Concomitant Diagnosis of Myeloproliferative Neoplasm and Non-Hodgkin's Lymphoma in a Patient with Portal Vein Thrombosis

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Abstract. *We describe here the rare coexistence, at the time of diagnosis, of a myeloproliferative neoplasm (MPN) and non-Hodgkin's lymphoma (NHL) in a 74-year-old patient who presented with thrombocytosis and signs of portal hypertension on physical examination. Abdominal computed tomography scan demonstrated extensive portal vein system thrombosis. Secondary causes of thrombocytosis were excluded. JAK2 V617F mutation was present in the peripheral blood, while bone marrow biopsy revealed marginal zone B-cell lymphoma. Molecular analysis failed to detect BCR–ABL rearrangement in peripheral blood cells. Simultaneous occurrence of MPN and NHL was diagnosed. This case may be of interest not only due to the rare coexistence of PMN and NHL, but also because of the undetermined clinical significance of JAK2 mutation in this subset of patients.*

The coexistence of a lymphoproliferative and a myeloproliferative neoplasm (MPN) is well documented following cytotoxic chemotherapy or radiation, while it is rare prior to therapy (1). As far as polycythemia vera (PV) or essential thrombocythemia (ET) are concerned, simultaneous or sequential occurrence with multiple myeloma and chronic lymphocytic leukemia has been reported in several cases (2-6) but the coexistence of PV or ET with malignant lymphoma in previously untreated patients is a rare event (7-9) and the etiologic association remains unclear.

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We report here a patient presented with extensive portal vein thrombosis. Thorough investigations revealed *BCR–ABL*-negative, *JAK2* V617F-positive MPN with concomitant non-Hodgkin's lymphoma (NHL).

Case Report

A 74-year-old man was admitted in our department with a 4-month-history of abdominal pain. On clinical examination, marked splenomegaly and collateral veins in the abdominal wall were observed. On admission, hematologic values were: hemoglobin 11.4 g/dL, white blood cell count 6300/μL with 75.9% neutrophils, 15.6% lymphocytes and 6.5% monocytes, platelets 621×10^3/μL. Endoscopy visualised oesophageal varices and portal hypertensive gastropathy. Computed tomography (CT) of the thorax did not illustrate any space occupying lesions, mediastinal enlargement, pleural effusions or enlarged lymph nodes. Doppler ultrasound demonstrated portal, posterior mesenteric and splenic vein thrombosis. Abdominal CT scan confirmed the above findings plus splenomegaly but neither enlarged lymph nodes nor any space-occupying lesions. Further tests for thrombophilia (protein S and C deficiency, lupus anticoagulant, anti-cardiolipin antibodies and factor V Leiden mutation) were normal. MPN was suspected on the basis of thrombocytosis and the massive venous thrombosis. Serum erythropoetin was normal. Bone marrow biopsy revealed 35% interstitial infiltration from small sized lymphocytes. Immuno-histochemical analysis of the lymphocytes revealed: $CD20^+$, $CD79^+$, $PAX\text{-}5^+$, Clg^-, $CD5^-$, $CD23^-$, Cyclin $D1^-$, $CD10^-$, $CD3^-$. Bone marrow was hypercellular with mild left shift of the myeloid lineage and increased dysplastic megakaryocytes. Blood test for *BCR–ABL* was negative but *JAK2* was positive. On the basis of these findings, the simultaneous occurrence of MPN and NHL was diagnosed. Low molecular weight heparin and beta-blockers were administered for long-term use and chemotherapy (cyclophosphamide, oncovin, prednisone,

Table I. *Concomitant diagnosis of essential thrombocytosis (ET) or polycythemia vera (PV) and non-Hodgkin's lymphoma.*

Authors	Year	ET/PV	LPN
Palandri *et al.* (12)	2009	ET	Lymphoplasmatocytic non-Hodgkin lymphoma (2 cases)
Palandri *et al.* (12)	2009	ET	Diffuse large B-cell lymphoma (1 case)
Palandri *et al.* (12)	2009	ET	Follicular B-cell lymphoma (2 cases)
Palandri *et al.* (12)	2009	ET	B-Cell chronic lymphocytic leukemia/small lymphocytic lymphoma (1 case)
Fujiwara *et al.* (9)	2001	ET	Skin tumor, diffuse large cell lymphoma
Carulli *et al.* (7)	1997	ET	Non-Hodgkin lymphoma
Rizzi *et al.* (13)	2002	PV	Follicle center non-Hodgkin lymphoma
Heinle *et al.* (14)	1996	PV	Lymphocytic lymphoma
Kurchan *et al.* (16)	1991	PV	T Lymphoma of immature phenotype
Khojasteh *et al.* (15)	1981	PV	Diffuse lymphocytic lymphoma
Guzzin *et al.*i (17)	1988	PV	Plasmacytoid lymphoma of the colon

rituximab) was initiated. The patient received 12 cycles of this therapy. After treatment, thorax and abdomen CT scans were negative for lymph node metastasis and bone marrow showed 5% residual disease. The patient remains stable five months after chemotherapy, in a very good partial response. He received no cytoreductive treatment for MPN and he is still on anticoagulation treatment. Recanalization of the portal vein was achieved and no complications of portal hypertension were evident. The patient is currently under close hematologic observation.

Discussion

The differentiation between PV and ET in the presence of portal hypertension is difficult since hypersplenism is a confounding factor. Therefore, diagnostic criteria for either PV or ET may not be fulfilled since red cell mass or hemoglobin values are useless as diagnostic criteria (10, 11) in the current case due to portal hypertension. Erythropoietin-independent red cell colony growth test is not an available tool in our clinical practice. On the other hand, thrombocytosis in peripheral blood, hypercellularity of all three lineages in the bone marrow, detection of *JAK2* mutation, normal erythropoietin values, absence of both fibrosis and *BCR–ABL* mutation in the bone marrow, as well as extensive thrombosis in the portal vein system, are consistent with diagnosis of either PV or ET (10, 11) but neither myelofibrosis nor chronic myeloid leukemia.

Concomitant or sequential occurrence of ET and NHL in untreated patients has been described in 3 sporadic case reports (7-9) and in a series of 6 cases (12). More specifically, Carulli *et al.* reported the simultaneous occurrence of ET and follicle center NHL in a 70-year-old male patient (7). Co-existence of these two entities has also been described in a 21-year-old female patient who developed diffuse large B-cell, high grade NHL three years following diagnosis of ET, for which no treatment had been administered, suggesting that there was no association of lymphoma with potentially carcinogenic drugs (8). More recently, a case of a huge diffuse large cell lymphoma of the skin associated with ET was reported in a 77-year-old male (9). In a series from a single-center in Italy, 6 cases of concomitant diagnosis of ET and NHL (40-77 years old) were reported. In three cases, aggressive NHL was documented, whereas in the remaining three, low-grade NHL was diagnosed (12).

PV coexistence, either concomitant or sequential with lymphoma, in previously untreated patients was reported in 7 male patients, aged 20-78 years (13). In 5 patients, both diseases were diagnosed simultaneously (13-17) and in the remaining two, lymphoma followed the diagnosis of PV (13). The lymphoma was of lymphocytic type in 2 cases, of T-cell type in 2 cases, and of follicle center cell, plasmatocytoid and Hodgkin's lymphoma in 3 cases. Cases of concomitant diagnosis of either ET or PV and non Hodgkin's Lymphoma are listed in Table I.

None of the cases described so far had any thrombotic events. The *JAK2* status was available in only 4 out of the 13 total cases, with simultaneous occurrence of 2 entities, and one case reported positive (12). On the contrary, the index case presented with extensive portal vein thrombosis resulting in portal hypertension. It would be interesting to examine the *JAK2* status in the cases of MPN and lymphoma co-existence reported in the literature.

To our knowledge, the detection of *JAK2* mutation in NHL is rare. Lee *et al.* analysed 117 NHLs by a single-strand conformation polymorphism assay and no *JAK2* V617F mutation was detected (18). In another series of 237 patients with lymphoproliferative disorders, *JAK2* V617F allele was identified in the bone marrow of 3 B-cell lymphoma patients and in the peripheral blood of 2 of the 3 patients, without any other diagnostic criteria for ET or PV or thrombotic events (19). Thus, the clinical significance of *JAK2* mutation in this subset of patients remains undetermined since it is not

known whether these patients with *JAK2* mutation and NHL had experienced or were going to experience in the future any thrombotic complications.

The pathogenetic mechanism of coexistence of both MPN and NHL, without any previous cytotoxic or radiation exposure, is not clear. However, one may speculate that anti-oncogene suppression or a common carcinogen could affect either a putative pluripotent stem cell or two different cell lineages, with subsequent bilineage proliferation. Nevertheless, a coincidental occurrence of two diseases can-not be ruled out since most of the patients were more than 70 years old and aging is correlated with progressive genomic instability, favoring the occurrence of second primary tumors. Further reports investigating this rare association between these different diseases are warranted.

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