Does Double Mean Trouble? Coexistence of Myeloproliferative and Lymphoproliferative Neoplasms: Clinical Observations and Implications

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DOES DOUBLE MEAN TROUBLE?

COEXISTENCE OF MYELOPROLIFERATIVE AND
LYMPHOPROLIFERATIVE NEOPLASMS:
CLINICAL OBSERVATIONS AND IMPLICATIONS

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Abstract

The coexistence of two clonal hematologic malignancies in the same patient is very rare. Although the occurrence of myeloid neoplasms evolves one into each other is largely known and also, the same potential has lymphoproliferative disorders, less is known about the permutation of a myeloid into a lymphoid malignancy and inversely, and about their co-occurrence. Fourteen patients have been identified with coexistence of MPNs and LPDs at Clinic of Hematology, University Clinical Center of Serbia and due to the unusual presentation, we singled out two cases in particular.

Introduction

The coexistence of myeloproliferative and lymphoproliferative neoplasms in a single individual is relatively rare. Myeloproliferative neoplasms (MPNs) and lymphoproliferative neoplasms (LPNs) are two distinct categories of blood disorders, and they involve abnormal growth of different types of blood cells.

Myeloproliferative neoplasms primarily affect the myeloid stem cells, leading to the overproduction of mature blood cells, such as red blood cells, white blood cells and platelets. Common types of MPNs include polycythemia vera, essential thrombocythemia and primary myelofibrosis. The MPNs are clonal hematological disorders characterized by increased
proliferation of one or more myeloid lineages in the bone marrow (BM) [1,2]. MPN are slowly progressing diseases which can transform to severe bone marrow failure or acute leukemia.

Lymphoproliferative neoplasms involve the lymphoid stem cells, characterized by uncontrolled production of lymphocytes that can cause monoclonal lymphocytosis, lymphadenopathy and can infiltrate bone marrow and/or solid organs [3]. Among LPDs there are indolent as well as aggressive types of the disease. In coexistence of MPN and LPNs it is usually seen chronic lymphocytic leukemia but it can be seen as one of the aggressive lymphomas such as diffuse large B-cell non-Hodgkin lymphoma (DLBCL). Considering MPNs and LPDs have different pathogenetic mechanisms, it is unclear which cause leads to the appearance of these two malignancies simultaneously. Some studies showed that risk of developing a second neoplasm was increased in patients with myeloproliferative neoplasms. The risk of developing a hematologic malignancy in these patients was also significantly increased [4, 5]. Development of secondary malignancies will affect the quality of life and therefore overall survival.

Methods

MPN diagnoses were made according to the most recent WHO classification and guidelines at a given time. Also, LPN were diagnosed using physical exams, blood tests (including flow cytometry immunophenotyping), pathohistological verification and radiographic methods. When possible, we used molecular tests to identify specific mutations (JAK2V617F, cytogenetic aberrations). Standard prognostics models were used for both MPNs and LPNs.

Results

Fourteen patients have been identified with both MPNs and LPNs in the Clinic of Hematology, University Clinical Center of Serbia (UCCS) from 2000-2022. More than 50% patients have MPNs as first diagnosis, in contrast to 21.5% patients with LPDs as first diagnosis as well as the two diagnoses were concomitant in 21.5% of patients. Gender distribution was similar with 57% males. Patients who had the first appearance of one and then another disease were significantly younger compared to those in whom the disease was presented simultaneously. The median age in the whole group was 53 years (range 22-69). The most common association was between PV and CLL (36%). The most common type of MPN was PV (57%) followed by PMF (33%) and ET (10%), while from LPN there was CLL in the same representation (57%)
then multiple myeloma (21%), DLBCL (15%) and lymphoblastic lymphoma (7%). The period until the development of LPN after the initial diagnosis of MPN is twice short and average time is 52 months, in contrast to the development of LPN followed by MPN which is 101 months. Analyzing the frequency of the cytogenetic-molecular markers, 2/3 of the patients had presence of JAK2V61F mutations, while 1/4 had cytogenetic aberrations, most often in LPNs followed by MPN. Overall, 57% of MPN patients required a myeloid-specific treatment while patients with LPNs were treated in 64.3% of patients. Nearly half of patients (42.8%) developed thrombotic complications in the whole group but more often in MPNs followed by LPNs. Interesting observation was development of a third malignancy in 21.4% of patients. Median follow-up was 7.5 years in the whole group and only median survival of 12.5 years reached patients in group MPNs followed by LPNs. During follow-up 35% of patients died due to progression of LPDs (2 patients), heart failure (1 patient), renal failure (1 patient) and COVID19 (1 patient).

Case report 1

A 55-year-old female patient was admitted to the Clinic of Hematology, UCCS in 2015 due to persistent thrombocytosis and splenomegaly. The patient reported no other symptoms. In her past medical history, she had ventricular arrhythmias on physical exam and she was an active smoker. A physical examination revealed splenomegaly (+2 cm), which was confirmed by ultrasonography (14.6x5.5 cm). The initial complete blood cell (CBC) count showed a white blood cell (WBC) level of 11.8x10^9/L with 65% neutrophils, 26% lymphocytes, 3% eosinophils, 5% monocytes and 1% basophils in formula, hemoglobin (Hb) level of 149g/L and platelet (Plt) count of 656x10^9/L. The results of biochemical analyses were normal except elevated serum lactate dehydrogenase (LDH) level to 400 U/L (150-320). The JAK2V617F mutation was detected by PCR analysis. Conventional cytogenetics showed a normal female karyotype. Spirometry was normal as well as the concentration of serum erythropoietin. Bone marrow (BM) biopsy showed features compatible with a primary myelofibrosis (PMF), prefibrotic stage with fibrosis grade 1. The patient was diagnosed with prePMF according to the 2016 revision of World Health Organization (WHO) classification. According to the International Prognostic Scoring System (IPSS) score of 1, the patient was classified as low risk and further was regularly followed every three months. She had only treatment with acetylsalicylic acid as antithrombotic
prophylaxis due to arrhythmias. In September 2021 spleen size by ultrasound was 16cm. Due to stomach pain in March 2022 the computer tomography (CT) scan was done and showed progressive splenomegaly, measuring 26x10cm, with necrosis segments. Therefore, the urgent splenectomy was indicated and done in a regional hospital. Before splenectomy, CBC count showed mild anemia (Hb 111g/L) with normal WBC (7.2x10⁹/L) and normal Plt count (380x10⁹/L). Initial histopathological examination of spleen showed diagnosis of marginal zone lymphoma. In April 2022, she had SARS-CoV-2 infection which was intensive and she was hospitalized in COVID hospital and treated with Sotrovimab. Due to progression of thrombocytosis with a Plt count of 1500x10⁹/L, cytoreductive therapy was started with hydroxyurea 3x500mg per day and after recover of SARS-CoV-2 infection she was referred to our Clinic for a reevaluation in July 2022. The pathohistological revision of spleen with immunohistochemistry was done at Faculty of Medicine, University of Belgrade and the final diagnosis of Diffuse large B cell lymphoma, NOS (DLBCL), double expressor (DEL) was confirmed with the absence of extramedullary hematopoiesis (EMH) signs. The Ki67 proliferative index was approximately 40%. In July 2022 the bone marrow biopsy showed MPN associated with 30% infiltration of small lymphocytes. CT scan of neck, thorax, abdomen and pelvis showed only axillary lymphadenopathy less than 2cm. The initiation of specific hematological treatment was indicated but the patient did not have done all necessary vaccination after splenectomy. Before vaccination was done, she had SARS-CoV-2 reinfection and the hospitalization was postponed again. In the meantime, the patient’s general condition worsened, her performance status was 3/4, in terms of her blood count, she had leukocytosis with a WBC of 32x10⁹/L and normal range of hemoglobin and platelet level. LDH was extremely elevated and hypoalbuminemia was observed. CT body scan showed further lymphoma progression with generalized lymphadenopathy and bilateral pleural effusions. In October 2022 at a regional hospital, the treatment with CHOP protocol (cyclophosphamide, doxorubicin, vincristine, prednisolone) was started due to vital indications. After three courses of CHOP chemotherapy, control scans showed further lymphoma progression, now staged as CS IV B E M+ according to the Ann Arbor staging. Despite all therapeutic measures, no clinical improvement was obtained and the patient died due to sepsis.
Case report 2

In March 2015, a 57-year-old female with a history of arterial hypertension and unstable pectoral angina was referred to hematologist due to unexplained persistent increase in platelet count for almost two years. Physical examination was unremarkable, with no organomegaly or enlarged lymph nodes. Her blood analysis showed Hb of 139 g/L, thrombocytosis of 728x10^9/L, WBC of 20.8x10^9/L, with neutrophil predominance (72%), and mild elevated LDH of 506 U/L (220-460). Chest x-ray and abdominal ultrasound showed no pathological findings. Karyotype was normal. Mutation of V617F in the JAK2 gene was not observed by PCR analysis. BM biopsy was performed in another medical center and showed hypercellularity, polymorphic and dysplastic megakaryocytes, with uneven distribution and clustering. According to WHO criteria, the diagnosis of prePMF was made. She was stratified as intermediate-1 risk group and treated with cytoreductive therapy (hydroxyurea 1g/daily), with complete and sustained remission. However, in April 2018, three years following PMF diagnosis and HU treatment, progressive leukocytosis (28x10^9/L) with lymphocytosis (83%) was observed, therefore flow cytometry immunophenotyping of peripheral blood was performed, which showed expression of CD5, CD23, in combination of dim CD20, CD22, CD43, with dim monoclonal surface immunoglobulin and negative CD38 and CD49b. According to the immunophenotypic characteristics of clonal B lymphocytes, Matutes CLL score was highest (5 points). Repeated BM biopsy at that time showed 60% of CD20+, CD5+, CD23+ infiltrative cells, with 10% Ki-67 positive cells. These findings were consistent with chronic lymphocytic leukemia (CLL). Our patient was initially managed with a “watch and wait” approach. Two years later, during the follow-up, she developed B symptoms, clinically significant lymphadenopathy (max diameter 4x2cm), as well as progressive leukocytosis (WBC 150x10^9/L) and lymphocytosis (absolute lymphocyte count, ALC 133.5x10^9/L) and lymphocyte doubling time <6 months which fulfilled criteria for treatment initiation. Fluorescence in situ hybridization (FISH) did not show any negative molecular prognostic markers and repeated cytogenetic analysis indicated normal karyotype. In our patient, diagnosis of CLL Rai stage II; Binet stage B was made, with cumulative index rating scale (CIRS) 6. In August 2020, the treatment with Obinutuzumab – chlorambucil therapy was started. After completing six consecutive immunchemotherapy cycles, complete remission of CLL was achieved and it was held until today. In April 2022, the
CBC count showed normal Hb level and normal WBC but progression of thrombocytosis up to 727x109/L and treatment with hydroxyurea 500mg per day was started.

**Discussion**

Occurrence of two distinct hematology neoplasms in the same patient is very rare, in these terms therefore a little is known about clinical characteristics, thrombotic complications and survival. Considered etiopathogenetic mechanisms, some of genetic abnormalities (*JAK2V617F, BCR/ABL1, PDGFRA, PDGFRB, TET2, SF3B1*) were described which can lead to either myeloid or lymphoid malignancies [6-8]. A Swedish registry study revealed a 5- to 7-fold elevated risk of MPN and a 1.6-fold increased risk of CLL among first-degree relatives of MPN patients [9]. The fact that family members of individuals with MPNs are at higher risk for the development of MPN and CLL suggests that host genetic modifiers also have a role in the pathogenesis of these malignancies. Study of Le Bousse-Kerdilès MC showed that in PMF, clonal cells produce inflammatory cytokines, and chronic inflammation promotes specific B-cell tumorigenesis by providing an environment where neoplastic B cells escape normal regulatory mechanisms [10]. Chronic inflammation is an accompanying manifestation of all types of MPNs and this may explain the higher rate of prior MPN over LPD in our study. External triggers, such as hematological therapies (hydroxyurea, ruxolitinib) may also favor the emergence of the second clone by reducing immune surveillance on the development of second tumors. The interest for the potential role of drugs in lymphomagenesis has been strengthened after the publication of an Austrian study [11] that raised the possibility that JAK inhibitor, ruxolitinib, treatment for myelofibrosis was associated with an increased risk for aggressive B-cell lymphomas [12, 13]. Neither one patient in our study did not receive JAK2 inhibitor ruxolitinib.

According to our results, the median age of the patients was less than 60 years and the youngest were in a group that first developed LPNs then MPNs (49 years). More than 50% of patients had firstly developed MPN then LPNs after twice shorter time then vice versa. One third of patients had a combination of PV and CLL. Median survival was only reached in a group of MPNs, then LPNs and it was 196 months. On the other hand, in systematic review by Marchetti *et al*, 214 patients were included harboring both MPN and LPD, diagnosed and treated from 2005-2016. Median age of the patients in the study was older than in our group (67 years).
Distribution of patients according to the type of MPN was different with mostly patients with essential thrombocythemia (44%) then polycythemia vera (29%), primary myelofibrosis (23%) and unclassified MPN (4%). In this study more often patients developed LPNs after MPNs but after a longer median time of 72 months. Patients mainly had indolent LPN like in our study, particularly chronic lymphocytic leukemia, while aggressive lymphomas and multiple myeloma were seen as part of LPNs occurring in the follow-up of MPN. Median survival after MPN diagnosis was much shorter than in our group (96 months vs 196 months). This is probably due to development during the course of MPN, a more aggressive type of LPNs then seen in our group. This thorough review also confirms that LPD are relevant clinical events in the history of MPN patients [14].

Splenic infiltration is often seen in DLBCL, but type of primary splenic DLBCL is rare and studies on its clinicopathological features are limited. Holst J. et al evaluate patients with confirmed dual diagnoses of myeloproliferative neoplasm and lymphoma [15]. They found that the 5-year overall survival rate of the patients with MPN+DLBCL was 19% as compared to 34% for patients in the matched reference cohort with presence only DLBCL. Also, 5-year overall survival of the patients with MPN+CLL was 65%, compared to 79% in patients with only CLL. Another study compared 66 patients with primary splenic DLBCL and 309 patients with DLBCL NOS [16]. They found that primary splenic DLBCL had a more favorable progression free survival (PFS) compared to the DLBCL control, but there is no difference in overall survival between above-mentioned groups. It is interesting that in our first case we was looking for sign of EMH in spleen after splenectomy, which is typically cause of organomegaly and it is relatively common complication of PMF, but although BM biopsy showed presence of myeloproliferative neoplasm associated with 30% infiltration of small lymphocytes, the histopathology of the spleen has showed an absence of EMH signs. Instead of that, diagnosis was primary splenic DLBCL. Beside that DLBCL is an aggressive tumor in itself, poor clinical outcome is increased by overexpression of MYC and BCL2 proteins (double-expressor lymphoma, DEL) and post-germinal immunohistochemical subtype of DLBCL (non-germinal center B-cell (non-GCB)-DLBCL) [17]. Both of these two unfavorable prognostic factors were present in our first described patient which led to rapid disease progression despite low initial risk. Patient had limited treatment efficacy with CHOP chemotherapy, The delay in necessary vaccinations and subsequent SARS-CoV-2 reinfection likely contributed to the patient's compromised immune
status, exacerbating the disease progression treatment complication with sepsis and shorter survival.

Second case described showed development of CLL in patients with prePMF. The patient's response to Obinutuzumab – chlorambucil therapy for CLL was successful, leading to complete remission and sustained improvement. The absence of negative molecular prognostic markers in FISH and normal karyotype indicates a relatively favorable prognosis for the CLL. Despite successful CLL treatment, the patient experienced progression of thrombocytosis, requiring the initiation of hydroxyurea therapy, suggesting the challenges in managing multiple hematological conditions concurrently. These presented cases indicate that the course of both diseases depends a lot on the presence of poor prognostic parameters previously defined for the diseases themselves. Laurenti L. et al evaluated patients with confirmed dual diagnoses of MPN and CLL and they found that MPN therapy does not interfere with the prognosis of patients with CLL [18]. Burgstaller S et al. showed lenalidomide was effective in patient diagnosed with a myeloproliferative and a lymphoproliferative disease at the same time [19].

The limitation of our study is the small sample of patients. However, some important observations were also seen beside unusual presentation, importance of assessment of prognostic factors and includes that nearly half of patients (42.8%) developed thrombotic complications. In our study, Throly score was successful in identifying patients at higher risk for venous thromboembolism [20]. The second observation was that 1/5 of patients developed a third malignancy. The first observation can be explained by the fact that the activation of the coagulation system is significantly increased in the presence of two malignancies [21] and that the JAK2V617F mutation which is associated with this complication was detected in 66.7% of patients. Second observation is possibly a consequence of genomic instability that leads to the development of multiple neoplasms [22-24].

In conclusion, our study confirms that LPN are relevant clinical events in the history of MPN patients. Controlled studies are needed to better refine individuals at higher risk of developing LPN and to avoid therapies possibly favoring their development. The cases underscore the importance of timely and accurate diagnosis following regular check-up, personalized treatment strategies and comprehensive patient care management to improve
survival in patients with complex hematological disorders. Additionally, prioritizing preventive measures such as vaccinations especially in immunocompromised patients and antithrombotic prophylaxis, is crucial in preventing complications and improving treatment outcomes of these patients.

References:


Statements and Declarations

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**Competing interest:** The authors have no relevant financial or non-financial interests to disclose.

**Author contributions:** All authors contributed to the study conception and design. D.L, J.I, A.B., D.A. designed the study and wrote the manuscript, T.T and M.P.J. analyzed bone marrow biopsy specimens and immunohistochemistry, D.L, J.I, I.A, collect clinical data, M.D.F mad J,J performed and analyzed cytogenetic and molecular data. All authors read and approved the final manuscript.

**The Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of University Clinical Center Serbia (protocol no 499/5 and date of approval 30/22/2021).

**Informed Consent Statement:** Patient consent was waived due to retrospective nature of the study, but there is agreement from the patient association.

**Data Availability Statement:** All data regarding this research are available upon reasonable request to the corresponding author.

**Conflict of interest:** The authors declare that they have no conflict of interests.
Table 1: Characteristics of patients according to time of MPNs and LPNs diagnosis

<table>
<thead>
<tr>
<th></th>
<th>MPNs as first diagnosis</th>
<th>MPNs+LPNs co-occurrence</th>
<th>LPNs as first diagnosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>8 (57%)</td>
<td>3 (21.5%)</td>
<td>3 (21.5%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td><strong>Age at diagnosis (years)</strong></td>
<td>52 (22-63)</td>
<td>59 (42-69)</td>
<td>49 (41-60)</td>
<td>53 (22-69)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>4/8</td>
<td>3/3</td>
<td>1/3</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td><strong>First and second diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 PV / NHL DLBCL</td>
<td></td>
<td>2 CLL + PV</td>
<td>2 CLL / PV</td>
<td>5 PV + CLL</td>
</tr>
<tr>
<td>1 PMF / NHL DLBCL</td>
<td></td>
<td>1 MM + PMF</td>
<td>1 atypical CLL (score 3) / PMF</td>
<td>2 PMF + CLL</td>
</tr>
<tr>
<td>1 PMF / CLL</td>
<td></td>
<td></td>
<td></td>
<td>1 ET + CLL</td>
</tr>
<tr>
<td>1 ET / CLL</td>
<td></td>
<td></td>
<td></td>
<td>1 PMF + MM</td>
</tr>
<tr>
<td>1 PV / CLL</td>
<td></td>
<td></td>
<td></td>
<td>1 ET + MM</td>
</tr>
<tr>
<td>1 ET / MM</td>
<td></td>
<td></td>
<td></td>
<td>1 PV + MM</td>
</tr>
<tr>
<td>1 PV / MM</td>
<td></td>
<td></td>
<td></td>
<td>1 PMF + NHL DLBCL</td>
</tr>
<tr>
<td>1 PV / lymphoblastic lymphoma</td>
<td></td>
<td></td>
<td></td>
<td>1 PV + NHL DLBCL</td>
</tr>
<tr>
<td><strong>Time before second diagnosis (months)</strong></td>
<td>Until the appearance LPDs: 52</td>
<td>Until the appearance MPNs: 101</td>
<td>65 (4 - 216)</td>
<td></td>
</tr>
<tr>
<td><strong>JAK2V617F+ (MPNs)</strong></td>
<td>4/7 (57%) *one not done</td>
<td>2/2 (100%) *one not done</td>
<td>2/3 (66.7%)</td>
<td>8/12 (66.7%)</td>
</tr>
<tr>
<td><strong>CG aberration (LPNs)</strong></td>
<td>1/8 (12.5%)</td>
<td>1/3 (33.3%)</td>
<td>2/3 (66.7%)</td>
<td>4/14 (28.5%)</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPNs</td>
<td>HU 6/8 (75%)</td>
<td>HU 1/3 (33.3%)</td>
<td>HU 1/3 (33.3%)</td>
<td>8/14 (57%)</td>
</tr>
<tr>
<td>LPNs</td>
<td>5/8 (62.5%)</td>
<td>2/3 (66.7%)</td>
<td>2/3 (66.7%)</td>
<td>9/14 (64.3%)</td>
</tr>
<tr>
<td><strong>Third malignancy</strong></td>
<td>1/8 (12.5%)</td>
<td>2/3 (66.7%)</td>
<td>0/3</td>
<td>3/14 (21.4%)</td>
</tr>
<tr>
<td><strong>Thrombosis</strong></td>
<td>4/8 (50%)</td>
<td>1/3 (33.3%)</td>
<td>1/3 (33.3%)</td>
<td>6/14 (42.8%)</td>
</tr>
<tr>
<td><strong>Follow-up median (months)</strong></td>
<td>99 (36-252)</td>
<td>60 (26-84)</td>
<td>101 (74-174)</td>
<td>90 (26-252)</td>
</tr>
<tr>
<td><strong>Overall survival median (months)</strong></td>
<td>196 (127-251)</td>
<td>Not reached</td>
<td>Not reached</td>
<td>200 (149-251)</td>
</tr>
<tr>
<td><strong>Cause of death</strong></td>
<td>4/8 (50%)</td>
<td>1/3 (33.3%)</td>
<td>Alive</td>
<td>5/14 (35.7%)</td>
</tr>
<tr>
<td></td>
<td>2 LPNs, 1 ABI, 1 HF</td>
<td>COVID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1  A: Spleen diffusely infiltrated by DLBCL (HE, x 400). Immunohistochemical stains demonstrated the neoplastic cells expressing B: CD20, C: bcl-2, D: c-myc, E: Ki-67+ 40%. F: Rare CD71+ erythroblasts in the sinusoids of the spleen. (Immunoperoxidase, x 400)
Figure 2 Fluorescence in situ hybridization showed bcl-2+ rearrangement
Figure 3  A: Bone marrow biopsy (HE, x40) (March 2015) showed B: morphology of pre PMF, without lymphocytic infiltration (HE, x400); C: Bone marrow biopsy (February 2020) demonstrated interstitial infiltration of small lymphocytes showing immunohistochemical staining for CD20, D: CD5, E: CD38, F: Ki67+ in 10% of lymphoid cells (Immunoperoxidase, x 400)