Swedish Hospital
Part of NorthShore

St George's University of London

Double Trouble: Concomitant Tuberculosis and Histoplasmosis Following TNF-α Inhibitor Treatment For Crohn's Disease

Michael Gianarakis, MS-4, BSc.[1,2]; Safia Ahmed, MS-4, B.S.[1,2]; Ushan Ranasinghe, M.D.[1]; Kavita Singh, M.D.[1]
[1] Swedish Hospital Northshore University Health System, Chicago IL [2] St George's University of London Medical School, United Kingdom

Introduction

- Tumor necrosis factor (TNF)-a inhibitor (TNFI) therapy has improved clinical response and remission rates in patients with IBD, however their use has been associated with increased susceptibility to infection.
- We present a case of concomitant pulmonary *Mycobacterium tuberculosis* (TB) and *Histoplasmosis capsulatum* in a patient with Crohn's disease receiving adalimumab.
- Co-infection is rare, and most cases have been reported in patients with HIV.
- One case of co-infection with TNFI has been reported, however, the patient had positive TB tests prior and was not treated. Our case is unique as our patient is HIV-negative and had negative TB screening.

Case Description

- A 74-year-old female with Crohn's disease treated with adalimumab, for 9 months, presented with a 3-month history of weakness, headache, dyspnea on exertion, fatigue, weight loss, subjective fevers and dizziness.
- Interferon-gamma release assay (IGRA) was negative prior to commencing adalimumab therapy.
- The patient discontinued adalimumab after 6 months due to fatigue, sore throat, and diarrhea and was treated for Crohn's flare with corticosteroids. Her condition improved and she recommenced adalimumab 2 weeks prior to her ED visit.
- Labs showed Hgb 7.6 g/dl, AST 89 IU/L, ALT 83 IU/L, ALP 666 IU/L.
- Computed tomography showed bilateral ground glass spiculated pulmonary nodules, mediastinal lymphadenopathy, and pleural thickening (Figure 1).

Case Description

- Symptoms worsened and the patient began to develop high grade fever 102.9F and was saturating at SpO2 88% on room air. Respiratory support was given, and liposomal amphotericin B was commenced with concern for fungal infection. 1-3-beta-d-glucan assay was positive. Urine histoplasmosis antigen was negative.
- Pulmonary histoplasmosis was diagnosed from methenamine silver stain of bronchial washings and treated with liposomal amphotericin B (transitioned to itraconazole). Despite fungal treatment, symptoms worsened and serial imaging revealing worsening confluent areas of ground glass nodular opacities bilaterally, with intervening areas of interstitial thickening (Figure 2). Corticosteroid therapy was commenced with concern for ARDS.
- TB PCR from bronchoalveolar lavage was positive and rifampin, isoniazid, pyrazinamide and ethambutol (RIPE) was initiated. The patient was discharged with improvement in symptoms.
- The patient was readmitted after 10 days with recurrence of symptoms and subtherapeutic itraconazole levels. Despite switching to liposomal amphotericin B, symptoms worsened, and pneumonia or immune reconstitution inflammatory syndrome (IRIS) was suspected. The patient was placed on respiratory support, antibiotics and liposomal amphotericin B. Symptoms resolved and the patient was discharged on itraconazole, and RIPE with moxifloxacin substituted for rifampin.

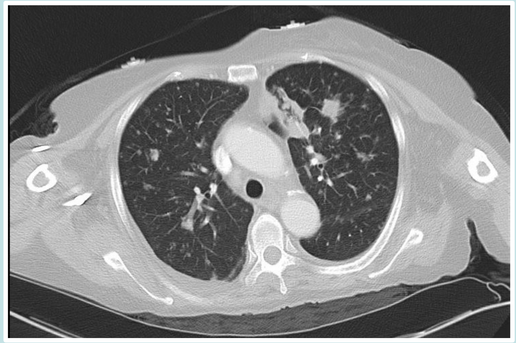

Figure 1: Axial CT chest with contrast demonstrating bilateral spiculated ground glass pulmonary opacities, pleural thickening/opacity of the left upper lobe pericardiac region and mediastinal lymphadenopathy.

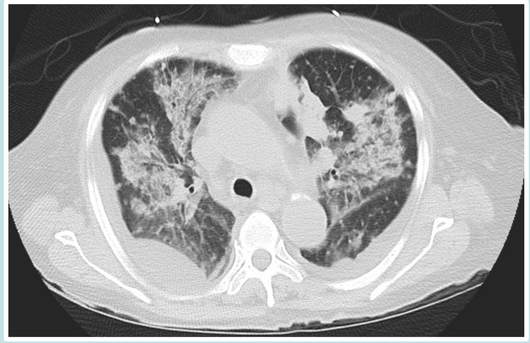

Figure 2: Axial CT chest demonstrating prior nodular opacities and new confluent areas of ground glass opacities with intervening interstitial thickening.

Discussion

- This was a challenging case for diagnosis and treatment due to overlapping symptoms, similar lab and radiographical findings, drug-drug interactions and worsening of symptoms despite therapy.
- Physicians must exercise a high clinical suspicion for co-infection of TB and other pathogens, particularly in patients with a complicated disease course and in endemic regions.
- Similarities in clinical presentation of both infections, include fever, dyspnea, cough, weight loss, night sweats, fatigue, hepatosplenomegaly, and lymphadenopathy. Pancytopenia, increased liver enzymes and elevated CRP and ESR are notable in both infections. Elevated ferritin is more common in histoplasmosis.
- The lung nodules, granulomas and infiltration of both histoplasmosis and tuberculosis present similarly on chest radiography and can mimic malignancy. Slow growing cultures for both infections and negative antigen screening tests can delay diagnosis.
- In co-infection with histoplasmosis, alternate therapies should be considered due to an itraconazole-rifampin drug interaction. Moxifloxacin is an effective substitute for rifampin, allowing a good response to itraconazole therapy for histoplasmosis.
- In TNFI-associated infections, a paradoxical worsening of symptoms should raise concern for immune reconstitution inflammatory syndrome (IRIS) secondary to TNFI cessation.
- IRIS following discontinuation of TNFIs has been described, with a median onset of 6 weeks. Paradoxical worsening of symptoms in TNFI-associated infections may be interpreted as treatment failure or additional infections, however, it is important to consider IRIS.