Here we report a patient with Rosai-Dorfman disease (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.

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.

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 remission phases. Despite its usual benign prognosis with relapsing/reliving 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. 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. 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.

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 analyze 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. Although both Langerhans cells histiocytosis (LCH) and RDD appear as diseases related to the monocytes/macrophagic system of differentiation, 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. Reactive inflammatory cells accompanying the pathologic cells also expressed in variable amounts both of these cytokines. Complex interactions between RDD histiocytes and these reactive cells, notably polycyonal plasma cells, probably occur such as autocrine and/or paracrine loop mechanisms with enhanced cytokines stimulation and activation. This hypothesis is supported by the efficacy of rituximab reported in one case. 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. Cladribine decreases viability and impairs functions of monocytes including inhibition of IL-6 production, that probably play a central role on RDD activity. 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 another case.13.14 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 symptomatic reliev, 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, relaxing 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.

References


