Secondary hemophagocytic lymphohistiocytosis possibly induced by interferon beta-1a therapy

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SUMMARY

A 57-year old woman with a history of multiple sclerosis, treated with interferon beta-1a in the last 5 months, was referred for hyperpyrexia (>40°C) that persisted for 15 days. At admission, there was elevation of transaminases, anemia (hemoglobin 8.9 g/dL), thrombocytopenia (platelet 135,000/mm^3), and hypofibrinogenemia (fibrinogen 1.26 g/L). C-reactive protein was 10.7 mg/dL, lactate dehydrogenase 1270 U/L and ferritin 2380 ng/mL, with hepatosplenomegaly and linfoadenomegaly. Hemophagocytic lymphohistiocytosis induced by direct stimulation of macrophages by interferon (IFN) was suspected. IFN was withdrawn as only measure and one-month later signs and symptoms disappeared, with complete normalization of laboratory examinations.

Key words: *Interferon, Hemophagocytosis, Macrophage activation syndrome, Hemophagocytic lymphohistiocytosis, Multiple sclerosis.*

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INTRODUCTION

The hemophagocytic lymphohistiocytoses (HLH) are rare and potentially fatal diseases that acutely occur with high fever, lymphadenopathy, splenomegaly, increased liver damage tests, pancytopenia, in particular thrombocytopenia, hypofibrinogenemia, and increased concentrations of D-dimer, lactate dehydrogenase (LDH), triglycerides, and ferritin (1).

They are characterized by the accumulation, in the bone marrow, of benign and well-differentiated cells with macrophage phenotype (1, 2), which can potentially infiltrate every organ.

The diagnosis of HLH is based on clinical findings and laboratory investigations, and is confirmed by the presence of hemophagocytosis in the bone marrow biopsy, as suggested by the criteria developed by the International Histiocyte Society in 2004 (3).

Macrophage activation syndrome (MAS) is a descriptive term to designate the condition when it is associated with autoimmune, diseases (1).

CASE REPORT

A 57-year old woman with a history of multiple sclerosis, treated with interferon (IFN) beta-1a in the last 5 months, was referred for hyperpyrexia (>40°C) that persisted for 15 days. She had been treated with azithromycin 500 mg/day for 5 days, then levofloxacin 500 mg/day for 7 days, without improvement. On physical examination, moderate hepatomegaly, splenomegaly and lateral-cervical and axillary lymhpnodes enlargement was observed. At admission, alanine transferase (ALT) was 97 U/L (nv<36 U/L), aspartate transferase (AST) 91 U/L (nv<31 U/L), hemoglobin 8.9 g/dL (nv>12 g/dL), platelet count 135,000/mm^3 (nv>150,000/mm^3), LDH 1,270 U/L (nv<280 U/L), C-reactive protein (CRP) 10.7 mg/dL (nv<0.5 mg/dL), erythrocyte sedimentation rate 84 mm/h (nv<35 mm/h), ferritin 2380 ng/mL (nv<150 ng/mL), and fibrinogen 1.26 g/L (nv>1.5 g/L). White blood cell count, beta2-microglobulin, thyroid function, C3 and C4, IgM rheumatoid factor, antinuclear antibody, antibodies to anti-extractable

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nuclear antigens, anti-native DNA antibodies, anti-neutrophil cytoplasmic antibodies, IgM antibodies for Epstein-Barr virus, cytomegalovirus, type 1 and type 2 herpes simplex virus, hepatitis B virus (HBV), hepatitis C virus, and toxoplasma, as well as repeated blood and urine cultures were in the normal range or negative.

On the basis of clinical and laboratory findings, HLH induced by direct stimulation of macrophages by IFN beta-1a was suspected. Although the patient refused a bone marrow or lymphnode biopsy, the revised diagnostic guidelines for HLH of the International Histiocyte Society were fulfilled, because of persistent fever, splenomegaly, cytopenia (hemoglobin <90 g/L, platelets $<135x10^9$/L), increased concentration of ferritin, and hypofibrinogenemia. According to these guidelines, 5/8 criteria or the molecular diagnosis, such as mutations in PRF1 or Munc13-4, are needed. IFN beta-1a was withdrawn and 27 days later signs and symptoms disappeared, in the absence of other treatments, including glucocorticoids. Laboratory tests showed hemoglobin 11.5 g/dL, platelets count 191,000/mm^3, ferritin 629 ng/mL, ALT 51 U/L, AST 44 U/L and LDH 352 U/L. After 2 months, complete disappearance of symptoms and complete normalization of laboratory examinations persisted: hemoglobin was 13.9 g/dL, platelet count 351,000/mm^3, ferritin 211 ng/mL, ALT 11 U/L, AST 10 U/L, CRP 0.17 mg/dL, and LDH 172 U/L.

DISCUSSION

HLH can be divided in a primary, genetically determined form (familial hemophagocytic lymphohistiocytosis) and a secondary or acquired form, which may be associated with infections, immunodeficiency states, malignancies or lymphoproliferative disorders, autoimmune and connective tissue diseases (1,4). It occurs when the natural regulation of inflammatory response is deficient, resulting in an excessive and persistent activation of T lymphocytes and histiocytes with progressive multiorgan failure.

Our patient fulfilled the minimum number of criteria necessary for HLH diagnosis, but biopsy of the bone marrow could not be obtained. For this reason, HLH is strongly suspected but not completely proven. We recognize that splenomegaly was diagnosed only on physical examination, that anemia and thrombocytopenia could be side-effects of INF beta-1a therapy, and that including thrombocytopenia, hypofibrinogenemia and hyperferritinemia were not as pronounced as expected in most cases of HLH. However, disease onset was very recent and laboratory findings were progressively deteriorating in consecutive examinations. In addition, alternative diagnoses, such as infections, were ruled out and the possibility of a drug-related side effect, although possible, is unlikely.

An increase in interferon gamma (IFN gamma) plasma concentration associated with that of CD8+ T cells activity, has been reported in HLH associated with HBV infection in a murine model (5). In a form of familial hemophagocytic lymphohistiocytosis (FHL3), a mutation of the gene Munc13-4, involved in the release of perforin (6) has been demonstrated. Natural killer (NK) cells and cytotoxic T lymphocytes fail to remove infected cells, and the persistence of antigenic stimulation could lead to persistent activation of T lymphocytes and disproportionate production of cytokines, including IFN-gamma, with consequent macrophage stimulation (7). IFN-beta activates the immune response through the type I IFN signaling pathway. Type I IFN (IFN-alfa/beta) and type II IFN (IFN-gamma) have no complete structural homology. However, functional similarities exist, with a wide overlap in the types of genes that they can induce (8). Type I IFNs are produced as direct response to viral infections and include IFN alfa, primarily synthesized by leukocytes, and INF beta, synthesized by most cell types, in particular fibroblasts. Type II IFN consists of IFN gamma, produced in response to the recognition of infected cells by activated T lymphocytes and NK cells (9). The mechanisms of self-regulation of IFN beta's pathway allow precise and environment-

dependent response of the cells in different conditions, and the immunomodulatory effect of IFN-beta signaling in macrophages relies on the transient oscillatory dynamics of the JAK-STAT pathway, whose specific relaxation properties determine the duration of the cellular response to the cytokine (10). MAS induced by adalimumab (11), tocilizumab (12), and etanercept (13) has been reported in the literature. For its mechanisms of action, IFN beta could be a potential HLH inducer in predisposed subject as suggested by our case report, perhaps because of the molecular mechanisms that involve the JAK-STAT pathway.

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