Severe T-mediated bone marrow aplasia in a patient with Splenic Lymphoma with Villous Lymphocytes (SLVL) previously treated with Fludarabine regimen

Splenic Lymphoma with villous lymphocytes (SLVL) is a B cell chronic lymphoproliferative disorder defined in the WHO classification as the leukemic form of splenic marginal zone lymphoma. Autoimmune diseases or second neoplasms in patients affected by B cell chronic lymphoproliferative disorders are well known conditions after fludarabine containing regimens (above all in the case of Chronic Lymphocytic Leukemia). However, T lymphoproliferative disorders able to induce a severe bone marrow aplasia were never described in patients affected by SLVL and treated with Fludarabine. We report a case of SLVL in which a severe T-mediated bone marrow aplasia occurred six months after Fludarabine treatment.

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Case Report
A 70-year old man was sent to our Hematology Division because of a leukocytosis (WBC 30×10^9/L) with lymphocytosis (20×10^9/L) and mild anaemia (Hb 115 g/L). At physical examination small nodes (size less than 1 cm) were present at all superficial sites. Moreover, it was found an increase of size (5 cm from left last rib) and of consistency of the spleen paralleled by a mild hepatomegaly. Total body CT scan confirmed the increase of spleen size without significant lymphadenomegaly of deep lymph nodes. The exam of the morphology of peripheral circulating lymphoid cells showed that they were small size lymphoid cells with, sometimes, a small evident nucleolus and short cytoplasmic extrusions (villi). At the cytochemical analysis these villous lymphoid cells resulted negative for the tartrate-resistant acid phosphatase (TRAP). The immunological pattern of this population was the following: CD19+, CD20+, CD22+, CD5+/-(expressed at low density only on a part of the B-lymphoid population), CD23-, CD43-, FMCG+, CD79b+, CD103-, CD11c-, CD10-, smIg+. The cytological examination of the bone marrow showed a lymphoid infiltration that was higher than 70% of total nucleate cells. Bone marrow biopsy confirmed the infiltration by an atypical CD20+ lymphoid population formed by “villous” cells. Molecular findings were positive for IgH rearrangement, but negative for Bcl2 and TCR. On the basis of these data we diagnosed a splenic lymphoma with villous lymphocytes (SLVL). Hepatitis C antibodies were negative. Therefore, the patient was subjected to the following treatment schedule: 25 mg/m²/die Fludarabine i.v. for 5 days every 4 weeks. Five total treatment cycles were administered and the treatment was well tolerated. One month after the last cycle the patient was subjected to a disease re-staging that showed normal size of spleen and liver and the absence of lymphadenomegaly at the superficial sites. WBC (6×10^9/L) and platelets (160×10^9/L) counts were normal while a mild anaemia (Hb 115 g/L) was still recorded. The histological examination of bone marrow showed a minimal infiltration by an atypical CD20+ villous lymphoid population, confirmed by the rearrangement of the IgH. TCR was negative. Thereafter, the patient was subjected to a follow-up without therapy. After 6 months the patient developed a severe anaemia (Hb 60 g/L), leukopenia (WBC 1.5×10^9/L) and thrombocytopenia (Plt 60×10^9/L). At the physical examination signs of disease recurrency were not present. Bone marrow examination showed a medullary hypoplasia with a minimal infiltration by an atypical CD20+ villous lymphoid population. The molecular analysis with PCR of the marrow blood revealed the presence of the rearrangement of the T gene of the T cell receptor (TCR) (Figure 1). After 2 weeks of supportive care the clinical conditions of the patient worsened and the pancytopenia increased. A new bone marrow examination showed a severe aplasia with the absence of CD20+ B lymphocyte infiltration but with the presence of CD45R0+ T lymphoid cells characterized by the absence of atypical features and of both granular and large granular lymphocytes. The immunophenotype of T cell population was the following: CD3+ 84%; CD4+ 20%; CD5+: 90%; CD8+: 60%; CD2+: 95%; CD57+: 26%; CD56+: 5%; CD16+: 4%. The molecular analysis confirmed the presence of the genetic clonal rearrangement of the T gene of TCR. Notably, signs of T-lymphoproliferative disorders were absent before the diagnosis of SLVL and one month after the end of the therapy with the fludarabine regimen, but they started after six months from the end of the therapy. The patient died for infective complications before any specific treatment could be started.

Discussion
SLVL is a low-grade B cell lymphoma. Clinical presentation and response to therapy have been widely described.1-7 Splenectomy, splenic irradiation or alkylating agents are active treatments for this disease, but recurrence is frequently observed. On the basis of its activity and favourable toxicity profile, fludarabine is often used as the first-line therapy for elderly patients and for the aggressive variant of SLVL.1-8 Immunological side effects like hemolytic anemia and immuno-suppression are well known after the use of fludarabine,1-4 but, at our knowledge, no reports of bone marrow aplasia exist. In our case, it can be hypothesized that fludarabine induced an immunsuppressive status that allowed the proliferation of a malignant T cell clone. However, further studies are needed to investigate on the role of fludarabine, if any, in the onset of a T-mediated aplasia in patients affected by SLVL and on the real incidence in the population of the SLVL since the latter is sometimes misdiagnosed and confused as a generic B cell chronic lymphoproliferative disease.
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References


