A case of Behçet's disease complicated by visceral Leishmaniasis and myelodysplasia: clinical considerations

Autoimmune diseases are treated with immunosuppressive drugs, including alkylating agents. Patients undergoing long-term therapy may develop myelodysplastic syndromes (MDS) with chromosomal abnormalities.[1-3] We describe a patient affected by Behçet's disease (BD), undergoing chlorambucil therapy, whose clinical picture was complicated by visceral Leishmaniasis and MDS associated with chromosome 7 monosomy.

A 35-year old man affected by BD with central nervous system vasculitis was treated with steroids and chlorambucil (10 mg/d for 3 years), with a favorable clinical response. The patient was admitted to our Department in June 1999 with a one-month history of fever and granulocytopenia. Physical examination showed no lymph node, spleen or liver enlargement. Routine blood examination revealed leukopenia, mainly granulocytopenia (mean values: 740/μL and 310/μL, respectively), anemia and reduced platelet counts (mean values: 65,000/μL). Serum immunoglobulins (Ig) were in normal ranges. Chlorambucil therapy was discontinued and steroid therapy reduced to a dose of 10 mg/daily. During the in-hospital period, the patient's clinical conditions worsened, with a high-spiking fever (40°C) (Figure 1). Liver and spleen as well as Ig levels remained unchanged. The search for infectious foci, including IgM and IgG antibodies to Epstein-Barr virus, cytomegalovirus (CMV) and *Leishmania* was negative as was the search for Cryptococcal antigen and CMV-antigenemia. Bone marrow (BM) aspirate showed trilineage MDS. Wide-spectrum antibiotics were introduced but the patient remained febrile. White blood cells (WBC) and granulocyte count were still reduced (Figure 2). A third BM biopsy led to the demonstration of *Leishmania* amastigotes. A therapy based on liposo-

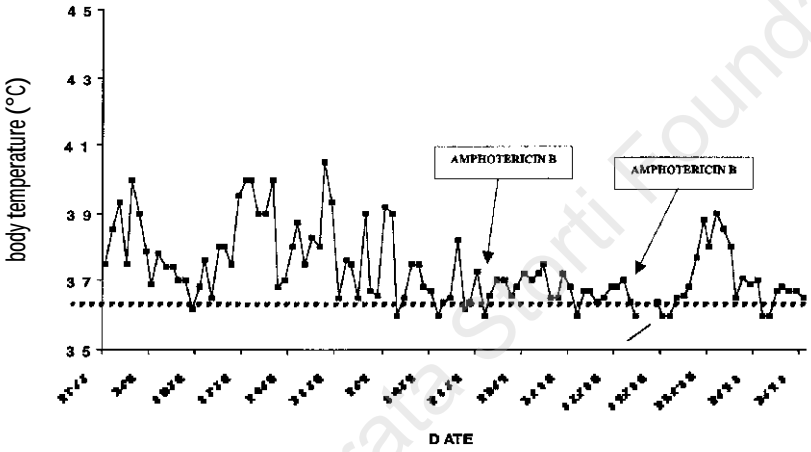

Figure 1. Body temperature schedule (°C) during the in-hospital observation period July 22-November 11, 1999. The arrows show the timing of amphotericin B therapy.

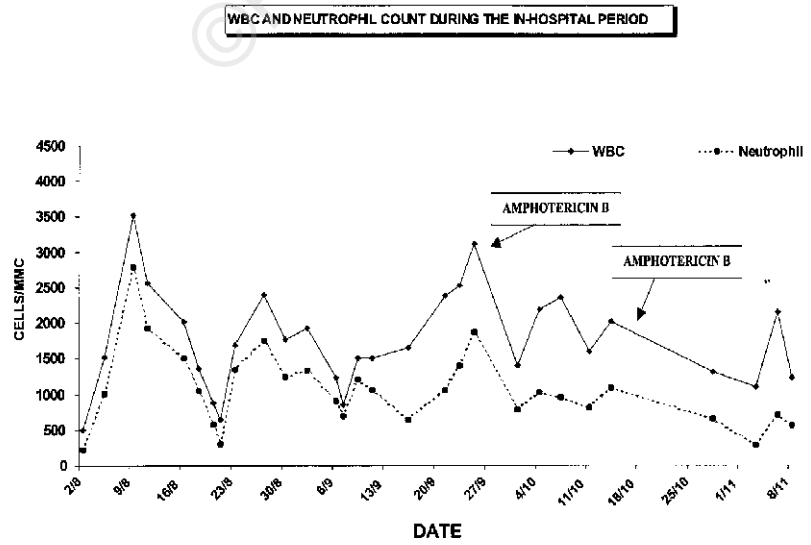

Figure 2. Absolute white blood cell (WBC) and neutrophil counts during the in-hospital observation period August 2-November 8, 1999. The arrows show the timing of amphotericin B therapy.

mal amphotericin B was then started together with discontinuation of steroids, which resulted in the apparent clearance of *Leishmania* from BM after several cycles of therapy, with a dose of 3 mg/kg/day, for 5 days in a month (Figures 1 and 2). The patient's clinical conditions improved and he became non-febrile. Anemia improved and the platelet count increased, whereas WBC and granulocyte counts persisted low. Finally, cytogenetic examination of BM showed chromosome 7 monosomy. Presently, repeated BM aspirates have not shown *Leishmania* parasites whereas MDS has evolved into acute leukemia.

Some BD cases treated with cytotoxic agents and developing MDS have been reported.[5-7] The risk of MDS development is related to the cumulative dose and treatment duration with the different cytotoxic agents[8] and most of the associated genetic abnormalities involve chromosomes 7 and 8.[1,2,5] Very few MDS cases are described after chlorambucil therapy,[5] whereas several patients have developed MDS after cyclophosphamide. As to this latter agent, McCarthy *et al.* found that a cumulative dose >100g was the critical value to start a long-term haematologic follow-up, due to the observation that, in their series of patients, MDS appeared even four years after therapy withdrawal.[2] The critical value for chlorambucil therapy is not known, nor is the mechanism underlying MDS development in these cases. The hypothesis that an MDS clone may be present even at the diagnosis of autoimmune diseases and discovered later may be postulated. Autoimmune diseases, including BD, are accompanied by a dysregulation of the immune response,[4] which may influence the appearance and outcome of MDS. In fact, a multistep pathogenesis of MDS, involving several components of the immune system, has been proposed.[9] Finally, alkylating agents may reduce marrow stem cells, with subsequent cytopenia.

Long-term and continuous immunosuppressive treatment of autoimmune diseases may lead to hematologic complications. Thus, we recommend a careful follow-up in these patients. A BM aspirate, with cytogenetic studies, should be performed immediately after the development of refractory cytopenia, even following therapy withdrawal and the exclusion of other causes of cytopenia, including infectious agents.

Maria Caterina Sirianni, Barbara Barbone,* Bruno Monarca,° Mauro Nanni,° Bruno Laganà,* Fernando Aiuti**

**Department of Clinical Immunology; °Department of Biotecnologie Cellulari ed Ematologia, University of Rome "La Sapienza", Rome, Italy*

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Correspondence: Maria Caterina Sirianni, M.D., Clinical Immunology, Department of Clinical Medicine, University of Rome "La Sapienza", viale dell'Università 37, 00185 Rome, Italy.
Phone: international +39.06.49972037.
Fax: international ++39.06.4466209.
E-mail: mariacaterina.sirianni@uniroma.1.it

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