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Case Report
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A Diagnostic Dilemma: MTX Induced Lung Toxicity

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Abstract

Methotrexate hypersensitivity pneumonitis is a rare diagnosis that is made through a complex series of clinical examinations, laboratory tests, and imaging. The unique case report presented herein is of an 88-year-old woman with a past medical history of polymyalgia rheumatica that was treated with methotrexate, which initially manifested as nausea and vomiting. Upon her arrival at the Emergency Department, the patient was hypoxic but denied shortness of breath or any other clinical symptoms of hypoxia. After ruling out infectious causes of pneumonia or pulmonary edema, chest computer tomography without contrast imaging on expiratory views indicated air trapping, which was suggestive of hypersensitivity pneumonitis or aspiration pneumonia. Without any acute clinical symptoms, aspiration pneumonia was ruled out, and the diagnosis of methotrexate hypersensitivity pneumonitis was made.

Introduction

Methotrexate (MTX) is widely used in the management of rheumatologic conditions, including polymyalgia rheumatica, but carries a recognized risk of pulmonary toxicity, most commonly hypersensitivity pneumonitis [1]. The incidence of MTX-induced pneumonitis ranges from 0.3% to 11.6%, with a meta-analysis of randomized controlled trials demonstrating a relative risk of 7.81 (95% CI 1.76–34.72) compared with controls [2]. The condition is a dose-independent hypersensitivity reaction that can occur at any point during therapy. Diagnosis of MTX-induced pneumonitis can be challenging, as the clinical and radiologic presentation frequently mimics congestive heart failure, Pneumocystis jirovecii pneumonia (PJP), and other causes of acute respiratory deterioration. Risk factors include age greater than 60 years, pre-existing lung disease, and renal impairment [1]. While typically reversible with drug cessation and systemic corticosteroids, mortality rates up to 11% have been reported [3].

Case Presentation

An 88-year-old woman with a medical history of atrial fibrillation, polymyalgia rheumatica treated with methotrexate, Alzheimer's disease with psychotic features, breast cancer, melanoma, and gastroesophageal reflux disease presented to the emergency department with several episodes of nausea and vomiting. On presentation, she was hypoxemic with an oxygen saturation of 84% on room air, requiring supplemental oxygen. Electrocardiography demonstrated atrial fibrillation without acute ischemic changes. Chest radiography revealed cardiomegaly with central pulmonary venous congestion and bilateral mid- and lower-lung interstitial opacities concerning for pulmonary edema (Figure 1). Computed tomography pulmonary angiography demonstrated diffuse bilateral ground-glass opacities with a crazy-paving pattern and mediastinal and right hilar lymphadenopathy (Figure 2). Point-of-care ultrasound demonstrated a collapsible inferior vena cava, arguing against significant intravascular volume overload (Figure 3).

Differential diagnosis and hospital course

Given the initial radiographic findings and history of atrial fibrillation, acute decompensated heart failure was suspected, and intravenous diuresis was initiated. Concurrently, the patient was started on empiric ceftriaxone and azithromycin for presumed community-acquired pneumonia. Despite 24 hours of aggressive diuretic therapy and antibiotic treatment, the patient's hypoxemia and radiographic abnormalities failed to improve. As the clinical course evolved, the consulting pulmonology service favored cardiogenic pulmonary edema, whereas the internal medicine team remained concerned for an infectious etiology, particularly *Pneumocystis jirovecii* pneumonia, given the diffuse bilateral ground-glass opacities and chronic immunosuppression with MTX. Serum β-D-glucan subsequently returned positive, further increasing concern for *Pneumocystis jirovecii* pneumonia. However, following multidisciplinary discussion and careful review of the patient's medication history, chronic methotrexate therapy for polymyalgia rheumatica was recognized as

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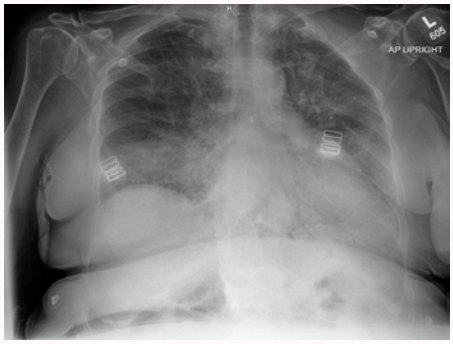

Figure 1: Initial chest radiograph.
Admission chest radiograph demonstrating cardiomegaly with central pulmonary venous congestion and bilateral mid- and lower-lung interstitial opacities, initially concerning for cardiogenic pulmonary edema.

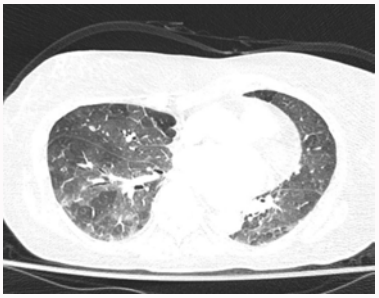

Figure 2: Computed tomography pulmonary angiography (CTPA).
CT pulmonary angiography demonstrating diffuse bilateral ground-glass opacities with a crazy-paving pattern and associated mediastinal and right hilar lymphadenopathy. No evidence of pulmonary embolism was identified.

a potential culprit. High-resolution computed tomography of the chest demonstrated centrally predominant patchy ground-glass opacities with interlobular septal thickening producing a crazy-paving pattern, along with areas of air trapping on expiratory imaging, findings concerning for methotrexate-induced pneumonitis (Figure 4). Although the positive β-D-glucan maintained concern for *Pneumocystis jirovecii* pneumonia, the overall clinical and radiographic presentation was ultimately considered more consistent with methotrexate-induced pneumonitis. Methotrexate was discontinued, systemic corticosteroid therapy was initiated, and the patient's respiratory status subsequently improved.

Discussion and Conclusion

Methotrexate has different mechanisms of action depending on its clinical application. As a chemotherapeutic, methotrexate inhibits the cell cycle by acting as an antifolate antimetabolite through binding to dihydrofolate reductase and inhibiting the production of tetrahydrofolate, which acts as a carbon carrier during DNA and RNA biosynthesis [4]. Additionally, methotrexate can be transported into the cell by human reduced folate carriers (SLC19A1) and is chemically modified to methotrexate-polyglutamate, which inhibits thymidylate synthase, a crucial enzyme in the biosynthesis of DNA [4]. Both mechanisms of methotrexate result in oxidative stress resulting in DNA double-strand breaks that inhibit the growth of rapidly dividing cancer cells [5].

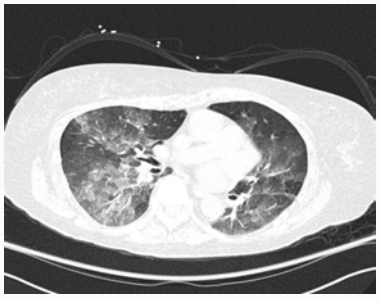

Figure 4: High-resolution computed tomography (HRCT) of the chest.
High-resolution CT of the chest demonstrating centrally predominant patchy ground-glass opacities with interlobular septal thickening producing a crazy-paving pattern and areas of air trapping on expiratory imaging, findings most consistent with methotrexate-induced pneumonitis.

When low-dose methotrexate is used to treat autoimmune diseases, it binds to and inhibits AICAR transformylase, thus halting the breakdown of adenosine monophosphate and adenosine, which get extracellularly transported [6]. The significant rise in extracellular adenosine and ATP represses T-cell activation, downregulates B-cell function, and increases the sensitivity of CD-95 T cells [4]. The immunosuppressive effects of methotrexate enable the broad clinical use of this medication for numerous autoimmune disorders like Rheumatoid arthritis and polyarticular juvenile idiopathic arthritis [4]. Additionally, there are numerous off-label indications for methotrexate such as Polymyalgia rheumatica and ANCA-associated vasculitis [4].

With the broad clinical indications for methotrexate, it is important to consider the side-effect profile when subscribing methotrexate. Common side-effects are nausea, fatigue, and mouth sores. Rare but serious side-effects can include organ-specific toxicity. One such rare side-effect is hypersensitivity pneumonitis.

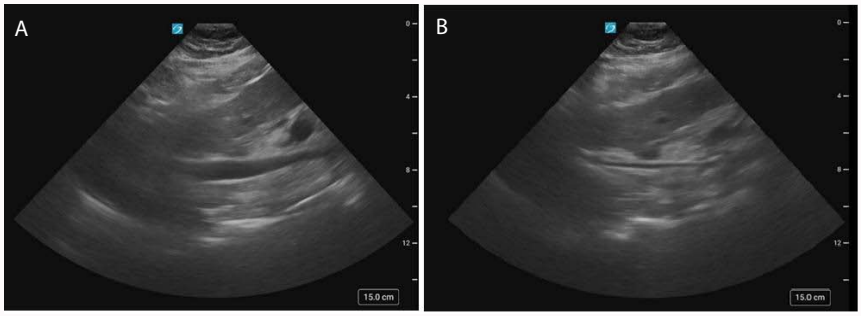

Figure 3: Point-of-care ultrasound of the inferior vena cava.
Point-of-care ultrasound demonstrating under 2cm (A), freely collapsible inferior vena cava (B), suggesting the absence of significant intravascular volume overload despite radiographic findings concerning for pulmonary edema.

The prevalence of methotrexate pneumonitis is 0.3-11.6% with a mortality rate of 13-17% [7]. The diagnostic criteria can be complicated depending on the patient's presenting symptoms and is often a diagnosis of exclusion. The differential diagnosis for patients with methotrexate-induced hypersensitivity pneumonitis will initially be very broad and may include atypical pneumonia, viral upper respiratory infection, Pneumocystis jirovecii pneumonia, pulmonary edema secondary to congestive heart failure, or aspiration pneumonia, etc. Due to the broad differential diagnosis, an extensive work-up will be required to finally arrive at the final diagnosis of methotrexate-induced hypersensitivity pneumonitis. A common initial symptom will be shortness of breath, especially upon exertion, though our patient denied shortness of breath, she had difficulty ambulating unassisted and therefore was mostly sedentary. Her SpO_2 of 84% prompted laboratory testing for SARS Coronavirus (COVID 19), Influenza A and B, and Respiratory syncytial virus (RSV), which were all negative. Initial imaging included a chest radiograph (Figure 1), which was significant for central predominant patchy ground glass opacities with septal thickening in a crazy paving pattern. Scattered bibasilar scarring and a mosaic attenuation of the lungs. These results prompted further imaging with a computer tomography (CT) of the chest with pulmonary angiogram to test for pulmonary embolism, which was negative (Figure 2). Bedside ultrasound of the chest and inferior vena cava (IVC) was indicated to test for pulmonary edema, which found a fully collapsable IVC and no evidence of pulmonary edema (Figure 3A and 3B). Cardiac echocardiogram was negative for pericardial effusion. With these nonspecific findings, the pulmonology care team was consulted and an in-depth discussion about the patient's vitals, history, medications, imaging, and laboratory results lead to additional laboratory testing and imaging. Though a definitive diagnosis had not been made, ceftriaxone, azithromycin was empirically started. These medications did not significantly improve the patient's SpO_2, so methylprednisolone (125 mg for 3 days) and prophylaxis bactrim were initiated. Additionally, in spite of the patient being afebrile, *Legionella pneumophila*, *Streptococcus pneumoniae*, HIV, and (1,3)-b-D-Glucan, C-reactive protein (CRP), and blood cultures were ordered. The only significant results were a CRP of 1.6 (normal 0-0.5 mg/dL) and a (1,3)-b-D-Glucan of 447 (<31 pg/mL, negative and >80 pg/mL, positive). These results were confusing given that the patient was afebrile, did not have nodular findings in her chest CT, and that her symptoms rapidly improved with methylprednisolone and a prophylaxis dose (not therapeutic dose) of bactrim. The pulmonology care team conducted another chest CT w/o contrast and high resolution with inspiratory and expiratory views, which indicated air trapping on expiration due to inflammation of the bronchioles and alveoli, which is indicative of hypersensitivity pneumonitis or aspiration pneumonia (Figure 4). Aspiration pneumonia was ruled out because the patient did not present with an acute change in symptoms or SpO_2. Bronchoscopy was not performed due to the patient's age (88 yo, risk outweighing the benefit) and the patient rapidly improved on methylprednisolone. During the patient's six day hospital stay, she went from six liters of oxygen/min by nasal cannula to maintain SpO_2 >90% to room air with a SpO_2>90%. Collectively, these results point to hypersensitivity pneumonitis due to methotrexate exposure.

Management of the patient included an oral prednisone taper with prophylactic bactrim (80mg tablet). Specifically, the prednisone taper consisted of: 40 mg prednisone 3 days, 20 mg for 7 days, 15 mg for 5 days, 10 mg for 5 days, 10 mg alternating with 5 mg for 7 days, and then 5 mg for 7 days. Calcium carbonate-cholecalciferol 500mg-10mg was given to counteract the reduced calcium absorption caused by steroid usage. Lastly, the patient needs to follow up with pulmonology a month after discharge to repeat a CT chest and to determine oxygen saturation.

Conclusion

In conclusion, this patient's presentation and hospital course was very unique and is an interesting case report that demonstrates the complex diagnosis of hypersensitivity pneumonitis due to methotrexate exposure. Hypersensitivity pneumonitis due to methotrexate exposure is a very rare clinical presentation that presents with nonspecific findings making a final diagnosis determination difficult. Furthermore, due to the rarity of this condition, physicians may only see 1-2 cases during their entire careers making hypersensitivity pneumonitis due to methotrexate exposure primarily a diagnosis of exclusion that requires collaboration across multiple health care teams, detailed imaging, and extensive laboratory testing. Most importantly, this case report demonstrates that critical thinking and analysis of a patient's clinical presentation and their hospital course strongly influences how imaging and laboratory testing is interpreted to finalize diagnosis and treatment plan.

Note: The patient provided consent for this case report.

Acknowledgment

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