Pneumocystis Jirovecii Pneumonia Complicating Treatment With Infliximab

R Fahy, P Diaz

Citation

Abstract
Blockade of TNF-α using tumor necrosis factor-α antibodies is used in the management of a number of chronic inflammatory diseases and is indicated for treatment of refractory Crohn's Disease. We report the development of Pneumocystis Jirovecii (Carinii) pneumonia and acute respiratory failure in a patient five weeks after the initiation of infliximab (Remicade®) therapy.

CASE REPORT
A 48 year old male was admitted with a three day history of fevers, progressive dyspnea and a non-productive cough. He had a 20 year history of Crohn's disease, complicated by sclerosing cholangitis and more recently peripheral arthritis. Intestinal symptoms were controlled with 5-aminosalicylic acid. Due to persistent arthritis and synovitis, unresponsive to non-steroidal anti-inflammatory therapy, he was given a three day pulse of 100 mg methylprednisone IV and then started on Infliximab therapy five weeks prior to admission. He received two intravenous infusions of 300 mg each, the last dose administered three weeks prior to presentation.

On examination he was afebrile, tachypneic, normotensive with bilateral crackles on auscultation. Room air pulse oximetry was 88%. Laboratory investigations revealed a normal white count and a PaO2 of 66 on 100% non-rebreather. Chest roentgenogram showed bilateral pneumonia. Intravenous imipenem/cilastatin and azithromycin were initiated. After failing to improve over 48 hours he underwent bronchoscopy with bronchoalveolar lavage. The lavage cell differential was 49% lymphocytes, 7% neutrophils and 43% macrophages. A modified Wright-Giemsa stain demonstrated diffuse Pneumocystis organisms. A HIV test and other cultures were negative. Intravenous trimethoprim-sulfamethoxazole 5mg /kg every 8 hours and prednisone 40 mg p.o. every 12 hours were added. He continued to deteriorate and required intubation two days later. On day 5 of hospitalization he developed septic shock complicated by ARDS. Repeated cultures were unrevealing. The patient expired 13 days after admission from septic shock.

DISCUSSION
Infliximab is a chimeric monoclonal antibody directed against tumor necrosis factor-α (TNF-α), indicated in the treatment of moderate to severe Crohn's disease and Rheumatoid arthritis. As therapy with TNF-α inhibitors has become more widespread for these and related chronic inflammatory and rheumatologic disorders and as its use expands to include dermatologic and pulmonary diseases, opportunistic infections with M. tuberculosis, Histoplasma, Aspergillus, Listeria monocytogenes, and occasionally Pneumocystis have been reported. The mechanism whereby TNF-α inhibition results in the development of Pneumocystis pneumonia (PJP) has recently been summarized. Macrophage derived cytokines, primarily TNF-α and interleukin-1, upregulate the CD4+ T cell initiated immune response to Pneumocystis. CD4+ stimulation of macrophages through, among other stimuli, interferon-γ, enhances macrophage cytokine production and phagocytosis, thereby helping clear the pathogen. In animal studies inhibition of TNF-α, or depletion of macrophages decreases clearance of Pneumocystis, indicating that coordination of the immune response to Pneumocystis may be significantly impaired in the absence of TNF-α, thus allowing a normal commensal organism to become pathogenic.

It is estimated that Pneumocystis may be carried by up to 20% of normal healthy populations, while hematological malignancies, organ and bone marrow transplant recipients, patients with autoimmune diseases and connective tissue disorders are at increased risk of PJP. It is pertinent to
note that in most studies identifying these disorders as having substantial risk for Pneumocystis infection the patients were taking significant doses of corticosteroids. Highlighting the steroid association was a recent study of immunocompetent non-HIV patients undergoing bronchoscopy where overall 18% were positive for P. jiroveci DNA; only 12% of patients not on steroids were positive, while 44% of those taking more than 20 mg of prednisone/day were positive. However, treatment with daily steroids for at least 3 months is usual prior to developing PJP. In this case the steroid dosage was relatively remote from the onset of symptoms and of short duration and therefore unlikely causative. Interestingly, the few reported cases where PJP complicated Infliximab therapy were invariably taking at least one additional immune modulating agent; in this clinical setting monitoring of CD4+ lymphocyte cell values and instituting prophylactic therapy for counts less than 200 cells/mm³ has been suggested.

Although the outcome for PJP in general has improved there remains a significant mortality for those admitted to the ICU, and this is especially so for HIV-negative cases. Given the prevalence of the organism Pneumocystis should be considered a potential pathogen in susceptible patients who develop pneumonia while receiving anti-TNF-ɑ therapy.

CORRESPONDENCE TO
R J Fahy 201 L Davis HLRI 473 W 12th Ave Columbus OH 43210 ruairi.fahy@osumc.edu

References
Author Information

Ruairi J. Fahy, M.B.
Division of Pulmonary & Critical Care Medicine, The Ohio State University Medical Center

Philip T. Diaz, M.D.
Division of Pulmonary & Critical Care Medicine, The Ohio State University Medical Center