



A case of chronic lymphocytic leukemia overwhelmed by rapidly progressing idiopathic myelofibrosis

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is sometimes associated with solid tumors but rarely coexists with other hematologic neoplasias in the same patient. There are isolated case reports in the literature of an association between CLL and idiopathic myelofibrosis, a representative disease of the group of the myeloproliferative syndromes. We describe the case of a 70-year old female diagnosed as having CLL and idiopathic myelofibrosis in a prefibrotic phase with an indolent course, managed only with observation. Twenty-eight months after diagnosis, the patient developed hepatosplenomegaly and progressively rising serum lactic dehydrogenase (LDH) levels; immature granulocytic cells and tear drop red cells appeared in the blood. A bone marrow trephine biopsy (after a dry tap sternal aspiration) was consistent with the diagnosis of overt idiopathic myelofibrosis and only residual foci of CLL cells were present. Three months later, the blood diagnostic features of CLL remained but a progressive fall in the numbers of CD5⁺/CD19⁺ cells was noted. Other observations related to this association in several chronological sequences, their possible pathogenesis, and the diagnostic value of the rise in serum LDH levels are discussed. The case reported here constitutes an extremely rare situation of CLL overwhelmed by rapidly progressing idiopathic myelofibrosis.

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Chronic lymphocytic leukemia (CLL) is a mature B-lymphocyte proliferative syndrome in which the lymphocytes, unlike in other B-cell malignancies, express low amounts of surface membrane immunoglobulin (smlg), form rosettes with mouse erythrocytes and express the CD5 marker.¹ The normal counterpart of the CD5 B-cells that proliferate in CLL was initially found to be located at the edge of the germinal center in human lymph nodes,² and bone marrow involvement is considered to be sec-

ondary. On the other hand, idiopathic myelofibrosis (IM) is a clonal panmyelopathy included among the chronic myeloproliferative syndromes, in which the non-clonal marrow fibrosis is thought to be related to the production of fibrogenic factors by proliferative and ineffective megakaryocytopoiesis.³ Changes in the microenvironment of the bone marrow coexist with alterations at cellular and extracellular levels of various cytokines that have not only fibrogenic, but also angiogenic and osteogenic potential.⁴

Although CLL has been classically associated with an abnormally high incidence of other neoplasms in the same patient,⁵ its association with myeloproliferative disorders is exceptional and only isolated cases have been reported.⁶⁻¹⁶ Secondary marrow fibrosis occurs in 20-30% of CLL cases, but usually in a discrete, *non-mutilating* way.^{17,18} The purpose of this report is to describe the case of a patient with B-CLL, whose clinical course was characterized by the development of rapidly progressing IM that overwhelmed the lymphoproliferative disease, an extremely rare circumstance. Possible etiopathogenic relationships between both disorders are discussed.

Case report

A 70-year old Italian female, with a history of gastroesophageal reflux, cholecystectomy, hysterectomy, upper digestive bleeding secondary to subcardial gastric vascular malformation (treated with endoscopic sclerotherapy), and herpes zoster, attended our clinic in November 1993. A diagnosis of chronic lymphocytic leukemia (stage 0 of Rai's classification), had been made in another country six months previously. Physical examination revealed only residual cutaneous lesions of herpes zoster on the left side of the back, and a medial infraumbilical laparotomy scar. No peripheral lymphadenopathy or hepatosplenomegaly was found. The hemoglobin concentration was 15.9 g/dL, the leukocyte count $38 \times 10^9/L$ with 76% small mature lymphocytes, mean corpuscular volume 103.6 fL, and the platelet count was $288 \times 10^9/L$. Remarkable biochemical laboratory data were: BUN 27 mg/dL, β_2 microglobulin 1.6 mg/L, IgG 1154 mg/dL, IgA 115 mg/dL, IgM 36 mg/dL, γ -GT 79 U/L, and lactic dehydrogenase (LDH) 787 U/L. Phenotypic analysis of blood lymphocytes by flow cytometry revealed: CD3⁺ 4.7%, CD19⁺ 94.4%, CD5⁺ 60.3%, CD5⁺CD19⁺ coexpres-

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sion 54.7%. Bone marrow trephine biopsy showed a normal cellularity/fat ratio, a lymphoid infiltration by CLL-type cells with interstitial pattern and focal tendency,¹⁹ megakaryocytic dysplasia (Figure 1) and absence of marrow fibrosis (Figure 2). All these findings were consistent with the above mentioned diagnosis of CLL, Rai stage, and the coexistence of very early (prefibrotic) stage of IM. Treatment was withheld and frequent monitoring in our clinic was started.

The CLL remained stable for 28 months, with the exception of a slow, fluctuating, but progressive rise of serum LDH (Figure 3), in the absence of hemolysis, or any other explanation. There was no palpable lymphadenopathy or hepatosplenomegaly. In June 1996 the patient complained of significant weakness and anorexia, and an enlarged spleen could be felt 2 cm below the left costal margin. Hemoglobin concentration was 11.8 g/dL, leukocyte count $23 \times 10^9/L$ with $13.3 \times 10^9/L$ small lymphocytes, platelet count $148 \times 10^9/L$; myeloma, erythroblastemia and some dacryocytes were present in a blood smear. A second trephine marrow biopsy revealed heterogeneous distribution of the cellularity, with disruption of the normal bone marrow architecture, megakaryocytic hyperplasia with bizarre forms, osteosclerotic changes and sinusoidal hyperplasia-ectasia; only discrete foci of small mature lymphocytes were observed. A silver staining technique showed grade III reticulin fibrosis,²⁰ and collagen deposition was made conspicuous by Masson's trichromic stain. All these findings led to the diagnosis of IM with osteosclerosis (MFO⁺ in the Lennert-Nagai classification)²¹ (Figures 4 and 5), while only vestiges of CLL involvement were present. Cytometric analysis of blood lymphocytes showed a persistent majority of B-cells (CD19⁺ 89.1%, CD3⁺ 6.9%), but a significant decrease of CD5 antigen (19.7%) and of CD5⁺CD19⁺ (17%) coexpressing cells. Three months later, a continued decrease of the neoplastic clone was observed: CD19⁺ 73.9%, CD5⁺ 17.4%, CD5⁺CD19⁺ 7.9% (Figure 6). At the time of writing this report, the CLL is stable, remains without leukocytosis and does not need to be treated.

Discussion

Various lymphoproliferative disorders, such as Hodgkin's disease, multiple myeloma, macroglobulinemia, hairy cell leukemia, non-Hodgkin's lymphomas, acute lymphoblastic leukemia, and CLL, are associated with the development of secondary bone marrow fibrosis of variable degree.^{17,18} In our patient, the histologic data (especially the presence of dysplastic megakaryocytes), the leukoerythroblastic syndrome, the rise of LDH, the decrease of hemoglobin concentration and platelet counts, and the appearance of splenomegaly without lymphadenopathy or progressive lymphocytosis, strongly suggest the development of overt IM.

Looking back, although CLL was diagnosed six months before the first bone marrow trephine biopsy was performed, and the lymphoproliferative disease probably had its onset several months before it was recognized, the megakaryocytic dysplasia in this

initial biopsy and the increased level of LDH at the same time support the possibility that, right from the start, the patient presented two independent disease entities. According to IM Cologne revised criteria, the patient's first bone marrow histopathologic findings were compatible with a very early (prefibrotic) stage of IM.^{22,23} However, we can neither exclude nor confirm the subsequent or simultaneous occurrence of both hematologic disorders.

The association or coexistence of CLL and IM is exceptional, and has only rarely been reported. A case of acute myelofibrosis (an entity related to acute megakaryoblastic leukemia or M7 acute non-lymphoblastic leukemia, more than to IM) developed in a patient with CLL who received intensive chemotherapy.¹² The case of a patient with an insufficiently documented CLL-related disorder, who developed a myeloproliferative process with acute eosinophilic leukemia and myelofibrosis in the final phase of the lymphoproliferative disease, has also been reported.¹³ A group of German authors has suggested the existence of a so-called myelofibrotic myeloma, a type of myeloma with marrow changes similar to those of IM (including clusters of atypical megakaryocytes), and they propose the separation of this entity from simple secondary myelofibrosis in multiple myeloma.²⁴ The reverse association, that is, the development of CLL in a patient diagnosed as having IM, has been reported.¹⁴⁻¹⁶ Furthermore, a blastic lymphoid crisis as a terminal event of IM is also possible.²⁵ Finally, the simultaneous diagnosis of CLL and IM, although extremely rare, has also been reported.¹⁶

Lymphocyte implication in bone marrow fibrosis development is well known. In hairy-cell leukemia, typical fine reticulin bone marrow fibrosis is at least partly caused by the synthesis and assembly of a fibronectin matrix by the hairy cells,²⁶ and basic fibroblast growth factor (bFGF) is expressed by CD19/CD11c-positive cells in this disease.²⁷ In CLL patients, it is possible that cytokines released by malignant B-cells are responsible for the development of some degree of marrow fibrosis. Kimura *et al.* reported a case of CLL with secondary myelofibrosis, and they confirmed the known role of interleukin 1-alpha (IL-1 α) secreted *in vitro* from the leukemic cells^{28,29} as a growth factor stimulating marrow fibroblasts.¹¹ As some authors support the hypothesis that autoimmune mechanisms may be involved in the development of bone marrow fibrosis³⁰ and associated autoimmune phenomena are frequently observed in CLL, this pathogenetic possibility must be taken into account too. However, it is very improbable in the present case that such an indolent lymphoproliferative disease (Rai stage 0) could be responsible for the appearance of this impressive bone marrow fibrosis (grade III), and we believe that the two diseases, CLL and IM, are pathogenetically independent.

On the other hand, we do not have an explanation for the drastic fall in the percentage of CD5⁺CD19⁺ lymphocytes in peripheral blood (from 54.7% to 17%) at the same time as the IM developed. In fact, three years after overt IM appeared, the lymphoid leukemic clone seemed to be *suppressed*, as the leukocyte count and a lymphocytic count around

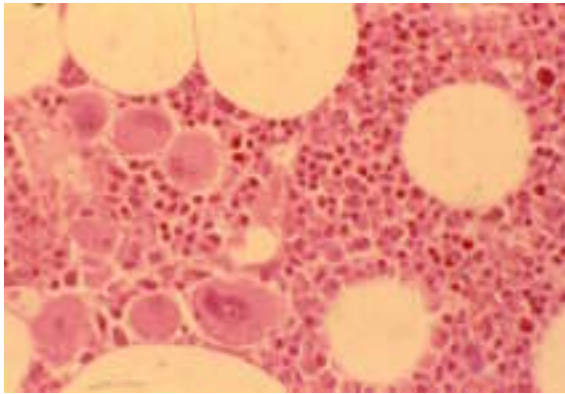


Figure 1. Initial bone marrow trephine biopsy showing a lymphoid infiltration by CLL-type cells with interstitial pattern, and megakaryocytic dysplasia with a trend to "cluster" formation ($\times 250$, hematoxylin-eosin stain).

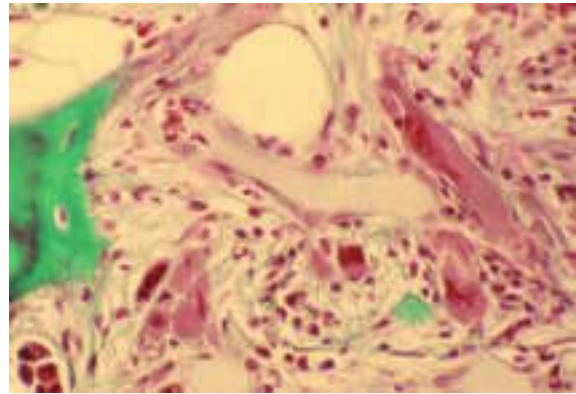


Figure 4. Cell architecture disruption, collagen deposition and osteosclerotic changes in the second bone marrow trephine biopsy ($\times 250$, Masson's trichromic stain).

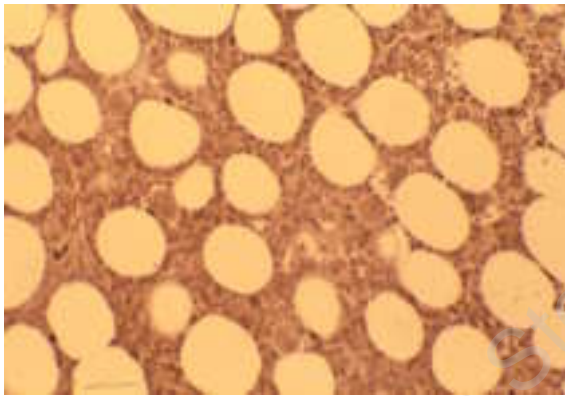


Figure 2. Absence of fibrosis in the initial bone marrow trephine biopsy ($\times 100$, silver stain).

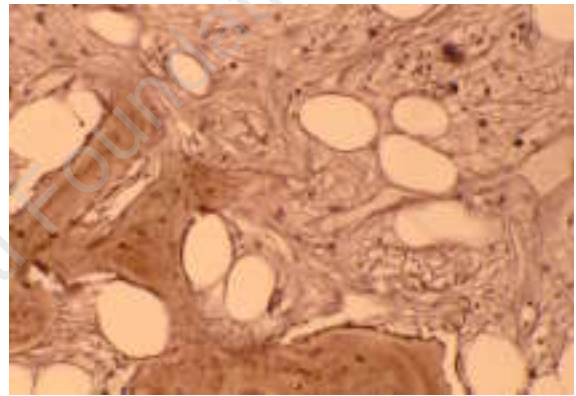


Figure 5. Second bone marrow trephine biopsy showing advanced IM, with grade III reticulin fibrosis ($\times 100$, silver stain).

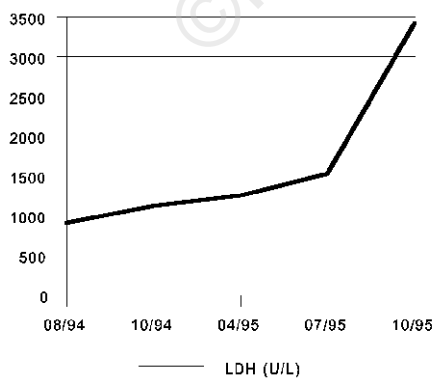


Figure 3. Serum LDH concentrations during the year prior to the diagnosis of overt IM.

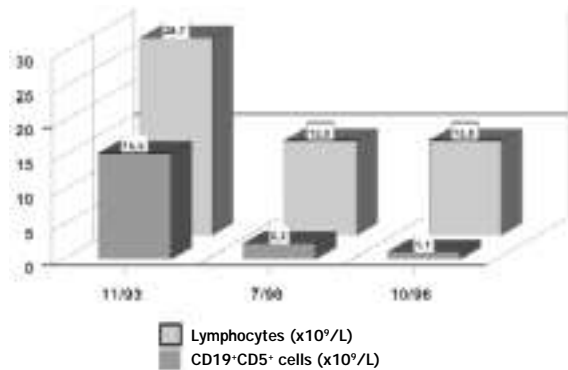


Figure 6. Evolution of lymphocyte counts and CD5⁺CD19⁺ cells in blood, before and after the diagnosis of overt IM.

$10 \times 10^9/L$ remained stable, without any sign of progression. Such a situation has been described in a case in which polycythemia vera and CLL coexisted.⁶ In our patient, a new bone marrow biopsy performed in March 1999 showed progression of osteomyelofibrotic changes, with very scarce lymphocytic disease. The gradual decline in the CLL mass as fibrosis increased might suggest that a cell surface and cytokine environment created by the myelofibrosis somehow inhibited CLL. It is now generally agreed that megakaryocyte-derived growth factors, such as platelet-derived growth factors (PDGF) and transforming growth factor- β (TGF- β), promote the development of secondary stromal proliferation in IM.³¹ These fibrogenic cytokines and others, such as bFGF, which is increased in platelets and megakaryocytes from patients with IM, may be implicated in a suppressive effect on the CLL clone. TGF- β has been shown to modulate immune and inflammatory responses in part by inhibiting the proliferation and activity of B- and T-lymphocytes, and regulating cytokine production by different cell types.³² TGF- β interacts with a number of distinct membrane proteins. Although the biological relevance of TGF- β binding to these proteins is not clear, it has been suggested that these proteins may alter the availability of ligand for signaling receptors and thus play a role in the disease.³³ However, a direct pathogenetic role of these cytokines in CLL suppression or stabilization has yet to be proven.

Finally, we remark on the importance of the rising serum LDH levels (inappropriate in low-risk, Rai stage 0 CLL) during the follow-up of our case, which led to the suspicion of rapidly progressing IM. The performance of a second trephine biopsy confirmed the overt IM, without doubt responsible for the LDH rise.³⁴

Contributions and Acknowledgments

LHN: conception, interpretation of data, critical intermediate and final review. JMRS: conception and design, drafting the article. HAA: analysis and interpretation of data. MLBB: Analysis and interpretation of data. BGG: partial drafting.

Disclosures

Conflict of interest: none.

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