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Fatal Invasive Pulmonary Aspergillosis Associated with Adalimumab Therapy

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With great interest we read the article by Sandborn et al. (Gut 2007;56:1232) about maintenance therapy of Crohn’s disease with adalimumab and the recent publication by Viget et al on opportunistic infections in patients with inflammatory bowel disease.\textsuperscript{1}

In their series including 276 patients, Sandborn et al. note no severe infectious complications apart from upper respiratory tract infections. Noteworthy, no cases of aspergillosis or other opportunistic infections were reported.

Unfortunately, serious infections are a well known problem of TNF-α antibody therapies. Here, we present a case report of a 69 year old female patient with a long history of stenosing Crohn’s disease. The patient began to have fever, dyspnea, and a productive cough five days after she took a subcutaneous injection of 40 mg adalimumab (Humira®), which necessitated hospitalisation. She had been on a stable treatment with adalimumab 40mg s.c. every other week for more than one year. At a routine outpatient consultation two weeks prior to admission, she was in good health with no signs of inflammation or neutropenia documented in the laboratory results. She was on adalimumab monotherapy and her medication did not include corticosteroids or other immunomodulating drugs. On admission the patient was tachy dyspnoic, tachycardic and hypotensive but not febrile. Her chest radiography showed massive bilateral infiltrates and laboratory examination revealed an elevated C-reactive protein and leukocytosis. Within 12 hours after admission, respiratory insufficiency developed. Ventilatory support was needed to achieve adequate oxygenation. A bronchoscopy was performed, which showed white coverings, histologically corresponding to invasive aspergillosis. The situation was complicated by a pre-existing renal insufficiency and a chronic metabolic acidosis. Despite intensive care treatment including antibiotics, fungostatic therapy, vasoactive drugs and hemofiltration the patient died two days after admission.
Our patient had no known risk factors associated with invasive aspergillosis. She had no neutropenia, nor did she take any corticosteroids or other immunosuppressive drugs during the twelve months before the infection. She had been a non-smoker, had not used marijuana, and had not had a prior influenza infection or any known exposure to aspergillus. Therefore, an association with the TNF-α blocker therapy is highly probable.

Infections are a well known complication of all TNF-α antibodies. In a recent review Tsiodras and colleagues have summarized fungal infections after TNF-α blockade therapy. Out of 281 cases of invasive fungal infections 11 cases (4%) were associated with adalimumab (compared to 80 % associated with infliximab and 16% with etanercept). For the two cases with aspergillosis on adalimumab no further data was available in this review. Whereas invasive pulmonary aspergillosis is associated with infliximab therapy it has to our best knowledge not been described for other anti-TNF-α antibodies so far. TNF-α inhibition can increase susceptibility to invasive fungal infections through inhibition of interferon-γ production, a decreased expression of pattern-recognition receptors and through leukocyte apoptosis.

With this fatal case we would like to support the observations that the use of antibodies against TNF-α including the new agents like adalimumab increases the risk of serious opportunistic infections through inhibition of an adequate TNF-α response. Clinicians should have a high level of suspicion for fast diagnosis and treatment of fungal disease in patients with TNF-α blockers.


No conflicts of interest exist.

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