CLINICAL VIGNETTE

An Unseen Opportunity for Histoplasmosis

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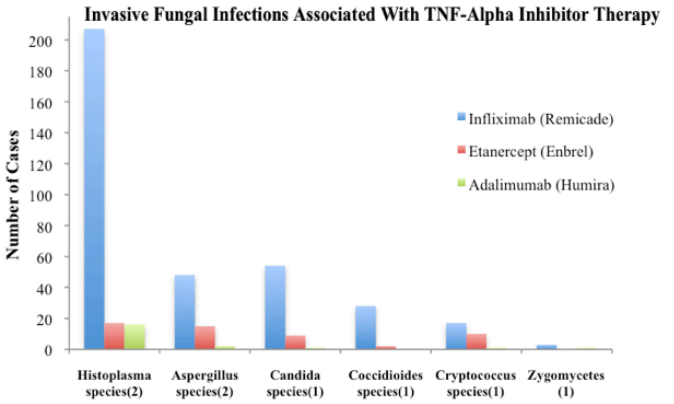
Overview

- TNF-Alpha inhibitors are associated with an increased risk of endemic fungal infections, especially with *H.Capsulatum*
- Amongst TNF-Alpha inhibitors, the greatest risk of Histoplasmosis appears to be with Infliximab[1,2]
- A thorough travel, social, and past medical history should be performed on immunosuppressed patients to screen for fungal infection.
- Delay in diagnosis & management of IFI can lead to poor outcomes.



Introduction

The use of biologic therapy has revolutionized the treatment of many inflammatory and autoimmune diseases. The most prescribed and widely used biologic drug is currently Infliximab, followed by Etanercept and Adalimumab, all of which are TNF-Alpha inhibitors. They can be used in rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, and plaque psoriasis. Recently, there has been a considerable increase in the use of this drug class, as the FDA continues to approve use in a broader spectrum of diseases. Though these drugs have excellent efficacy in managing the symptoms of patients' inflammatory diseases, they increase risk of invasive fungal infections (IFI) due to their immunosuppressive mechanism of action. The most common IFI related to TNF-Alpha inhibitor usage is caused by *Histoplasma Capsulatum*. As the use of TNF-Alpha inhibitors increases, so does the potential for life threatening IFIs. Recognizing the signs and symptoms of IFIs, especially in patients residing in areas of endemic mycoses, involves maintaining a high index of suspicion for IFI for patients on TNF-Alpha inhibitor therapy. Early recognition and treatment of IFIs is generally effective and reduces mortality significantly.

Clinical Case

A 64-year-old man with ulcerative colitis (UC) presented to the emergency room with 2 weeks of progressively worsening generalized weakness, confusion, dizziness, and lower extremity edema. His UC was being managed with Prednisone, Infliximab, and Mesalamine. Mesalamine had been discontinued three days prior to presentation due to suspicion that it was contributing to his symptoms., Amoxicillin was started one day prior to admission for possible upper respiratory infection given his flu-like symptoms for several weeks. Vital signs were normal but physical exam was notable for scleral icterus, bilateral expiratory crackles, and +2 pitting edema of the lower extremities. Laboratories noted transaminitis. Abdominal ultrasound suggested fatty infiltration of the liver and subsequent Doppler of the portal and hepatic vein revealed patent flow.

The next day he became febrile. The concern of hepatitis secondary to medication or infection was considered, resulting in stopping Infliximab and starting Azithromycin and Levofloxacin. He was also treated with Lactulose for possible hepatic encephalopathy. However, his transaminases continued to increase substantially with an elevated sedimentation rate, persistent low-grade fever and decreasing oxygen saturation. He also developed abdominal distension with hepatosplenomegaly. Computed tomography scan of the chest, abdomen, and pelvis revealed multiple small hypoenhancing lesions in the spleen, with mediastinal and hilar lymphadenopathy. Infectious testing included Epstein Barr virus serology, pneumocystis infection, and bacterial blood cultures, all of which were negative. Given the possibility of lymphoma, lymph node biopsy and liver biopsies were obtained, as the patient clinically deteriorated. Liver biopsy pathology revealed multiple areas of Histoplasmosis consistent with Disseminated Histoplasmosis (DH). He was transferred to a tertiary facility and was started on Lipid Amphotericin B, with improvement, ultimately saved his life.

Discussion

<u>*Histoplasma Capsulatum* Characteristics and Epidemiology</u>

Histoplasmosis is the most common endemic fungal infection in humans. It is endemic in the Ohio, Missouri & Mississippi river valleys and Central America. Highly infectious soil is found near areas inhabited by bats and birds. Exposure can occur during demolition work on old buildings, exposure in attics or basements, disrupting soil in endemic areas, spelunking,

outdoor activities near endemic riverbanks, and clearing decaying brush and trees.

Progressive DH occurs in 1 case per 2000 cases in immunocompetent adults. However, DH occurs in 4-27% of immunosuppressed patients. The subacute form of DH, results in death within 2-24 months in untreated cases. The acute form, if untreated, results in death within weeks. In 2008, the FDA reviewed 240 cases of Histoplasmosis in patients being treated with TNF-Alpha inhibitor therapy. The majority of patients came from areas endemic to *H. Capsulatum.* In at least 21 of the 240 cases, Histoplasmosis was not diagnosed until late in the clinical course, with substantial treatment delay and deaths in 12 of those 21 patients.[3]

Pathophysiology of Histoplasmosis due to TNF-Alpha Inhibitor Therapy

TNF-Alpha plays a key role in the host immune response to infectious pathogens, especially fungi. A massive amount of TNF-Alpha is released by alveolar macrophages in response to antigen presentation, which initiates granuloma formation. By blocking TNF-Alpha, the assembly and stability of the granuloma is compromised, thus allowing the pathogen to easily replicate and disseminate.

Signs and Symptoms of Histoplasmosis or Other IFI's

Presenting symptoms include several weeks of fever, malaise, dyspnea, cough, anorexia, chills, sweats. Physical exam can reveal rales, hepatosplenomegaly, skin lesions (pustular, nodular, ulcerated), or painful mouth ulcers. Chest radiographs can reveal hilar/mediastinal lymphadenopathy, patchy infiltrates, or cavitations in the upper lobes. Pancytopenia is very common as are elevated liver transaminases.

Diagnostic Tests for Histoplasmosis

1) Biopsy of lung, liver, or bone marrow can reveal oval budding yeasts of *H.Capsulatum* on methenamine silver stain. 2) Urine antigen assay for the capsular polysaccharide of *H.Capsulatum* , although can cross reacts with Blastomycosis.

Treatment[4]

As soon as the diagnosis of DH is made, the TNF-Alpha inhibitor should be discontinued. The Infectious Diseases Society of America (IDSA) recommends the initial dosage 3 or 5mg/kg of liposomal or lipid complex Amphotericin B. Once clinical improvement occurs, therapy is changed to Itraconazole 200mg three times daily for 3 days and then twice daily for 1 year. If the TNF-Alpha inhibitor is restarted after *H. Capsulatum* antigen tests are negative, then concomitant Itraconazole therapy is recommended for duration of immunomodulator treatment.

Conclusion

- Opportunistic infection of fungal etiology should be highly suspected during early hospitalization given history of TNF-Alpha inhibitor therapy.
- Recognizing the signs and symptoms of an IFI can be difficult in patients with inflammatory or autoimmune disease who are on TNF-Alpha inhibitor therapy.
- Diagnostic tests and appropriate antifungal therapy should be ordered promptly, delays in treatment may rapidly lead to poor outcomes.

REFERENCES

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