMX).

This case highlights the importance of prompt diagnosis and treatment of PJP in rheumatoid arthritis patients undergoing methotrexate regimens. An adequate folic acid supplementation and regular blood count monitoring may minimize this risk. Primary prophylaxis could be effective, preventing PJP in selected cases; further investigation is needed to assess the efficacy and safety of prophylaxis regimens.

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Introduction

Pneumocystis jirovecii Pneumonia (PJP) is a fungal infection that most commonly affects the immunocompromised and, in some cases, can be life-threatening. Its incidence in people with Human Immunodeficiency Virus (HIV) infection has declined substantially thanks to the widespread use of prophylaxis and antiretroviral therapy. Lately, PJP has been emerging as a serious problem among non-HIV immunocompromised patients, including those under antirheumatic immunosuppressive regimens. Methotrexate (MTX) is considered the first-line agent for most patients with Rheumatoid Arthritis (RA), given its anti-inflammatory properties. MTX has also antiproliferative and toxic effects due to the inhibition of an enzyme involved in the metabolism of folic acid, dihydrofolate reductase. Myelosuppression and pancytopenia are the most common hematological toxicity, which can be minimized with folic acid supplementation. Although rare, severe myelosuppression can occur even with low dose MTX and facilitate the potential development of opportunistic infections, such as PJP.

Case Presentation

A 57-year-old man with RA presented to our emergency department with a one-week history of productive cough, sneezing, progressive dyspnea, anorexia and abdominal pain. A 6-month history of unintentional weight loss of nearly 20 kg was also mentioned. Significant prior medical history included an ischemic cerebrovascular accident in 2005 (with mild dysarthria as sequela) and RA diagnosis in 2008. He was on a long-term treatment with MTX in a weekly oral dosage ranging between 15 mg to 20 mg, along with prednisolone 5mg id. Two years earlier, he discontinued attendance at follow-up appointments and had been taking both medications without surveillance. On physical examination, the patient appeared ill and underweight, had fever (38.3°C), tachycardia (117 beats per minute) and tachypnea (28 cycles per minute), with saturation of 89% on air. Breath sounds were decreased on the left lung base. The abdominal exam was notable for diffuse tenderness

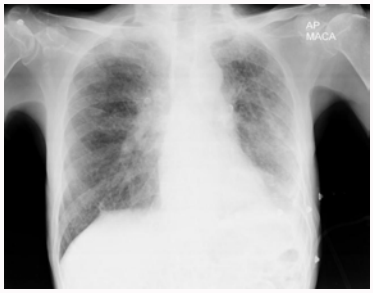

Figure 1: Chest radiography revealed diffuse alveolar opacities and micronodules in the left mid lung zone and.

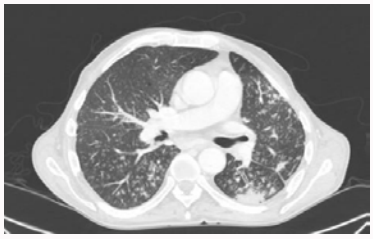

Figure 2: Chest computed tomography demonstrated widespread diffuse micronodules resembling a miliary pattern, associated with areas of parenchymal densification and septal thickening.

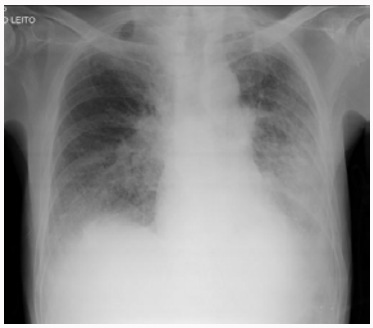

Figure 3: On the 10th day of hospital admission, radiography of the chest showed bilateral, diffuse interstitial infiltrates.

to palpation.

A chest radiograph demonstrated widespread alveolar opacities and micronodules in the left mid lung zone (Figure 1). Blood analysis revealed severe pancytopenia: hemoglobin level 7.7 g/dl, total white blood count 0.58×10^3/uL (82.8% neutrophils, 13.8% lymphocytes, 1.70% monocytes and 1.70% eosinophils) and platelet count 10.000/mm^3. C-reactive protein level was 20.5 mg/dL. Features of both hepatocellular and cholestatic injury were present. Neutrophil hyper segmentation was visible in blood smear, attributed to megaloblastic anemia secondary to severe folate deficiency (folic acid <2 ng/mL). Screening for influenza virus confirmed influenza virus type A. Therapeutic regimen was started with oseltamivir 75 mg twice daily along with empiric antibiotic coverage with piperacillin-tazobactam, admitting bacterial co-infection. MTX was immediately discontinued; folic acid supplementation and granulocyte colony-stimulating factor were added to the therapeutic regimen, concerning MTX-related pancytopenia. Blood and urine culture samples were negative. Three negative sputum acid-fast bacillus smears ruled out pulmonary tuberculosis. Further research for opportunistic and atypical microorganisms, including HIV screening, were all negative.

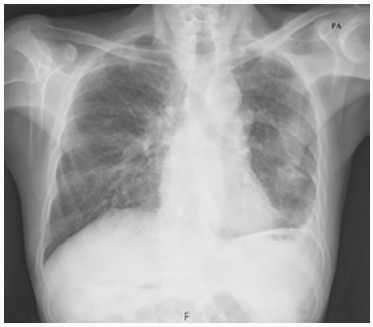

Figure 4: Chest radiography on the 29th post-admission day showed radiological improvement.

Despite positive markers for RA, remaining autoimmune study was negative. The patient slowly improved over the course of the first week admission, with important immune system recovery. Chest computed tomography revealed widespread diffuse micronodules, resembling a miliary pattern, with a centrilobular distribution (Figure 2). On the tenth day of hospital admission, his respiratory status suddenly declined with severe hypoxemic respiratory failure, accompanied by a hyperinflammatory reaction. Radiography of the chest showed bilateral, diffuse interstitial infiltrates (Figure 3). He was started on broad-spectrum antibiotics, meropenem and vancomycin, concerning nosocomial pneumonia. Cultures remained negative. Enhanced lung injury and respiratory decline following immune reconstitution in the setting of an immunosuppressed patient raised suspicion of PJP. Bronchoscopy was performed and bronchoalveolar lavage fluid identified nearly 20*Pneumocystis jirovecii* oocysts *via* indirect immunofluorescence staining.

The patient was successfully treated for PJP. He completed a 21-day course of Trimethoprim-Sulphamethoxazole (TMP-SMX) along with corticosteroid tapering strategy, with clinical and radiological improvement (Figure 4). Upon discharge, 5 mg/day prednisolone dose was maintained to control his symptoms of arthritis. No evidence of lung disease was found at 3-month and one-year post-discharge appointments.

Discussion

Pneumocystis jirovecii is an opportunistic fungal pathogen that can cause a fulminating potentially life-threatening interstitial pneumonia in immunocompromised hosts. Lately, the incidence of PJP among non-HIV-infected patients is increasing with widespread use of chronic immunosuppressive regimens [1].

Among immunosuppressive therapy, long term moderate-to-high dosage of corticosteroids (>20 mg/day of prednisolone or equivalent for longer than 1 month) is the most commonly identifiable risk factor [2]. Other immunosuppressive drugs, such as MTX, are also associated with increased risk of developing PJP. MTX is an antimetabolite that interferes with the metabolism of folic acid, therefore inhibiting cellular proliferation. In addition to its antiproliferative effects, MTX has anti-inflammatory and immunomodulating properties. In RA, MTX is used in long-term, low-dose regimens, ranging 7.5 mg to 25 mg weekly. However, even at low doses, bone marrow suppression can occur [3], with low lymphocyte counts playing an important role [1]. Regular monitoring of CD4 cell counts in patients receiving cumulative MTX doses exceeding 400 mg has been suggested [4]. Oral folic acid supplementation is also recommended as it may prevent MTX induced myelosuppression [3].

Total cumulative dosage of MTX used in our patient was extremely high, reaching nearly 10 g. Despite CD4 cell counts were not measured, an important lymphocytopenia (80 cells/ uL) was present at admission, suggesting a mechanism for the development of PJP. In addition, he had not been taking folic acid supplementation for a long time. Several other factors may have played a role in the development of PJP. The concomitant use of long-term low-dose systemic corticosteroids may have contributed to the reduction of CD4+ lymphocyte count and impaired cell-mediated immune activity. The development of PJP may have also been facilitated by a pre-existing lung disease, such as MTX-associated pneumonitis or RA-interstitial lung disease.

This case highlights the importance of considering PJP among patients receiving low-dose MTX therapy presenting with low respiratory tract symptoms, especially those with concomitant use of systemic corticosteroids. These patients should have their blood counts closely monitored for early recognition of hematological toxicity, including CD4 cells count. Primary prophylaxis could be effective in selected cases, based on patients' risk factors for PJP. However, to date, there are no consensual recommendations. Further investigation is needed to provide definitive guidelines regarding primary prophylaxis in patients receiving immunosuppressive therapies for rheumatic diseases.

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