Visceral leishmaniasis in a patient with systemic juvenile arthritis treated by IL-1RA agonist (Anakinra)

Sirs,

The treatment of patients with severe systemic idiopathic juvenile arthritis (sJIA) is likely to improve thanks to the advent of new biotherapies. Tumour necrosis factor (TNF) blockade by TNF receptor analog (Etanercept) was demonstrated to be effective in approximately fifty percent of sJIA patients having polyarthritis but with restriction of no systemic symptoms (1). More recently, Verbsky *et al*. and Pascual *et al*. reported their experience with recombinant IL1-RA agonist Anakinra, in a few patients with sJIA, showing early remission of both systemic symptoms and arthritis (2, 3). In spite of apparent high benefit for sJIA patients, anti-cytokine therapies may induce serious and unpredictable side effects. We report a case of visceral leishmaniasis (VL) in a patient with sJIA while receiving treatment by Anakinra.

This 9 year-old girl, living in the southeast of France, had sJIA since the age of 4 years old. In spite of high dose steroids, she developed severe polyarthritis, unresponsive to methotrexate and cyclosporine. In addition, she developed three episodes of MAS in which one was under treatment by Etanercept. In November 2004, her arthritis was very active with thirty-four affected joints. She also had rash, splenomegaly, adenopathies and biological inflammation. She was treated with Anakinra [Kineret®] at 1 mg/kg/day with dramatic effect on systemic symptoms. After three months of treatment the number of affected joints decreased to fifteen and she had no biological inflammation. In May 2005, she presented with unremitting fever, scarlet fever-like pruritic rash and hepatosplenomegaly. Laboratory work showed: leukocytes: 10 6000/L, platelets: 82.000/L, haemoglobin: 8,1 g/dL, fibrinogen: 3.12 g/L, sedimentation rate: 30mm/h: triglycerides: 4.64 mmol/L. Bone marrow examination was normal but blood cultures detected *Leishmania infantum* infection. Kineret® was stopped and she was treated by liposomal Amphotericin B as well as steroids to cover the risk of MAS. All systemic symptoms resolved and blood cultures became negative.

Infection is the main complication in patients receiving anti-cytokine therapy with increased reports of tuberculosis and fungal infection. To date, most cases were reported with anti-TNF agents, including two reports of VL related to infliximab administration and, few with Anakinra (4-7). However, the occurrence of VL in our patient can be explained by both the nature of her underlying disease and the life style of this opportunist. VL is endemic in southern France where the reservoirs are chronically infected dogs. The disease is due to a protozoa transmitted by sandflies *Phlebotoma*. In the host, *Leishmania* live in macrophages as obligate intracellular amastigotes, and as flagellated free promastigotes in the intestine of the sandfly vector. Young children and immuno-compromised hosts are the targets of the infection. The clinical pattern of VL includes fever, splenomegaly, hepatomegaly and enlarged lymphnodes (8). Cytopenia, hypergammaglobulinemia and hypertriglyceridemia are common reflecting various degrees of MAS (9). These features are shared with sJIA patients in whom macrophages present high level of activation mediated by proinflammatory cytokines especially IL-6, IL-1β and TNF (10). SJIA patients have episodes of MAS triggered by viral infection and medications. Cytokine blockade induces experimental macrophage tolerance to intracellular opportunist all the easier as *Leishmania* amastigotes develop strategies to protect against immune destruction. They adapt to the acid and warm environment of the phagolysosome, as well as they alter macrophages cytokine production, oxydative burst activity, and antigen presentation (11). VL is a trap in patients with sJIA because it mimics the disease and induces MAS. Identification of the parasite in bone marrow may be negative but serologic test or parasite genome amplification in blood cultures may help. SJIA patients living in endemic areas and receiving anakinra may develop VL either by new infection or by parasite reactivation.

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