short report
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ROSAI-DORFMAN SYNDROME WITH EXTRANODAL LOCALIZATIONS AND RESPONSE TO GLUCOCORTICOIDS: A CASE REPORT

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ABSTRACT

A case of sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman syndrome) in a 42-year-old man is described. The disease involved the respiratory tract and skeletal apparatus, led to considerable general impairment and was unusually responsive to glucocorticoids. Molecular and immunophenotype analysis seem to confirm the reactive nature of a disorder that shows profound T-cell immunodeficency.

Key words: histiocytosis, Rosai-Dorfman disease

Sinus histiocytosis with massive lymphadenopathy (SHML) was first described by Rosai and Dorfman in 1969[1] and is now considered a non malignant inflammatory disorder[2] in which the precise origin of pathologic cells is still controversial.[3,4]

Although its etiology is unknown, a characteristic diagnostic lymph node histology is usually present and extranodal extension is described in about 30-40% of cases. Different treatments have had little effect on the clinical course of the disease.[5,6] We describe here a case of SHML investigated through molecular analysis, whose clinical presentation and response to glucocorticoids were unusual.

Case report

A 42-year-old man was evaluated for prominent bilateral cervical, supraclavicular, axillary and inguinal adenopathy of five months' duration. Asthenia, minimal dyspnea, marked weight loss (around 10 kg), intermittent fever (max 38°C), hepato-splenomegaly, arthralgias and erythema nodosum were present. Routine hematological tests showed slight microcytic anemia, profound lymphocytopenia (0.3×10^9/L; CD4/CD8 ratio: 0.7), a polyclonal increase in γ-globulins, a high erythrocyte sedimentation rate and a high β2-microglobulin level (5.6 mg/L). Serologic tests did not indicate any recent EBV or herpes virus infection. Chest X-ray revealed mediastinal and hilar adenopathy, together with diffuse reticulonodular lung infiltration. Abdominal and pelvic NMR detected bulky lymphadenopathy at the aortic, preaortic and iliac sites, that compressed and dislocated the lower vena cava, renal vessels, aorta and bladder. Moreover, spinal column and pelvic bone diffusely showed abnormal signals suggestive of possible bone involvement. Total body scintigraphy with Ga67 registered intense lymph node and lung captation.

A cervical node biopsy established the diagnosis of SHML. The lymph node architecture was partially effaced; there was massive sinus dilatation with proliferation of histiocytes expressing S-100 protein, and massive plasma cell and immunoblastic infiltration with the presence of epithelioid cells (Figure 1).

Although a marrow aspirate gave a normal

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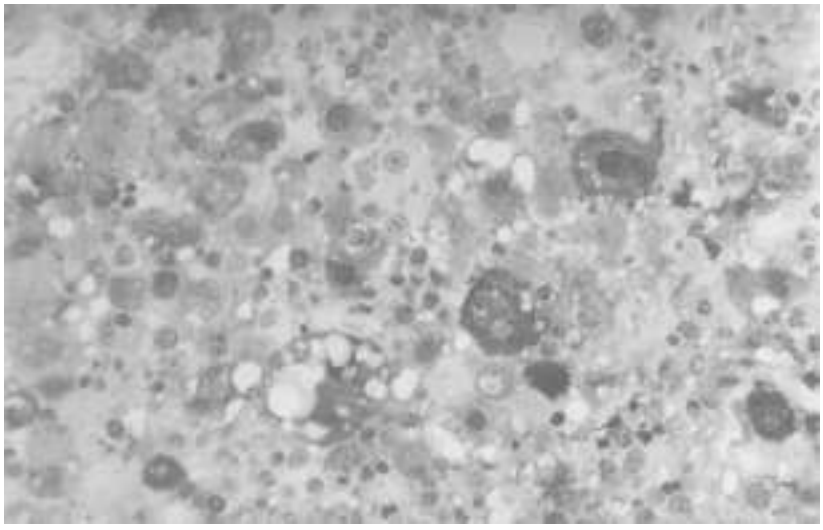

Figure 1. Intense immunohistochemical positivity of S-100 protein in phagocytizing histiocytes (400 X).

differential count, bone marrow biopsy showed distended sinusoids engorged by erythrocytes, as well as myeloid and eosinophil hyperplasia. Molecular analysis of the DNA extracted from the lymph node cell populations did not detect any clonal rearrangement of the immunoglobulin (Ig) heavy chain genes or T-cell receptor (TCR) genes.

Prednisone 75 mg/day p.o. was initiated and after 15 days very good clinico-radiographic remission was obtained. The prednisone dosage was slowly reduced to 25 mg/day. After three months of therapy the patient was clinically asymptomatic, and total body NMR showed an almost complete regression of lymphadenopathy and lung infiltration, as well as a normalization of the skeletal picture. One year after diagnosis, while continuing prednisone (12.5 mg/day), the patient is completely asymptomatic with a normal chest radiogram. Lymphocytopenia (0.5×10^9/L), a high erythrocyte sedimentation rate and a small polyclonal increase in γ-globulins are still present.

Discussion

SHML (also known as Rosai-Dorfman syndrome) is a rare, benign and self-limited disorder (433 cases were described in 1990 by Foucar *et al.*)[6] that occurs most frequently in the first two decades of life.[7,8] Its etiology is largely unknown. Sporadic cases have been associated with EBV or herpes virus[6] infections, and two cases with malignant lymphoma.[8] Although it was initially considered a lymph node-limited disease that involved the cervical stations in particular with a biphasic course (slowly progressive adenopathy followed some months later by gradual recovery), it has since been shown to be a more complex clinico-pathologic entity. In fact, in about one third of cases[6] there is extranodal involvement, especially at the level of the mucosal membranes of the upper and lower respiratory tract, skin, bone, joints, thyroid, uveal tract, orbit, eyelids, kidney, testes, lungs, thymus, heart, liver, salivary and lacrimal glands, pancreas, jejunum, central nervous system and meninges.[5,9] As in our case, node biopsy shows characteristic pathologic features: medullary and subcapsular sinusoid dilatation, proliferation of S-100-positive histiocytes, often phagocytizing lymphocytes and erythrocytes, marked and progressive fibrosis in the capsular and pericapsular areas, abundance of lymphocytes and plasma cells in the intersinal spaces, and effacement of the node in a later phase.[1,3,10,11]

The clinical behavior of our case was unusual for the concomitance of important systemic symptoms (with long-lasting intermittent fever, marked weight loss, arthralgia, erythema nodosum), extensive extranodal involvement (lungs, liver, spleen, probably bone) and a good

response to relatively high doses of prednisone (whereas this and other treatments usually have little effect on the course of the disease).

Whether a histiocytic proliferation is reactive or malignant cannot easily be defined on clinical grounds alone.

Clonal cell proliferation must be demonstrated by detecting a particular chromosomal marker, or sometimes (owing to demonstrated *lineage infidelity*) a clonal rearrangement of Ig or TCR genes.[8] In agreement with Paulli *et al.*, who recently showed the polyclonal nature of the cell infiltrate in SHML,[2] molecular analysis of our case failed to detect any clonal rearrangement of the Ig heavy chain or TCR genes.

Although SHML is generally regarded as a benign disorder, some patients may have a fatal outcome. The spread of the disease to vital organs seems to be the direct cause of death in very rare instances, but death is more frequently due to a significant defect in immune function,[5] particularly at the level of the T-cell network.[6] In accordance with the findings of other authors,[6,12] we observed a profound defect in circulating lymphocytes, with a reversed T4/T8 ratio. Fortunately, this immune deficit did not lead to severe infection in our case.

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