Sequential development of large B cell lymphoma in a patient with peripheral T-cell lymphoma

Lymphomas of different histologic type can occur in the same patient. Two types of lymphomas can be diagnosed in the same lymph node (*composite* lymphoma) or in different sites. In the latter case, terms as *simultaneous* and *sequential* have been proposed to define the detection of two lymphomas at the same time or at different times, respectively.

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A 67 year-old man was referred to the oncohematologic clinic because of sudden onset of supraclavear lymphoadenopathy.

His medical history was remarkable for pulmonary tuberculosis at the age of 19. Six months before admission mild thrombocytopenia (platelet count 100 x 10^9/L) and relative lymphocytosis (WBC 4.9x10^9/L, L 54%) were noted at routine follow-up. The patient was referred to a hematologist who noted a palpable spleen and recommended a neck, chest and abdomen CT scan. The diagnostic imaging showed a slight spleen enlargement and diffuse small lymph node enlargement predominantly involving mediastinal and intraabdominal nodes. During the following months, physical examination and laboratory data were unchanged.

On physical examination, the patient appeared well. The lungs and heart sounds were normal. There was a mass of non-tender left sovraclavear lymph nodes, 15 cm in diameter. Other small lymph nodes were palpable in axillas bilaterally and the spleen was palpable 2 cm below the left costal margin. Other physical findings were unremarkable. There was no history of fever, sweats, cough, weight loss, dyspnea, and skin changes.

The results of laboratory investigation showed moderate thrombocytopenia (86x10^9/L), mild normocytic, normochromic anemia (10.9 g/dL); white cell count, albumin levels, lactate dehydrogenase, urea nitrogen, conjugated and total bilirubin, aspartate aminotransferase, alanine aminotransferase were normal. Serological tests were negative for viral hepatitis and suggestive of previous Epstein-Barr (EBV) virus and cytomegalovirus infections. A tuberculin skin test (5 TU) was negative.

A total body CT scan disclosed a bulky mass extending from the left cervical region into upper thoracic region. Spleen enlargement and diffuse small lymphadenopathy were stable compared to previous CT scan evaluation.

A biopsy of the left supraclavicular mass showed diffuse lymph node infiltration by large CD20$^+$ centroblast or immunoblast-like cells, sometimes with anaplastic features, consistent with diffuse large B-cell lymphoma (DLBCL) (Figure 1). Unexpectedly, a bone marrow biopsy revealed diffuse infiltration by CD3, CD5, and CD7-positive small-sized mature lymphoid cells accounting for 50% of the cellularity. A concomitant scanty infiltration of large cells with positive staining for CD20 was also detected. Immunohistochemical analysis of TCL-1 expression in the T cell infiltrate was negative.

Flow cytometric analysis performed on bone marrow aspirate confirmed the presence of a T cell population expressing TCR α/β, CD2, CD3, CD4, CD7 and CD5+ (negative for CD10, CD30, CD16 and CD56 expression). Cytogenetic analysis of the bone marrow cells revealed no abnormalities.

TCR γ and IgH rearrangement studies were performed in specimens collected from peripheral blood, lymph node and bone marrow. A monoclonal pattern of IgH rearrangement was detected in the lymph node with a polyclonal pattern of TCR γ rearrangement. As expected and consistently with immunohistochemical results, the bone marrow showed a monoclonal rearrangement of the TCR γ as well as a concomitant IgH monoclonal rearrangement. Finally, TCR γ monoclonality was detected in the peripheral blood.

In situ hybridization for EBV-latent membrane protein-1 as well as EBV-DNA quantification by real-time PCR in lymph node samples, following previously described methods,[1] were negative.

The patient was started on chemotherapy with R-CHOP-21 regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), for a total of 6 courses followed by involved-field radiotherapy for a total of 30 Gy. A PET-CT scan at restaging (6 months from the

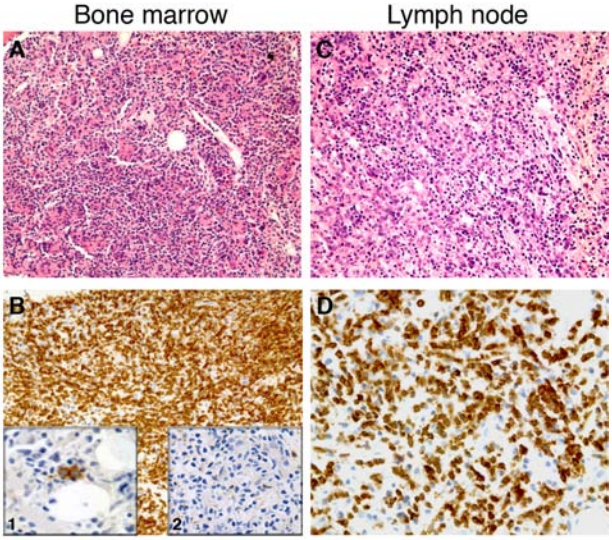

Figure 1. Bone marrow sections showing a diffuse pattern of infiltration by small sized cells. A concomitant distinct population of large cells is visible (A; H&E stain, original magnification x 100). Immunohistochemical stain showing scattered CD20 positive cells (B, inset 1, magnification x 400) in the context of a background of CD3-positive small lymphocytes (B, magnification x100). Negative TCL-1 staining in the context of T cell infiltration (cells (B, inset 2, magnification x400). A biopsy specimen from supraclavear lymph nodes showing diffuse proliferation of large cells (C; H&E stain, original magnification x100) immunohistochemically positive for CD20 (D; original magnification x400).

conclusion of therapy) showed no evidence of residual disease and the molecular analysis of peripheral blood TCR γ rearrangement disclosed a polyclonal pattern.

Lymphomas of different histologic type can occur in the same patient.[2] Two types of lymphomas can be diagnosed in the same lymph node (*composite* lymphoma) or in different sites.[3] In the latter case, terms as *simultaneous* and *sequential* have been proposed to define the detection of two lymphomas at the same time or at different times, respectively.

The combination of more than one histological type of lymphoma may represent the progression of an indolent lymphoma into a more aggressive form.[4] At the same extent, the presence of two lymphomas of the same lineage but with divergent histologies may still have a common origin when evaluated by molecular biology techniques.

A more intriguing situation is represented by the combination of two lymphomas of different immunologic origin as coexistence of B and T cell lymphomas.[2] The case here reported is consistent with the sequential occurrence of a large B cell lymphoma in a patient with an indolent peripheral T cell lymphoma unspecified (PTCL/U). One could argue that the coexistence of a large B cell population, although scanty, in the context of a diffuse bone marrow T cell clonal infiltration deserves a more extensive differential diagnosis including *large B-cell-rich T-cell lymphomas*.

In particular, angioimmunoblastic T cell lymphoma and peripheral T-cell lymphomas complicated by a proliferation of large B cells may be worth considering.[5,6] Lack of hypergammaglobulinemia, increase in vascularity and burned-out appearance do not support AILT. Peripheral T-cell lymphomas complicated by a proliferation of large B cells is a recently described entity characterized by a proliferation of large B cells in the background of peripheral T-cell lymphoma, unspecified. Transformed large B cells are more frequently EBV-positive. Most authors consider this entity in presence of more than 25% of large cells in the context of a T cell background. Our case showed scanty EBV-negative large B cells interdispersed in a T-cell background, and more importantly, no concomitant T cell infiltration was found in the context of the supraclavear lymph node large cell population, which is less consistent with a composite lymphoma. Although no histological data have been collected at the time our patient presented with diffuse small lymphadenopathy, splenomegaly and cytopenia, the sequence of an indolent clinical course concomitant to the presence of a clonal T cell population in the peripheral blood and the subsequent rapid development of a bulky supraclavicular mass strongly suggests an indolent T lymphoproliferative disorder preceding the development of a high grade B cell lymphoma.

Among T cell proliferative disorders, T-cell prolymphocytic leukemia (T-PLL), T-large granular lymphocyte leukemia (T-LGL) and hepatosplenic T-cell lymphoma deserve some considerations in the differential diagnosis of our case. T-PLL is usually characterized by an aggressive clinical course with lymphadenopathy, splenomegaly, skin lesions and lymphocytosis.[7] However, some patients may experience an initial indolent clinical course.[8] T-cell leukemia 1 (TCL1) oncogene is activated in 70-80% of T-PLL but not in other T-cell tumors types. Complex chromosomal abnormalities have been reported in more than 90% of cases.[8] Our immunohistochemical evaluation of the T cell population infiltrating the bone marrow did not show expression of TCL-1. Although it cannot be completely ruled out, this data together with the normal cytogenetic analysis of the bone marrow cells makes T-PLL less likely.

T-LGL is a chronic and often indolent T cell lymphoproliferation is characterized by the clonal expansion of cytotoxic T lymphocytes. It has been previously defined that the $CD3^+/CD16^+$ phenotype is central in the differential diagnosis of this lymphoproliferative disorder.[9] The phenotype $CD3^+/CD4^+/CD16^-$ of circulating clonal T cells in our case is not consistent with a diagnosis of T-LGL.

Hepatosplenic γ/δ T-cell lymphoma (HTCL) is a distinct entity among peripheral T-cell lymphomas characterized by the expression of the γ/δ TCR by tumor cells. It typically presents with marked hepatosplenomegaly in the absence of lymphadenopathy. The neoplastic cells have a phenotype that resembles that of immature or resting γ/δ T-cells, often negative for CD4 and CD8, CD5 and positive for CD56.[10] Although the expression of TCR α/β has been seen in a small subset of patients, the overall clinical, pathological and immunophenotypic pattern is not suggestive of HTCL.

The development of DLBCL in the context of PTCL/U has been reported very rarely. Although only limited data were made available, a recent retrospective study of distinct types of lymphoma developed in the same patient reports only 1 case (out of 46) with a nodal PTCL/U complicated by the development of a DLBCL, with an interval time of 39 months.[2]

If any relationship may exist in the development of a high grade B cell lymphoma in a patient with an indolent T cell malignancy is a matter of debate. An EBV-driven proliferation of B cells in the context of a peripheral T cell lymphoma has been reported but our immunohistochemical and molecular data failed to show a role of EBV in lymphomagenesis. Among alternative speculative interpretations, there are intriguing data showing that a derangement of the T cell compartment expressing the γ/δ TCR may have a role in impairing immune surveillance of B cell lymphomas.[11]

A. Furlan, F. Pietrogrande, F. Marino, C. Menin, G. Polato, F. Vianello

Oncohematology Unit, Department of Medical and Surgical Sciences (AF, FP, GP, FV); Istituto Oncologico Veneto (CM); Department of Pathology (FM); Padua University School of Medicine, Padova, Italy

Correspondence: Fabrizio Vianello, MD, Second Chair of Medicine, Padua University Hospital, via Giustiniani 1, 35100 Padua, Italy. Phone: +39.049.8212971. Fax: +39.049.8212661. E-mail: fabvian@unipd.it

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