Dramatic clinical efficacy of cladribine in Rosai-Dorfman disease and evolution of the cytokine profile: towards a new therapeutic approach

Rosai-Dorfman disease (RDD) is a rare disorder, often benign but with possible life-threatening prognosis. In most cases, specific treatment is not necessary; when required, the management of RDD is not codified to date, and various chemotherapies have been shown to be ineffective. Here, we report a patient with RDD who presented a dramatic and sustained response with cladribine. Analysis of the cytokine profile evolution shows a clear correlation between serum levels of TNF-alpha and IL-6 and disease activity. Our findings show the promising efficacy of cladribine and suggest that therapies targeting specifically cytokines might be useful in some cases of active RDD.

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Rosai-Dorfman disease (RDD) or sinus histiocytosis with massive lymphadenopathy (SHML) is a rare disorder of unknown etiology characterized by a nonmalignant proliferation of distinctive histiocytic/phagocytic cells within lymph node sinuses and lymphatics in extranodal sites.[1] RDD shows variable evolution, most often as prolonged clinical course with exacerbation and spontaneous remission phases.[1,2] Despite its usual benign prognosis with relapsing/remitting but finally self-limiting course, RDD may be complicated by organ compression and/or extranodal involvement responsible for a wide spectrum of clinical manifestations; it also may be life-threatened because of secondary organs involvement responsible for dysfunction and profound impairment of general health status.[1,3] Because prospective therapeutic studies are lacking, management of RDD is not codified yet. Various chemotherapies, interferon and radiotherapy are usually ineffective to improve general status and reduce tumor mass. When required, surgical debulking might be useful but debilitating, and should be proposed as the last option.[2] Here we report a patient with RDD who presented a dramatic and sustained response after treatment with cladribine, and discuss new therapeutic approaches regarding cytokine profile evolution.

Study design

Case report

A 45-year-old woman was admitted for massive bilateral cervical lymph nodes (LN). LN biopsy in March 2002 showed characteristic features of RDD (Figure 1). Initial therapeutic abstention was decided, and clinical course was marked by exacerbation phases with spontaneous remissions. In April 2003, the patient experienced an important exacerbation phase with bilateral massive LN of the cervical and axillary areas, fever and deterioration of the general health status, without any extranodal involvement. Corticosteroids allowed a rapid but transient improvement, followed by a new exacerbation phase with generalized massive LN and important systemic symptoms. Blood tests showed increased white blood cells with neutrophilia (13.4×10^9/L), anaemia (9.8 g/dL), increased platelet count (693×10^9/L) and increased C-reactive protein level (107 mg/L). Liver function tests and serum lactate deshydrogenase were normal. Blood flow cytometry analysis did not reveal any clonal or abnormal population. A thoracic and abdominal CT scan revealed many deep LN. The patient

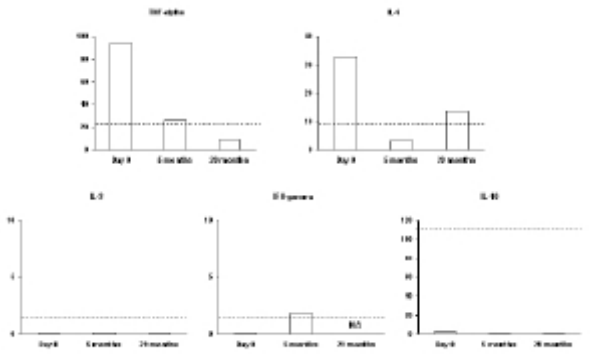

Figure 1. Lymph node biopsy. (A) Markedly sinus dilatation, compressing the lymphoid parenchyma by lymphocytes and hyperplastic large phagocytic histiocytes with multiple intracytoplasmic vacuoles containing viable lymphocytes (arrow). (B) S-100 protein positivity of these sinus histiocytes showing active emperipolesis (arrow).

Figure 2. Cytokine profile evolution. Cytokine levels before treatment (Day 0), and 5 and 29 months after treatment. The normal values are indicated by the dotted lines (NA= not available).

was treated with 2 courses of vinblastine (6 mg/m^2) every 15 days in September 2003, with no efficacy. Treatment with cladribine (infusion of 2.1 mg/m^2/day for 5 days) alone, without steroids, was begun for 3 cycles every 28 days. Marked resolution of systemic symptoms and all LN was rapidly obtained after the first infusion, as normalization of all biological inflammatory parameters. Thoracic and abdominal CT scan and abdominal ultrasonography revealed regression of deep LN. After a 30 months follow-up off therapy, complete clinical and biological response is sustained without any recurrence.

Serum cytokines levels

Levels of cytokines (interleukins (IL)-2, IL-6, IL-10, tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma) were assessed by Enzyme Linked Immuno Sorbent Assay (ELISA) test (BioSource Europe, Belgium) in serum samples before treatment with cladribine, and 5 and 29 months after the first infusion of cladribine.

Results and discussion

Serum cytokines levels were assessed before and after treatment with cladribine to analyse the cytokine profile evolution (Figure 2). Serum concentrations of cytokines before treatment revealed increased levels of TNF-alpha (94.4 pg/mL; N < 20) and IL-6 (32.9 pg/mL; N < 8.6), and normal levels of IL-2 (0 UI/mL; N < 1.2), IL-10 (2 pg/mL; N < 112) and IFN-gamma (0 UI/mL; N < 1.2). Five and 29 months after treatment, serum concentrations showed a sustained normalization of TNF-alpha (26 and 8.7 pg/mL respectively) and IL-6 (3.3 and 13.8 pg/mL respectively). IL-2 (0 and 0 UI/mL respectively), IL-10 (0.3 and 0 pg/mL respectively) and IFN-gamma (1.8 UI/L and not available respectively) levels remained within normal values. Thus,

analysis of the cytokine profile evolution clearly shows a positive correlation between serum cytokines levels of TNF-alpha and IL-6 and disease activity. The pathophysiology of RDD is poorly understood. However, a cytokines and/or chemokines-mediated migration of monocytes might be involved in histiocytes accumulation and activation. This functional activation may be triggered by different stimuli, as suggested by the coexistence of RDD and hematological malignancies, autoimmune diseases or post-infectious conditions.[1,4-6] Although both Langerhans cells histiocytosis (LCH) and RDD appear as diseases related to the monocytes/ macrophagic system of differenciation, which are associated with increased cytokines production, their profile of cytokine expression is different. Histiocytes of RDD strongly expressed both transcripts of TNF-alpha and IL-1beta and also moderate IL-6 specific signals, while in LCH, transcript expression is variable for TNF-alpha, weak and occasional for IL-1beta and negative for IL-6.[7] Reactive inflammatory cells accompanying the pathologic cells also expressed in variable amounts both of these cytokines.[7] Complex interactions between RDD histiocytes and these reactive cells, notably polyclonal plasma cells, probably occur such as autocrine and/or paracrine loop mechanisms with enhanced cytokines stimulation and activation.[6,7] This hypothesis is supported by the efficacy of rituximab reported in one case.[8] We thus formulate the hypothesis that RDD could be a good candidate for therapies targeting TNF-alpha, IL-6 and IL-1 cytokines, which are probably directly responsible for its systemic symptoms. The origin of histiocytes of RDD and LCH from a common bone marrow precursor related to the monocyte/macrophage lineage and the promising results of cladribine for recurrent and/or high risk LCH 9-11 provide a strong rationale to use this drug in RDD. Cladribine is a purine analog with an important toxicity for both mature non-dividing lymphocytes and monocytes.[12] Cladribine decreases viability and impairs functions of monocytes including inhibition of IL-6 production, that probably play a central role on RDD activity.[13] Cladribine was previously reported in RDD in 4 patients, and showed a very good and sustained response in 2 patients, as observed in our patient, a moderate and transient response in one case and an absence of efficacy in an another case.[14,15] Analysis of the cytokine profile evolution may suggest that other immunomodulators and/or biotherapies targeting powerfully and more specifically TNF-alpha and/or IL-6 such as thalidomide 16, lenalidomide, anti-TNF-alpha blockers or anti-IL-6 antibody could be promising therapies in this disease, at least in symptoms relieve, and should be evaluated in prospective studies. However, these cytokines may only represent markers of disease activity and help in monitoring efficacy of therapy. All these treatments, however, should be used with caution because they may induce serious adverse events including myelosuppression, infections, autoimmune diseases and lymphoproliferative disorders, which may be also observed spontaneously in the course of RDD. Therefore, since RDD had most often a benign prognosis, the use of these therapies must be limited to recurrent, refractory and/or life-threatening disease. In conclusion, our study suggests that pro-inflammatory cytokines such as IL-6 and TNF-alpha may play a role in the pathophysiology of RDD and may be used as biomarkers of RDD activity. Furthermore, beside cytotoxic drugs of the monocytic lineage, biotherapies or drugs specifically targeting these cytokines in recurrent, relapsing and/or life-threatening disease might be used. Further prospective studies are warranted to confirm our findings and to assess the safety and effectiveness of these treatments in a larger group of patients with RDD.

Achille Aouba[1,2] Benjamin Terrier,[1]* Viorel Vasiliu,[3] Sophie Candon,[4] Nicole Brousse,[3] Bruno Varet,[4] Olivier Hermine[1,5]*

[1]Department of Adult Hematology, [3]Department of Pathology, 4epartment of Immunology, [5]CNRS UMR 8147, Hôpital Necker Enfants-Malades, Paris V University, Assistance Publique-Hôpitaux de Paris (AP-HP), 49-161 rue de Sèvres, 75743 Paris Cedex 15, France.

[2]Department of Internal Medicine, Hôpital Cochin, AP-HP, 27 rue du faubourg Saint-Jacques, 75014 Paris, France.

** AA and BT contributed equally to this work. A.A., B.T. and O.H. wrote the paper, B.V. participated to the follow-up of the patient, V.V. and N.B. provided the figures, and S.C. performed the cytokines dosage.*

Keywords: Rosai-Dorfman disease, sinus histiocytosis with massive lymphadenopathy, cladribine, TNF-alpha, interleukine-6

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