Mucormycosis in a patient with low risk myelodysplasia treated with anti- tnf- alpha

Accelerated programmed cell death or apoptosis appears to play an important role in the pathogenesis of myelodysplasia. As overexpression of TNF-alpha has been described to induce cell death in myelodysplasia, treatment with anti-TNF-alpha is currently being explored.[1,2] Caution is needed because of an increased risk of opportunistic infection during anti-TNF-alpha treatment. We here describe a patient who was treated with anti-TNF-alpha for low risk myelodysplasia and died of invasive mucormycosis.

Haematologica 2006; 91:(10)e139-e140

Clinical Case

A 64-year-old woman was admitted to the hospital in 2005 because of high fever and rigors since one day. In 1998 she had been diagnosed with myelodysplastic syndrome, refractory anaemia with ring-sideroblasts, according to the French-American-British (FAB) and World Health Organisation (WHO) classification, with an IPSS score of 0.5. She was dependent on transfusion with red cells, leading to secondary hemochromatosis, for which she had been treated with deferoxamine. In 2003 treatment with erythropoietin and G-CSF was started.[3] There was no haematological response. Therefore, it was decided to start treatment with anti-TNF-alpha (3 mg/kg), according to the EORTC protocol 06023.4 Three weeks after the 5th infliximab infusion, she presented with fever. She complained of progressive pain in her right hip and leg since two weeks. On physical examination, including a full neurological assessment, no abnormalities were found apart from bladder retention and a compromised movement of her right hip. Laboratory tests showed a highly elevated ESR of 115mm/hour (n 0-10 mm/hour) and CRP of 583 mg/l (n 0-8 mg/L), which had been normal two weeks earlier. Her blood counts showed a haemoglobin level of 5.5 mmol /l (n 7.5-10.0 mmol/l), thrombocytes of 466×10^9 (n 150-400×10^9) and leucocytes of 18.1x1×10^9 (n= 3.0-10.0×10^9) with 89% granulocytes showing toxic granulation. To exclude osteomyelitis or epidural masses, radiologic examination, including X-ray of chest, abdomen, and hip and an MRI of the spine and hip, showed no abnormalities. Empirical broad-spectrum antibiotic treatment was started with imipinem/cilastatine. However, her clinical condition deteriorated within 24 hours. She developed a paresis of her left arm and clinical signs of an acute coronary syndrome. Right heart catherisation revealed no apparent coronary occlusions. She was transmitted to the intensive care unit and intubated because of respiratory failure and somnolence. A lumbar punction showed elevated levels of protein (703 mg/l (n 0-500 mg/l)) and leukocytes (800/ul (n 0-4/ul)), suggestive of infectious meningitis. Peripheral blood and liquor cultures revealed no microorganisms. Despite a change of antibiotics to meropenem, high dose amoxicilline and the addition of aciclovir, she died several hours later of refractory sepsis. Obduction revealed a systemic and invasive fungal infection with metastatic abscesses in nearly all organs including the central nervous system and vaso-invasion in the coronary arteries leading to ischaemia. PAS and Grocott staining showed broad, non-septated hyphae with right-angled branches, classified as mucormycosis. (Figures 1-2)

Figure 1.

Figure 2.

Discussion

Myelodysplasia comprises a group of myeloid clonal disorders characterized by ineffective haematopoiesis. An increased rate of apoptosis of myeloid progenitors in the bone marrow, either due to a lack of positive signals (growth factors) or an up-regulation of negative signals (TNF-alpha or FAS and its ligand), appears to play an important role. Several *in vitro* studies show overexpression of TNF-alpha in bone marrows of patients with myelodysplasia, probably being responsible for induction of apoptosis of haematopoietic progenitor cells.[1,2,5] Accordingly, blocking the function of TNF-alpha has been described to favour haematopoietic cell growth and maturation. This forms the basis for several trials of cytokine inhibition in the treatment of myelodysplasia. A pilot study with infliximab® (anti-TNF-alpha) showed haematological improvement in 5 out of 28 evaluable patients, with minimal side effects.[6] However, post-marketing surveillance reveals growing evidence of an increased risk of opportunistic infection, in patients with Crohn's disease or rheumatoid arthritis during anti-TNF-alpha treatment, especially with microorganisms that can survive in human cells. This can be explained by the fact that TNF-alpha is a pro-inflammatory cytokine playing an important role in initiating an inflammatory and cellu-

lar immune response against infection.[7,8] Opportunistic infections were mostly found to occur in patients using concomitant immune modulating drugs such as methotrexate, azathioprine or prednisolon.[8] A recently published meta-analysis shows a pooled odds ratio of 2.0 for serious infections in rheumatoid arthritis treated with anti-TNF-alpha versus placebo.[9] Moreover, a high incidence of 48% fungal infections is noted during anti-TNF-alpha treatment for steroid recractory acute graft versus host disease following allogeneic haematopoietic stem celI transplantation.[10] To our knowledge, this is the first case of mucormycosis during therapy with anti-TNF alpha. In contrast to the widespread distribution of fungi, infection is rare due to low virulence potential. Major predisposing factors are non-specific and include prolonged granulocytopenia, use of steroids, broad-spectrum antibiotics, hyperglycaemia and immunosuppressive therapy. A striking association has been noted in the dialysis population between the risk of mucormycosis and treatment with deferoxamine for iron or aluminium overload. Iron is an essential nutrient for fungal growth. In human serum, iron is highly bound to carrier proteins such as transferrin and therefore not available for fungal growth.[11] However, mucorales are able to use deferoxamine as a siderophore, providing iron to promote growth, an ability not shared with other filamentous fungi like aspergillus fumigates. The higher susceptibility of dialysis versus haematological patients using deferoxamine can be explained by the prolonged accumulation of ferroxamine due to the pharmacokinetic alterations in haemodialysis patients.[12] Iron also adversely affects the phagocytic, chemotactic and bactericidal capacity of neutrophils and monocytes, compromising host defence mechanisms.[12] In addition, myelodysplasia itself is associated with granulocyte dysfunction. A low neutrophil count is not the sole cause of increased susceptibility to infections in myelodysplasia, as neutropenia was not found to correlate with infective episodes.[13] However, several in vitro studies show granulocyte dysfunction. Chemotaxis and aggregation is delayed due to defective reorganisation of the cytoskeleton linked to defective CD11b/CD18 glycoprotein complex expression on granulocytes.[14,15] Phagocytosis and killing of bacteria is compromised because of deficient contents of primary and specific granules.[15]

In conclusion, a fatal mucormycosis occurred in a patient treated with anti-TNF alpha in low risk myelodysplasia. Blocking TNF-alpha might have been the crucial step in allowing a low virulent fungus to cause a lethal infection in a highly immune compromised host due to myeloid dysfunction. In addition, the use of deferoxamine could have contributed to optimise fungal growth.

A. Keijzer, P van der Valk, G.J. Ossenkoppele, A.A. van de Loosdrecht

Keywords: TNF alpha, infliximab, myelodysplastic syndrome, mucormycosis, deferoxamine

Correspondence: A. Keijzer, VU-University Medical centre Amsterdam, department of haematology, de Boelelaan 1117, BR 240,1081 HV, Amsterdam, the Netherlands.
Tel: +31204442604 Fax: +31204442601
E-mail: A.Keijzer@vumc.nl

References

1. Stasi R, Amadori S. Infliximab chimaeric anti-tumour necrosis factor alpha monoclonal antibody treatment for patients with myelodysplastic syndromes. British journal of haematology 2002;116:334-337.
2. Mundle SD, Ambereen A, Cartlidge JD, Reza S, Alvi S, Showel MM, et al. Evidence for involvement of Tumor Necrosis Factor-? in apoptotic Death of Bone Marrow Cells in Myelodysplastic Syndromes. American Journal of Hematology 1999;60:36-47.
3. Hellström-Lindberg E, Fulbrandsen N, Lindberg G, Ahlgren T, Dahl IMS, Dybedal I, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. British Journal of Haematology 2003;120:1037-1046.
4. www.eortc.be/protoc/Details.asp?protocol=06023
5. Gersuk GM, Beckham C, Loken MR, Kiener P, Anderson JE, Farrand A, et al. A role for tumour necrosis factor-?, Fas and Fas-Ligand in marrow failure associated with myelodysplastic syndrome. British Journal of Haematology 1998;103:176-188.
6. Appelbaum FR. Immunobiologic therapies for myelodysplastic syndrome. Best Practice and Research Clinical Haematology 2004;17:653-661.
7. Dinarello AC, Anti-cytokine therapeutics and infections. Vaccine 2003;21:S2/24-S2/34.
8. Giles JT, Bathon JM, Serious infections Associated With anticytokine therapies in the Rheumatic Diseases. Journal of Intensive Care Medicine 2004;19:320-334.
9. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systemic review and meta-analysis of rare harmful effects in randomised controlled trials. JAMA 2006;295(19):2275-2285
10. Couriel D, Saliba R, Hicks K, Ippoliti C, Lima de M, Hosing C, et al. Tumor necrosis factor-? blockade for the treatment of acute GVHD. Blood 2004;104:649-654
11. Sugar AM. Agents of Mucormycosis and related species, principles and practice of infectious diseases 1995;239:2311-2317. In: principles and practice of infectious diseases, 1995 (fourth edition). Edited by Mandell GL, Dolin R, Bennett JE.
12. Maertens J, Demuynck H, Verbeken EK, Zachee P, Verhoef GEG, Vandenberghe P, Boogaerts MA. Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplantation 1999;24:307-312.
13. Cunningham I, MacCallum SJ, Nicholls MD, Byth K, Hewson JW, Arnold B, et al. The myelodysplastic syndromes: an analysis of prognostic factors in 226 cases from a single institution. British journal of haematology 1995;90:602-606.
14. Fuhler GM, Knol J, Drayer AL, Vellenga E. Impaired interleukin-8 and GRO? induced phosphorylation of extracellular signal-regulated kinase results in decreased migration of neutrophils from patients with myelodysplasia. Journal of leukocyte Biology 2005;7:257-266.
15. Mazzone A, Porta C, Possati G, Gritti D, Mazzucchelli I, Ricevuti G. Granulocyte dysplasia and dysfunction, and CD11/CD18 defects in myelodysplatic syndromes. Leuk Lymphoma 1996;23:267-275.