Common variable immunodeficiency patient with large granular lymphocytosis developing extranodal diffuse large B-cell lymphoma: a case report

Here we describe a Common Variable Immunodeficiency (CVI) patient with large granular (LG) lymphocytosis and systemic non-malignant lymphadenopathy who developed diffuse large B-cell lymphoma of the stomach. This is the first report of gastric high-grade lymphoma with widespread lymphadenopathy in a patient with LG lymphocytosis associated with CVI.

Haematologica 2006; 91:(12)e166-e167

Common Variable Immunodeficiency (CVI) is a primary immunodeficiency disease characterized by decreased (or absent) levels of immunoglobulins and recurrent bacterial infections of the respiratory and gastrointestinal tracts.[1] Importantly, more than half of the patients has T-cell abnormalities including decreased lymphocyte response to mitogens and microbial antigens.1 However, the relationship between T and B-cell abnormalities remains unclear.[1] A subset of CVI patients harbors a polyclonal expansion of large granular lymphocytes (LGLs) with a distinctive T-cell immunophenotype characterized by CD4/CD8 ratio ≤ 0.9,2 in some cases due to an increase in $CD8^+$ T-cells expressing CD57.3 A higher frequency (16%) of neoplastic diseases, especially non-Hodgkin lymphoma (1.4-7%), has been reported in these patients.4 Non-caseating granulomatous lesions occur in 5.4-10% of CVI patients.5 Here we describe a CVI patient with persistent LG lymphocytosis and systemic non-malignant lymphadenopathy who developed diffuse large B-cell lymphoma (DLBCL) of the stomach.

A 28 year-old man was admitted in March 2003 because of widespread lymphadenopathy. He had been diagnosed with CVI since the age of 12 and treated with intravenous immunoglobulins (IVIGs). Because of severe thrombocytopenia and rapidly increasing splenomegaly, the patient underwent splenectomy at the age of 22 followed by normalization of platelets count.

Two months before admission he had melena and underwent upper gastrointestinal tract endoscopy. Histology and immunoistochemistry of the stomach revealed $CD10^+$ and bcl-6- germinal center B-cell-like DLBCL (Figure 1a) according to Hans *et al.*[6] algorithm. A total body computed tomography scan detected laterocervical, supraclavicular, axillary, paraaortic and mesenteric lymphadenopathy. The axillary lymph node biopsy demonstrated follicular hyperplasia, but not granulomatous or neoplastic lesions (Figure 1b). A bone marrow biopsy showed lymphocytic infiltration with nodular and interstitial pattern. Immunocytochemical staining demonstrated that lymphocytes were $CD20^+$ or $CD4^+$ in nodular infiltrates and $CD8^+$ in interstitial infiltrates (Figure 2) as expected in patients with LG lymphocytosis.[7] The B-cell nodular infiltrates did not show κ or λ light chains restriction. Flow cytometry analysis of bone marrow aspirate revealed the following lymphocyte population: $CD3^+$ 78%; $CD4^+$ 19%; $CD8^+$ 62%; $CD8^+/CD57^+$ 34%; $CD3^-/CD16^+/CD56^+$ 4% and $CD20^+/CD19^+$ 13%. Laboratory tests were as follows: leucocytes, 30300/mm^3, lymphocytes 21900/mm^3; platelets 466000/mm^3; Hb11,4 g/dl; neutrophil granulocytes were normal. Flow cytometry analysis of peripheral blood lymphocytes revealed 83% of T cells, 60% $CD8^+/CD57^+$ and 20% $CD4^+$, 8% $CD3^-/CD16^+/CD56^+$ and 19% $CD20^+/CD19^+$ cells. Lymphocytes detected in peripheral blood smears were small lymphocytes (50%) and LGLs (50%). The peripheral lymphocytosis was discovered three years before DLBCL. There was no preferential use of any Vκ region in the TCR repertoire of $CD3^+$ lymphocytes using specific anti-TCR Vκ region antibodies in flow cytometry. No monoclonal rearrangement of TCRβκ was found using PCR. $CD8/CD57^+$ lymphocytes were negative for KIR2D1; KIR2D2 and KIR3DL1. TCR γ/δκlymphocyte percentage was normal. Anti-HBSAg positivity was demonstrated while other viral infections (HCV, HIV, EBV, CMV) were excluded with serology.

The patient received six cycles of combined chemotherapy CHOP achieving complete remission (CR). During treatment there was a progressive reduction of peripheral $CD8^+/CD57^+$ lymphocytes: from 13140/mm^3 to 3911/mm^3 at the end of the treatment. Thereafter $CD8^+/CD57^+$ lymphocytes have gradually grown up to 9177/mm^3 within 27 months. The patient is in CR and good performance status.

A subset of CVI patients with a distinct T-cell immunophenotype, splenomegaly and granuloma formation has been described.[3] Hyperplasia is more frequent than malignant disorders,[4] with approximately 50% of CVI patients presenting with lymphadenopathy, splenomegaly and/or gastrointestinal nodular lymphoid hyperplasia. Instead, widespread lymphadenopathy synchronous to the occurrence of aggressive non-Hodgkin lymphoma (NHL) in a CVI patient with LG lymphocytosis has never been reported. A recent review 8 of extranodal marginal zone lymphomas in CVI patients reports eight cases of MALT-lymphomas, none of them of gastric location. Particularly, this is the first report of gastric high-grade lymphoma, whereas the higher risk of gastric carcinoma in antibody deficient patients is well documented.[9]

Figure 1. (a) Gastric biopsy. Non-Hodgkin diffuse large B-cell lymphoma (DLBCL) showing strong surface staining for CD20 (x200). There is neither evidence of lymphoepithelial lesions nor of follicular colonization: DLBCL without concomitant low-grade component (de novo DLBCL). (b) Lymph node biopsy. Reactive lymphoid hyperplasia. Lymphoid follicles with germinal centers and prominent mantle zone; the nodal architecture is clearly preserved (haematoxylin and eosin-stain x100).

Figure 2. Bone marrow biopsy pattern of staining for CD20, CD4 and CD8. (a) CD20 positive B-cells in nodular aggregate (x200); (b) CD8 positive T-cells in nodular aggregate and in interstitial pattern of infiltration (x100). (c) CD4 positive T-cells in nodular aggregate (x100).

Some patients with increased numbers of LGLs may be diagnosed with lymphoproliferative disease of GLs (LDGLs).[10] A variety of haematological diseases are associated with LDGLs; particularly, although rare, the association with lymphoproliferative disorders is well recognized.10 Papadaki11 described eight patients with simultaneous occurrence of T-cell-clonal LDGLs and B-lymphoproliferative disorders suggesting that LGLs grew concomitantly with neoplastic diseases. However, in our case, LGLs expansion was neither clonal nor simultaneous to the diagnosis of lymphoma. Although, usually, in reactive/transient polyclonal lymphocytosis, LGLs count does not exceed 4×10^9/L and does not persist more than 6 months, disappearing with treatment of underlying disease,[10] our patient's lymphocytosis has grown from the end of treatment on.

Recent observations[2] indicate that CVI should be added to the list of diseases associated with increased numbers of LGLs; clearly, further studies and a longer follow-up are warranted to better understand the possible link between immunodeficiency and the mechanisms leading to LGLs proliferation and NHL.

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Source of funding: This work was supported by MIUR (Ministero dell'Università e della Ricerca Scientifica e Tecnologica) and AIL (Associazione Italiana per la lotta alle Leucemie-Linfomi e Mieloma/Bari)

Key words: CVI, large granular lymphocytes, NHL

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