CASE REPORT

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Interferon-α activity in a case of severe autoimmune lymphoproliferative disease

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Abstract Autoimmune lymphoproliferative disease (ALD) is a rare familial disorder. Clinical and laboratory features of this disease include a generalized lymphadenopathy, splenomegaly, increased levels of circulating CD3+ with low levels of CD4+, CD8+ T-cells, and autoimmune phenomena, characteristics that the autoimmune lymphoproliferative syndrome (ALPS) have in common. Treatment usually consists of different supportive therapies. We report on the case of a young man affected by ALD who became resistant to steroids and was unresponsive to cyclosporine. Nevertheless, he was successfully treated with interferon (IFN)-α, resulting in a long-lasting, clinically complete remission.

Keywords Autoimmune lymphoproliferative syndrome · Defective Fas ability · interferon-α

Introduction

Among lymphoproliferative disorders, a rare disease has been described by Fisher et al. [6] and called autoimmune lymphoproliferative syndrome (ALPS). Clinical characteristics of this disorder are generalized lymphadenopathy, splenomegaly with increased levels of CD3+, CD4−, CD8− T-cells (double negative) in the peripheral blood and autoimmune phenomena (haemolytical anaemia, thrombocytopenia and neutropenia). In vivo abnormalities of cytokine secretion have been reported with elevated interleukin (IL)10 levels and a mild increase in IL2 levels [7]. In this disease, mutations in the Fas gene are often present and lead to a deficiency in Fas-induced apoptosis [8, 11, 15]. This defect is inherited as an autosomal recessive trait [12, 14]. Recently, a variant of ALPS, autoimmune lymphoproliferative disease (ALD), has been described. It is characterized by autoimmune manifestations, lymphadenopathy, splenomegaly and a defective Fas ability to induce T-cell death, but without Fas gene mutations [4, 9]. Recently, patients with similar clinical symptoms resulting from a functional Fas deficiency, without Fas gene mutations, have been described and reversible monoclonal lymphadenopathy has also been reported in this functional Fas deficiency [16].

We present the case of a man, followed for 6 years (from 14 to 20 years old), with a history of clinical and laboratory manifestations suggestive of ALD. After several years of treatment the patient became resistant to steroids and unresponsive to cyclosporine. He was then successfully treated with interferon (IFN)-α.

Treatment of such patients is usually restricted to supportive therapy. Autoimmune disorders and lymphadenopathies have been treated with either cyclophosphamide or corticosteroids, even splenectomy [4, 5]. A severely affected child has been cured by a bone marrow transplantation [2]. Recently, a patient has been successfully treated by joint administration of pyrimethamine and sulphadoxine [17].

Case report

A 14-year-old Caucasian male presented in November 1991 with a fever of undetermined origin and anaemia. Physical examination revealed pale skin; jugular, axillary and inguinal lymph node enlargement; and splenomegaly. Laboratory analysis revealed a haemoglobin (Hb) level of 6.4 g/dl and increased levels of immunoglobulin (Ig)A. IgG and acute phase reactants. Tests for viruses, bacteria, fungi and parasites were negative. Other laboratory findings, including urea and liver function tests, were unre-
Fig. 1 T-cell receptor rearrangement evaluated by Southern blot. Monoclonal T-cell rearrangement is revealed by the appearance of an additional band (>) after DNA digestion with EcoRI restriction enzyme.

Flow cytometry revealed elevated levels of CD3+ (71%), with low levels of CD4+ (4%) and CD8+ (31%). Levels of CD19 + B-lymphocytes and CD23+ were 14% and 1.6%, respectively. CD4−, CD8− double negative T-lymphocytes in the peripheral blood amounted to 36% of total lymphocytes. Virological and microbiological tests, including one for HHV-6, were negative. Bone marrow examination revealed a subtotal substitution for activated lymphocytes. Southern blotting performed on these samples showed a clonally rearranged T-cell receptor (β-chain) (Fig. 1). Steroids were readministered, but this time without response.

A new node biopsy described a hypercellular lymph node, where all main topographical markings (follicles, paracortex and sinususes) were still recognizable. Germinal centres tended to be relatively small, while the paracortex was extensively expanded by a mixed lymphoid proliferation, featuring a spectrum of activated cells with many immunoblasts and sheets of mature plasma cells (Fig. 2). The patient was diagnosed as having ALD on the basis of the described clinical presentation and histological features. Treatment consisted of IFN-α at a dosage of 1.5 MU three times weekly for 9 months. Complete remission was achieved, which has been maintained for 3 years.

Besides a transient reduction in white blood cells and platelets, no side-effects have been reported by the patient, and no laboratory findings related to INF toxicity have been detected. Moreover, during INF therapy, the patient did not take any other drugs.