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Acute myeloid leukemia after infliximab: a case report

F. Kemta Lekpa[1], K. Zahra[2], C. Pautas[2], S. Maury[2], X. Chevalier[1], P. Claudepierre[1]

[1]*Rheumatology Department and* [2]*Hematology Department, Henri Mondor Hospital, Paris XII University, Créteil, France.*

Fernando Kemta Lekpa, MD
Kmira Zahra, MD
Cécile Pautas, MD
Sébastien Maury, MD, PhD
Xavier Chevalier, MD, PhD
Pascal Claudepierre, MD

Please address correspondence to: Prof. Pascal Claudepierre, Rheumatology Department, Henri Mondor Hospital, 51 Av Maréchal de Lattre de Tassigny, 94000 Créteil, France.
E-mail: pascal.claudepierre@hmn.aphp.fr

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ABSTRACT

Concern has arisen regarding a possible increase in the risk of malignant diseases such as lymphoproliferative disorders in a patient taking TNF-α antagonists for the treatment of chronic inflammatory diseases. The evidence of a causal link remains unclear. We report a case of 60-year-old male patient who developed acute myeloid leukemia during infliximab therapy for ankylosing spondylitis.

Introduction

Infliximab is a chimeric monoclonal antibody that binds specifically to human tumour necrosis factor alpha (TNF-α), thereby neutralizing its biological activity. Infliximab is approved for the treatment of chronic inflammatory diseases including ankylosing spondylitis. Concern has been voiced that infliximab might increase the risk of malignancies, most notably lymphomas (1, 2). Five cases of acute leukemia during TNF-α antagonist therapy have been reported (3-7). We managed a patient in whom acute myeloid leukemia (AML) developed during infliximab therapy for ankylosing spondylitis.

Case report

A 60-year-old man was referred to our hematology department for evaluation of leukocytosis and thrombocytopenia. He had been diagnosed eight years earlier, in 1999, with axial ankylosing spondylitis. In June 2000, failure of nonsteroidal anti-inflammatory drugs to improve his symptoms prompted the initiation of infliximab therapy, 5 mg/kg every 8 weeks. In November 2006, at the time of his 40th infliximab infusion, he was in good health and his blood cell counts were normal. In January 2007, however, he had pharyngitis, asthenia and anorexia. His leukocyte count was 19.6×10^9/L with 83% blasts, his hemoglobin level was 12.9 g/dl, and his platelet count was 76×10^9/L. Myeloid blasts accounted for 83% of cells in the bone marrow aspirate. Immunophenotyping was positive for HLA-DR, CD13, CD33, and CD34. Cytogenetic analysis showed a complex hyperploid karyotype (48, XY;+8;+21/49, idem +12/49, idem +21/50, idem +8+21/46,XY). The molecular biology study was negative. The final diagnosis was monoblastic acute myeloid leukemia (AML-M5). Infliximab was stopped and standard induction therapy with anthracycline and cytarabine was given. A hematological and cytogenetic remission was achieved in February 2007. Three courses of consolidation therapy have been administered. At the last follow-up, 21 months after the diagnosis of leukemia, he was in complete remission without treatment or evidence of active ankylosing spondylitis.

Discussion

Whether infliximab therapy precipitated the development of acute myeloid leukemia in our patient deserves discussion. The dramatic effectiveness of TNF-α antagonists in chronic inflammatory diseases may come only at the cost of severe adverse effects. More specifically, concern has arisen about a possible increase in the risk of malignant diseases such as lymphoma (1, 2). However, a matched-pairs case-control study in patients with Crohn's disease showed no increase in the risk of malignancies in the group treated with infliximab (8). A review of the 26 cases of lymphoproliferative disorders following TNF-α antagonist therapy that had been reported to the US Food and Drug Administration through December 2000 found no convincing evidence of a causal link (1). Although an increase in the lymphoma risk has been shown in patients taking TNF-α antagonists (1,2), there is no proof that this risk increase is causally related to the medication exposure. Moreover, TNF-α antagonists have not been shown to cause an excess mortality although there remains a lack of long-term follow-up data (9). Five cases of acute leukemia, including 4 cases of AML in patients taking TNF-α antagonists have been reported (3-7). Clinical characteristics of these published cases are summarised in Table I. Previous immunosuppressive treatments were methotrexate (3, 7), sulfasalazine (4), 5 aminosalicylic (3), leflunomide (7), azathioprine (3, 4). One patient had a recent history of breast carcinoma treated by conserva-

Table I. Clinical characteristics of the published cases of acute leukemia after TNF-α antagonist therapy.

References	Age (years)	Sex	Diagnosis	Disease duration	Type of leukaemia	Delay after start of anti-TNF-α	Type of anti-TNF-α	Prior immunosuppressive drugs
Alcaín (3)	40	M	Crohn's disease	4 years	ALL, B	6 weeks	Infliximab	Methotrexate, 5 aminosalicylic, azathioprine
Bakland (4)	31	F	Ankylosing spondylitis	15 years	AML, M2	4 months	Etanercept	Sulfasalazine, azathioprine
Bachmeyer (5)	40	M	Psoriasis	10 years	AML, M2	4 months	Etanercept	Bachmeyer ()
Nair (6)	57	M	Psoriatic arthritis	Since childhood	AML	14 months (9 months of treatment)*	Etanercept	–
Saba (7)	44	F	Juvenile rheumatoid arthritis	Since childhood	AML	Approx. 6 months	Adalimumab	Methotrexate, leflunomide, breast carcinoma chemotherapy
Our patient	60	M	Ankylosing spondylitis	8 years	AML, M5	78 months	Infliximab	–

*AML was diagnosed 5 months after discontinuation because of stabilization of disease and cost of the drug.
AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia.

tive surgery, adjuvant chemotherapy with doxorubicin, cyclophosphamide, and docetaxel, followed by adjuvant radiation therapy (7). Leukemia was diagnosed between 6 weeks to 14 months after TNF-α antagonist therapy initiation (3-7), suggesting exacerbation by the drug of a preexisting silent process. Conversely, in our patient, leukemia occurred after 6 and a half years of infliximab therapy, consistent with a cumulative effect on bone marrow precursor cells. However, TNF-α is a major effector and regulatory cytokine involved in the pathophysiology of lymphoma and leukemia, and etanercept was recently tried in the treatment of refractory hematological malignancies (10). An experimental study (11) showed that TNF-α significantly inhibited the growth of human $CD34^+$ myeloid leukemic cells, by inducing both apoptosis and necrosis. This effect was mediated by activation of the nuclear transcription factor NF-kappa B pathway, which was related chiefly to the p55 TNF-α receptor, as opposed to the p75 TNF-α receptor. The inhibiting effect of TNF-α was abolished by TNF-α antagonists directed against the p55 receptor (11). However, in 198 patients with untreated acute myeloid leukemia, low serum TNF-α levels were significantly associated with higher rates of complete remission, survival, and event-free survival; whereas high serum TNF-α levels were associated with decreased survival and event-free survival (12). Thus, whether a link exists between TNF-α antagonists and leukemia remains unclear.

In conclusion, the occurrence of leukemia in our patient, who had no pre-leukemic abnormalities, probably reflects a coincidence rather than an adverse effect of infliximab. Nevertheless, given the paucity of data, patients treated with TNF-α antagonists should be closely monitored (1). TNF-α antagonists should not be used in patients with pre-leukemic abnormalities, leukemia, or lymphoma (4).

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