CASE REPORT

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# Diffuse large B-cell lymphoma and polycythemia vera discovered at the onset – a rare association and its possible importance in lymphoma prognosis

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## Abstract

Diffuse large B-cell lymphoma (DLBCL) represent the most frequently non-Hodgkin's lymphoma (NHL) (over 30%), especially in developing countries. Many associations of NHL with another neoplasia were described following chemotherapy or radiotherapy regimens. The coexistence of DLBCL with myeloproliferative neoplasms (MPNs) JAK2V617F positive at the onset was very rare reported in the literature. We describe a clinical case of a 52-year-old man who presented both diagnoses at the onset – DLBCL and MPN – polycythemia vera (PV) type. The patient was treated with two CHOP cycles (Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisolone) followed by six R-CHOP (Rituximab-CHOP) cycles, together with a platelet-reducing agent, achieving remission for 20 months, followed by a relapse which is under treatment. The clonally expansion of an abnormal pluripotent hematopoetic stem cell could be responsible for both, PV and DLBCL. However, recent reports suggested the possible involvement of two different clones. The clinical significance and the role of JAK2 mutation in the evolution of patients with NHLs, including DLBCL are still unknown. Further genetic and clinical studies have to point out common gene mutations for the two diseases and their connection with the diseases behavior under the treatment. *Conclusions*: The coexistence of NHLs and especially DLBCLs and MPNs JAK2 positive is very rare. Although DLBCL alone has good prognosis, other prognostic factors should be checked when it is associated with PV. The presence of JAK2V617F seems to be a candidate but whose role in DLBCL evolution, natural or under treatment has to be cleared up.

*Keywords*: JAK2 mutation, polycythemia vera, diffuse large B-cell lymphoma, prognosis.

## ⊟ Introduction

Diffuse large B-cell lymphoma (DLBCL) represent the most frequently non-Hodgkin's lymphoma (NHL) (over 30%), especially in developing countries [1, 2]. An alternative microarray technology (gene expression profiling – GEP) allowed the identification of three types of DLBCL not otherwise specified (NOS): GEP profile of germinal center B-cells (GCB-like), GEP profile of activated peripheral B-cell (ABC) and few cases that cannot be classified in these categories (type 3 DLBCL). The GEP classification is very important for prognosis of these patients: ABC-DLBCL patients have a worse prognostic than GCB-DLBCL [3]. GCB-DLBCL subtype is associated with amplifications of the REL loci, BCL-2 translocations and hypermutations of the immunoglobulins loci; the other type, ABC-DLBCL is associated with activation of the nuclear factor-kappa B (NF-$\kappa$B) pathway. The amplifications at 9p corresponding to JAK2 was associated with DLBCL primary mediastinal subtype [2]. Patients with myeloproliferative neoplasms (MPNs), especially patients with polycythemia vera (PV) have JAK2V617F mutation (93% of patients with PV; 50%

patients with primary myelofibrosis or essential thrombo-cythemia) [4]. The presence of JAK2V617F mutation was not implicated in evolution of other lymphoproliferative disease, like B-cell chronic lymphocytic leukemia (B-CLL) [5]. In MPNs patients, this mutation plays a major role in myeloid maturation induced by cytokines and grows factors signaling (including interleukin-3, erythropoietin, granulocyte and granulocyte-macrophage colony-stimu-lating factor, thrombopoietin). A few patients also have associated chromosomal abnormalities (9p or 20q deletion) [6].

The association between NHLs and PV is rare [7, 8]. Although an infrequent event, the spectrum of clinical situations gathers together no more than three different forms: (a) either the two diseases are coexisting from the onset, especially in previously untreated patients [8–12], (b) or, much more rarely, the myelodysplastic syndrome is following the lymphoma and its therapy [13–15], (c) or lymphoma was reported subsequent to diagnosis of PV [7, 16, 17]. We will present a clinical case of one patient with simultaneously diagnosis of DLBCL and PV and will make a brief review of the other 18 cases about we could find data reported in the literature. Written informed

consent was obtained from the patient for publication of this case report and the accompanying images.

### ⊡ Case presentation

#### Patient's status at admission

A 52-year-old male, without significant medical history, was admitted in the Emergency County Hospital, Pitesti, Romania, for altered health state, nocturne sweats, weight loss, lymphadenopathies. On clinical examination, the patient was afebrile, with good general state [performance status ECOG 1 (*Eastern Cooperative Oncology Group*)], multiple peripheral mobile unpainful lymphadenopathies (supraclavicular, axillar and inguinal), with a diameter of 1–3 cm; bloating, upper abdominal increased sensitivity, and liver border at the 2 cm bellow costal margin, consistency moderately increased, rounded edge, spleen palpable with bottom pole from 2–3 cm below costal border.

#### Clinical laboratory investigations

The white blood cell (WBC) count showed leukocytosis (18 500/mm$^3$) with slight left shift deviation, without blasts or promyelocytes but with basophils (3%), high platelet count (869 000/mm$^3$) with giant platelets and platelet aggregates, but hemoglobin (Hb) and hematocrit (Ht) in normal values (Hb 15.2 g/dL, Ht 41.9%). Blood biochemistry was normal except lactate dehydrogenase (LDH) level, which was mild elevated (250 IU/mL). Serology was negative for hepatitis viruses (HBV, HCV). Serum erythropoietin (EPO) was very low (<1 U/mL). The mutant homozygote status for JAK2V617F was determined by real-time polymerase chain reaction (RT-PCR).

#### Pathology and immunohistochemistry (IHC)

We performed a bone marrow trephine biopsy (BMB) from posterior-superior iliac crest, after local anesthesia. After fixation in 10% buffered formaldehyde, BMB sample was decalcified for 3–4 hours in Na$_2$EDTA (Disodium ethylenediaminetetraacetate), processed and paraffin embedded. The sections of 4 μm were stained with Hematoxylin–Eosin (HE). The BMB histological examination revealed a hypercellular bone marrow, with panmyelosis (Figure 1a), normal myeloid:erythroid (M:E) ratio (3:1), moderate megakaryocytic hyperplasia with giant hyperlobulated megakaryocytes, dispersed and in small perivascular clusters (Figure 1b), without lymphoid infiltration.

We have also performed biopsy of an axillary lymph node. The microscopic examination of the lymph node was typical for a large cell NHL (loss of normal architecture, diffuse malignant infiltrate with large-sized atypical lymphoid cells, round vesicular nucleus, 2–4 medium-sized nucleoli, moderately basophilic cytoplasm) (Figure 2, a and b).
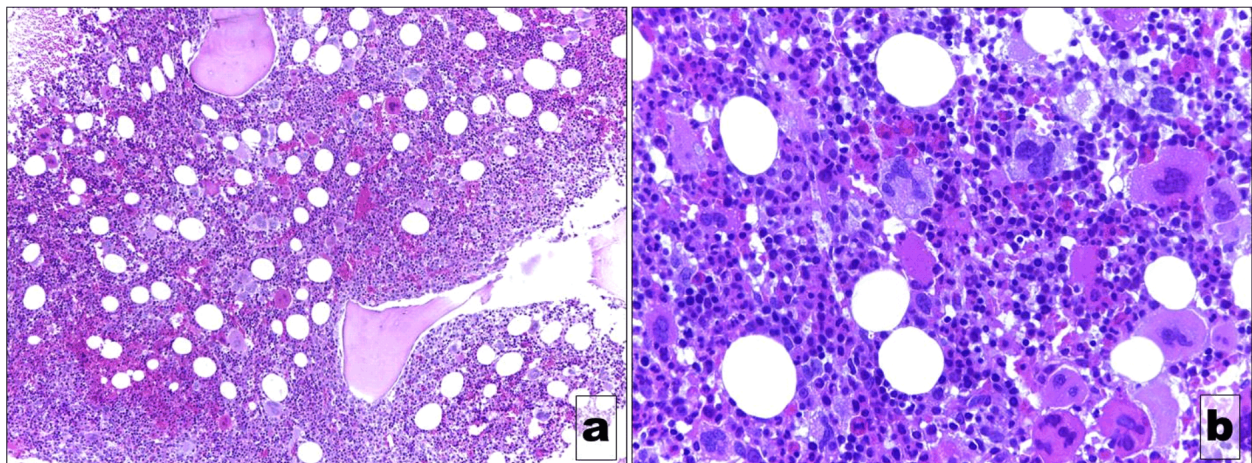


**Figure 1 – *Bone marrow biopsy: (a) Hypercellularity, panmyelosis; (b) Clusters of large megakaryocytes. HE staining: (a) ×100; (b) ×400.***
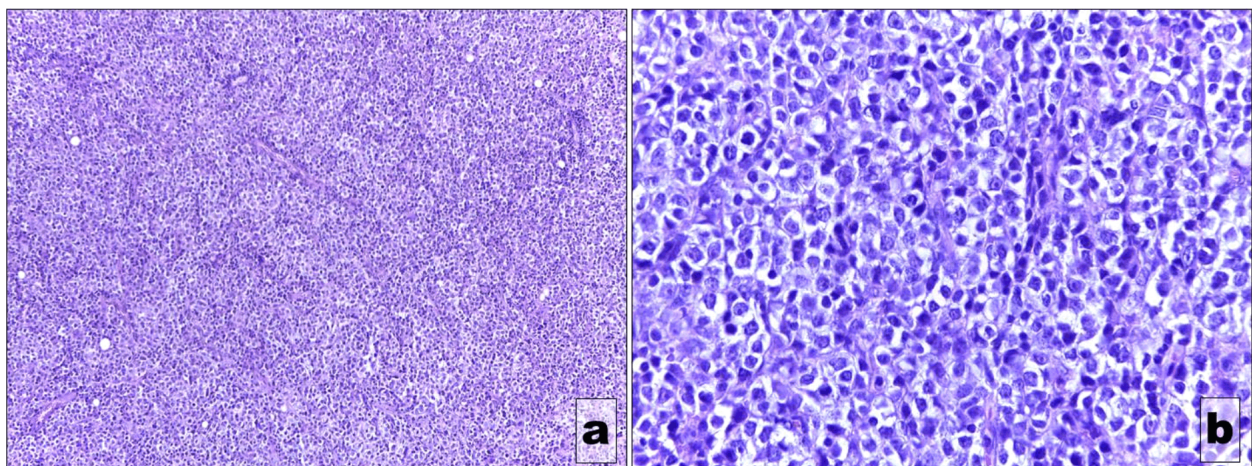


**Figure 2 – *Lymph node biopsy: (a) Diffuse large cells lymphoid infiltrate; (b) Tumor cells are large lymphoid cells, with vesicular nucleus and 2–3 nucleoli. HE staining: (a) ×100; (b) ×400.***

IHC staining was carried out on paraffin sections using MaxPolymer Novolink (Leica, UK), in accordance with the manufacturer's protocol. We performed IHC stainings with B-cell marker anti-CD20 (clone L26, 1:250 dilution, Novocastra, Leica, UK) and T-cell marker anti-CD3 (clone LN10, 1:400 dilution, Novocastra, Leica, UK).

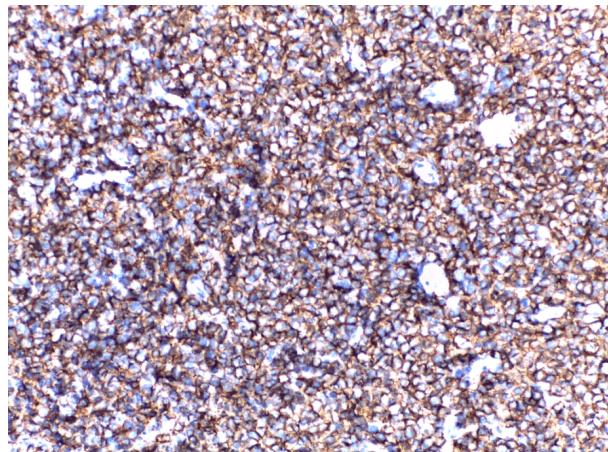The tumor was diffusely positive for CD20 (Figure 3) and CD3 negative.



**Figure 3 – *Lymph node biopsy: tumor cells are large B-cells, CD20 positive. IHC staining for CD20, ×200.***

The final diagnosis was DLBCL associated with MPN, JAK positive homozygous, PV type.

Computed tomography (CT) scans performed for DLBCL staging showed mild hepatomegaly (right hepatic lobe 17.4 cm, left hepatic lobe 7 cm), moderate spleno-megaly (16.7 cm), two inguinal adenopathies (3.5/3.2 cm and 3.2/3.6 cm) with homogenous structure, without pulmonary or mediastinal lesions, advocating for III B clinical stage of DLBCL. The prognosis score, according to the *Revised International Prognostic Index* (R-IPI) was 2, meaning a good prognosis.

### Patient outcome

The patient was treated with two CHOP cycles [Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine) and Prednisolone], followed by six cycles of CHOP with anti-CD20/Rituximab (R-CHOP) chemotherapy. He has also received Anagrelidum (a platelet-reducing agent) 0.5 mg×2 daily.

The patient achieved hematological remission of DLBCL, confirmed by positron emission tomography (PET) scans, after eight months, but relapsed after 20 months with pleural effusion and mediastinal tumor. He was planned for another chemotherapy schedule, R-ICE type (Rituximab, Ifosfamid, Carboplatin and Etoposidum) and his treatment is ongoing.

### ⊟ Discussion

The association between a MPN, especially PV and a NHL at the time of diagnosis is rare, as we already mentioned above. We identified in the literature only 26 cases, including ours, in the last 50 years since Heinle *et al.* [9] reported the first case with this association (Table 1).

**Table 1 – *Synopsis of cases identified in the accessible literature with non-Hodgkin's lymphoma and polycytemia vera since the first case communicated in 1966 by Heinle et al. [9] (modified after Papageorgiou et al. [8] and Jeong et al. [12] and extended)***

| No. | Year | Ref. | Gender | Age [years] | Type of NHL | Therapy | Outcome |
|---|---|---|---|---|---|---|---|
| | | | | | **Simultaneous at the onset** | | |
| 1 | 2016 | [12] | F | 61 | Follicular (grade 1) | Local excision; radiation; phlebotomy; Aspirin; HU | NHL – CR; stabilization of Hct; leukocytosis; thrombocytosis |
| 2 | 2014 | [20] | M | 14 | Mixed diffuse lymphocytic kidney infiltration | Chemotherapy (NoS) | Favorable after chemotherapy Improvement in renal parameters |
| 3 | 2002 | [10] | M | 66 | Follicle center cell (grade 1) | m-BACOD; MIT + PDM; HU | NHL – CR and reduction of PV; PV – recurrence of after four years of chemotherapy withdrawal |
| 4 | 1991 | [19] | M | 20 | Immature phenotype | CHOP + VM26 CNS prophylaxis (MTX + DEX) PDN + VCR + DNM + Asparaginase m-BACOD | No response and progression of NHL, followed by close mortality |
| 5 | 1988 | [21] | M | 73 | Plasmacytoid, colon | Melphalan | NoS |
| 6 | 1985 | [22] | F | 53 | **Large B-cell** | Chemotherapy (NoS) | Favorable after chemotherapy |
| 7 | 1981 | [23] | NoS | NoS | Diffuse, lymphocytic | RAMI | RAMI |
| 8 | 1966 | [9] | F | 86 | Lymphocytic | Phlebotomy + radioactive phosphorus | RAMI |
| 9 | 2016 | OC | M | 52 | **DLBCL** | R-CHOP | NHL – CR after eight months and relapse after 20 months Under treatment with new scheme |
| | | | | | **NHL first at the onset** | | |
| 10(1) | 2013 | [15] | M | 72 | **DLBCL** – brain (three years before PV) | RAMI | RAMI |

| No. | Year | Ref. | Gender | Age [years] | Type of NHL | Therapy | Outcome |
|---|---|---|---|---|---|---|---|
| 11(2) | 2011 | [26] | M | 90 | Follicular (24 years before PV) | NoS | NoS |
| 12(3) | 2006 | [14] | M | 64 | Small lymphocytic | CTX + VCR + PDN and RXB | Favorable post-chemotherapy Hb and EPO normalized |
| 13(4) | 1996 | [13] | F | 74 | Diffuse centroblastic (11 years before PV) | ADM + VCR + PDN + MTX | NHL – remission PV – NoS |
| 14(5) | 1992 | [24] | M? | NoS | **DLBCL** (4.5 years before PV) | CTX and Procarbazine | NHL in CR PV – NoS |
| | | | | | **PV first at the onset** | | |
| 15(1) | 2011 | [26] | M | 75 | **DLBCL** (10 years after PV) | NoS | NoS |
| 16(2) | 2011 | [26] | M | 64 | **DLBCL** (23 years after PV) | NoS | NoS |
| 17(3) | 2011 | [26] | M | 79 | **DLBCL** (9 years after PV) | NoS | NoS |
| 18(4) | 2009 | [27] | F | 69.6 | **DLBCL** (6.6 years after PV) | NoS | NoS |
| 19(5) | 2009 | [27] | M | 65.6 | Mantle cell (1.6 years after PV) | NoS | NoS |
| 20(6) | 2009 | [27] | M | 79.9 | NoS (10.9 years after PV) | NoS | NoS |
| 21(7) | 2006 | [17] | NoS | NoS | **DLBCL** | RAMI | RAMI |
| 22(8) | 2002 | [7] | F | 61 | **DLBCL**, high-grade malignancy, oral cavity (17 years after PV) | m-BACOD Local radiotherapy | Oral lesion – CR Favorable at 10 months after treatment |
| 23(9) | 1995 | [16] | M? | NoS | Anaplastic **B-cell** (Ki-1) | RAMI | RAMI |
| 24(10) | 1994 | [25] | NoS | NoS | **B-cell**, high-grade malignancy | RAMI | RAMI |
| 25(11) | 1994 | [25] | NoS | NoS | **B-cell**, high-grade malignancy | RAMI | RAMI |
| 26(12) | 1994 | [18] | M | 78 | Cutaneous T-cell (one year after PV) | Phlebotomy Photochemotherapy | Resolution of skin lesion; stabilization of Hct; leuko-cytosis; thrombocytosis |

Ref: Reference; NHL: Non-Hodgkin's lymphoma; F: Female; HU: Hydroxyurea; CR: Complete remission; Hct: Hematocrit; M: Male; NoS: Not specified; m-BACOD: Second-generation combination chemotherapy regimen – Methotrexate (MTX), Bleomycin, Adriamycin/Doxorubicin (ADM), Cyclophosphamide (CTX), Oncovin–Vincristine (VCR), Dexamethasone (DEX); MIT: Mitoxantrone; PDM: Prednimustine; PV: Poly-cythemia vera; CHOP: Regimen containing CTX, ADM, VCR and Prednisone (PDN); VM26: Teniposide; CNS: Central nervous system; DNM: Daunomycin; RAMI: Restricted access to minimal information; OC: Our case; DLBCL: Diffuse large B-cell lymphoma; R-CHOP: Regimen which combines CHOP with Rituximab (RXB); EPO: Erythropoietin.

## Clinical morphological aspects

A first remark is concerning the sequence the two diseases appeared in the patient's life. The most numerous group, gathering together almost half of the identified cases, is the one including those cases with PV as the first disease. At the opposite, the least numerous group, including only five cases, was the one where the NHL arose the first.

A second remark is concerning the NHL's morphology. More than 45% of the identified cases were B-cell lymphomas and two-thirds of these belonged to the group where PV was first at the onset.

Overall, the association between the two types of proliferation was most frequently encountered in men, with some differences. Thus, in the group with NHL at the onset almost all cases were males whereas in the group with both diseases discovered at the onset, one-third of the cases were females. The males prevailed also in the group with PV at the onset even one-quarter of the cases had no gender specification. Finally, the males were prevailing in the group with B-cell lymphomas too but in one-quarter of cases, the patients' gender was not specified.

The age range is also different from one group to another. Thus, the group with NHL at the onset seems to be the preserve of elderly people whereas in the group with both diseases at the onset we found also young patients, of 14 and 20 years old. In the group with PV at the onset, two-thirds of patients had the age specified and it was higher than 60 years. In the group with B-cell lymphomas, patients were adults over 50 years and elderly but, again, we have to mention the lack of data in one-third of the cases.

The therapeutic strategy was focused in most of the cases and irrespective the group on the lymphoproliferative disease. In only four cases [9, 10, 12, 18] are mentioned therapeutic procedures for PV. Unfortunately, we have to mention again that the restricted access to the published data (half of the cases) did not allow a complete assessment of the applied therapy. If we do not take into consideration the 15 cases with no data concerning the patient's outcome, then in most of remaining cases the outcome was favorable first and foremost for the NHL. There was only one case [19] where the complex and sustained chemotherapy could not stop the progression of the lymphoproliferative disease and the patient died.

The prognosis of our patient was good (score IPI 2, PET scan negative). Patient was treated by R-CHOP chemotherapy schedule for DLBCL, but he relapsed after 20 months with mediastinal determination.

To treat patients with different concurrent cancers, including lymphoproliferative and myeloproliferative neoplasms, is a difficult task. In the past, IPI score brought more information about the prognosis of DLBCL patients. In present, many investigations improve the prediction of outcome for treatment of these patients. Fluorodeoxy-glucose–positron emission tomography (FDG-PET) brings an important role in predicting of outcome after completion of first-line therapy for DLBCL patients.

Patients who are PET negative have a 0% to 16% probability of relapse, compared with 87% to 100% of PET-positive patients [28]. DLBCL patients with negative and mild metabolism PET/CT following first-line treatment had good prognosis, who needed no additional therapy [29].

## Pathogenic and genetic aspects

The nature of the relationship between NHL, especially high grade, and PV is not clear [13]. The studies of last decades could not prove clearly a mechanism of coexistence of the two diseases, without any previous cytotoxic or radiation exposure [8, 12] or of a mechanism by which one can induce other, taking into consideration that they can be sequential at the onset. There are many hypotheses concerning their mechanisms of appearance, both when it happens sequentially or in the same time.

Thus, when we talk about coexistence:
▪ The coincidence cannot be excluded [13];
▪ Chromosomal abnormalities consisting in random mutations that occur in distinct initiating cells in both PV and NHL are suggesting the possible involvement of two different clones [12, 25, 30];
▪ Both malignancies may have evolved by clonal expansion of the same abnormal pluripotent hematopoietic stem cell although the karyotypes were not studied [13, 16].

When we talk about sequence of the onsets:
▪ The genomic instability characteristic to myeloproliferative neoplasms may contribute to subsequent lymphoproliferative neoplasms occurrence [26, 27];
▪ PV could be secondary to the ectopic production of erythropoietin by the lymphoma cells [14];
▪ PV could develop as a consequence of therapy for the NHL. However, there are an increasing number of patients surviving long term after chemotherapy for the malignant lymphoproliferative disease [13].

The genetic investigations could represent further a key tool in the elucidation of the relationship between the two types of proliferation. A starting point was the study of tyrosine kinase gene JAK2 (Janus Kinase 2) mutations. Thus, the JAK2V617F mutation, a point mutation in the JAK2 gene, has an important role in the pathogenesis of the MPNs. The JAK2 mutation induces the activation of the JAK-STAT signaling pathway, and leads to autonomous cell growth [31, 32].

The JAK2V617F was identified not only in MPNs patients, but also in NHL patients. However, the detection of JAK2 mutation in NHL is rare. For instance, Wang *et al.* reported the presence of JAK2 V617F allele in only three of 237 patients with lymphoid neoplasms [8, 31, 32]. Another study reported that patients with primary mediastinal DLBCL have a relative increase in JAK2 transcripts, but the JAK2 signaling in these cases was represented by mechanisms distinct from JAK2V617F or JAK2 exon 12 activating mutations, described in MPNs [33].

Najfeld *et al.* showed that patients with Ph-negative MPNs and non-MPNs have two types of JAK2 rearrangements. Gain and amplification of JAK2 was primarily observed in patients that were JAK2V617F-positive; rearrangements of JAK2 were seen in patients who lacked the JAK2V617F mutation. There are many JAK2 rearrangements, including a novel JAK2-NF-E2 interaction, JAK2 translocation to chromosomes 3, 4, 12, 14, and 21 and detection of TEL/ETV6-JAK2 translocation. In NHL patients, the presence of JAK2 attracts multiple gene partners and may contribute to disease progression [34].

In other studies, the presence of JAK2V617F mutation was not found in normal B- and T-lymphocyte populations and had no relevance in B-CLL patients because no evidence that the proliferative behavior of B-CLL clone is mediated through this mutation was found [35, 36].

The patterns of gene expression, as well as individual genes have also had an important prognostic significance. Three genes (LMO2, BCL6 and FN1) were correlated with prolonged survival and three (BCL2, CCND2 and SCYA3) were correlated with shorter survival. Expression of bcl-6 and CD10 was associated with a favorable outcome compared with MUM1 or cyclin D2 expression.

However, the clinical significance and the role of JAK2 mutation in the evolution of patients with NHLs, including DLBCL are still unknown [32].

Our study revealed that the paucity of cases reported in the literature and the lack or restricted access to the data included in the identified reports could not offer solid arguments in favor of certain influence of PV on NHL prognosis. Further genetic and clinical studies who should gather together a significant number of cases have to point out common gene mutations for the two diseases and their connection with the diseases behavior under the treatment.

## ⌗ Conclusions

The coexistence of NHLs and especially DLBCLs and MPNs JAK2 positive is very rare. Although DLBCL alone has good prognosis, other prognostic factors should be checked when it is associated with PV. The presence of JAK2V617F seems to be a candidate but whose role in DLBCL evolution, natural or under treatment has to be cleared up.

### Conflict of interests

The authors declare that they have no conflict of interests.

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