

Systemic mast cell disease associated with B-chronic lymphocytic leukemia

Patients with systemic mastocytosis (SM) are at a high risk of developing life-threatening myeloid malignancies such as acute myeloid leukemia, chronic myeloid leukemia or myelomonocytic leukemia. Lymphoproliferative disorders may also occur, although more rarely. We report a case of a patient with SM who developed chronic lymphocytic leukemia ten years after the diagnosis of his original disease. To our knowledge, this is the first reported case of this association.

Systemic mastocytosis (SM) is a rare disease characterized by an abnormal proliferation of mast cells that infiltrate bone marrow, spleen, liver, or lymph nodes with or without skin involvement.¹ This disorder produces a wide spectrum of clinical presentations with different prognostic implications leading to diverse classification systems.² The association of a range of pre-malignant and malignant myeloid hematologic disorders with SM is well recognized (occurring in up to 30%) and suggests a possible myeloid origin for mast cells.³ Lymphoproliferative disorders (LPD) may also develop in patients with SM, although their frequency is much lower than that of myeloid neoplasms.

We report the case of a patient who developed chronic lymphocytic leukemia (CLL) ten years after the initial diagnosis of SM.

In February 1993, a 36-year old man suffering from urticaria pigmentosa was referred to us in order to rule out a systemic mast cell disease. The patient complained only of clinical symptoms of urticaria. Physical examination showed diffuse brown-erythematous lesions. Blood counts and serum biochemical parameters were normal. A bone marrow biopsy showed multifocal mast cell infiltrates. A radiological study showed multiple sclerotic lesions in the pelvis and total body technetium scintigraphy revealed increased uptake in the skeleton, both findings considered compatible with SM. The patient was treated with antihistamine agents which produced good control of symptoms. In January 2000, a leukocytosis of $19 \times 10^9/L$, with an absolute lymphocytosis of $12.2 \times 10^9/L$ was found. Physical examination was unremarkable. There was no anemia or thrombocytopenia and liver and renal function tests, lactate dehydrogenase and β -2-microglobulin were normal. Neoplastic CD19 cells were immunophenotyped using a wide panel of monoclonal antibodies which showed the following results: CD5⁺ CD19⁺ CD23⁺ CD22⁺dim CD79b⁻ CD20⁺dim FMC7⁻ CD25⁺dim CD103⁻ Cd10⁻ and κ light chain restriction with faint intensity. Malignant mast cells showed the classical aberrant immunophenotype CD2⁺ CD25⁺. A bone marrow biopsy demonstrated nodular infiltration by mature lymphocytes; immunohistochemical stain for CD117 showed many mast cells in fibrotic areas (Figure 1). The bone marrow aspirate demonstrated an infiltration of more than 75% by mature lymphocytes. A thoracoabdominopelvic CT scan showed splenomegaly, nodular images of less than 1 cm located in mediastinum, right axilla and mesentery and a single para-aortic nodule bigger than 1 cm. The patient was diagnosed as having CLL stage A and he remains alive and well without specific treatment 12 months after the diagnosis.

SM has been described in association with many malignant diseases. Most hematologic malignancies associated with SM are of myeloid origin. A non-random association between SM and myeloid disorders has been postulated by some authors and recently, mast cells have been considered of myeloid origin.³ LPD may also develop in patients with SM, although their frequency of occurrence is much lower than that of myeloid neoplasms. Two well-documented cases of Hodgkin's disease,^{4,5} one with hairy cell leukemia,⁶ one with multiple myeloma⁷ and several cases of non-Hodgkin's lymphomas have been described.^{8,9} Nevertheless, to the best of our knowledge, this is the first case that reports an asso-

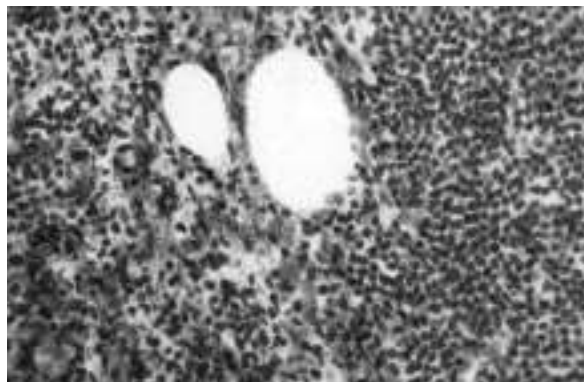


Figure 1. A histologic picture showing mast cell infiltrates (CD117), lymphocytes and prolymphocytes.

ciation between CLL and SM.

Sometimes, the diagnosis of both coexisting entities, SM and a LPD, can be difficult. Frequently, high numbers of lymphocytes are found infiltrating the bone marrow of patients with mast cell disease, mimicking a LPD. However, in such cases a polyclonal origin of lymphocytes can be demonstrated. On the other hand, mast cell infiltrates, occasionally observed in some hematologic malignancies, are reactive disorders. For this reason, immunophenotyping of the cell lines is essential in order to demonstrate the aberrant phenotype (CD2⁺ and CD25⁺), never present in normal reactive mast cells.¹⁰ More recently, mutations in c-kit and clonal cytogenetic abnormalities have been used to discriminate malignant mast cells further.¹ Although the low incidence of LPD in patients with SM does not allow a non-random association between the two entities to be demonstrated, it is interesting to note that all LPD associated with SM are of B-cell origin, that monoclonal gammopathies are detectable in a significant proportion of cases with SM⁷ and that in patients with SM, c-kit mutations are also detectable in peripheral blood B-cells. All these data suggest that a single uncommitted neoplastic progenitor cell can give rise to both malignancies in individual patients.

In summary, we present the first reported case of an association between an indolent SM and CLL. Specific flow cytometry, cytogenetic and molecular analyses of the different cellular subpopulations are needed to try to elucidate a possible common origin of both pathologies.

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