Chronic Lymphocytic Leukemia With Essential Thrombocythemia: Asbestos Exposure Association?

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Introduction

We describe a patient with essential thrombocythemia (ET) who developed chronic lymphocytic leukemia (CLL) 10 years after his initial diagnosis. The association of ET and CLL is very rare, and only a handful of cases have been described in the literature. Although the association may be one of chance, some evidence suggests that the 2 neoplasms may be related. Such evidence includes the occurrence of B-cell malignancy and ET in different generations of the same family, with anticipation demonstrated in the pedigree.

Case Report

A 57-year-old white man sought medical attention for fatigue of several weeks duration in 1994. He worked as an electrician at a navy shipyard. He is a nonsmoker and previously had a right orchiectomy for trauma in 1962 and a left inguinal herniorrhaphy. His father died of lung cancer. Physical examination was unremarkable. Blood studies revealed a white blood cell count (WBC) of 8400/µL with a normal differential WBC, hemoglobin and hematocrit of 12.7 gm/dL and 39.2%, respectively, and a platelet count of 1,017,000/mL. A bone marrow biopsy showed an increased number of megakaryocytes, but was otherwise normal. After exclusion of causes for secondary thrombocytosis, a diagnosis of essential thrombocythemia (ET) was made, and the patient was treated with varying doses of anagrelide. Anagrelide was started at 0.5 mg by mouth daily, aiming at a target platelet count of approximately 500,000/mL; the dose was progressively escalated to 2.5 mg daily, at which time the platelet count stabilized at 400,000–500,000/µL, and he was continued on maintenance anagrelide at that dose. The patient never had hemorrhagic or thrombotic episodes. He tested negative for Janus kinase 2 (*JAK2*) mutations in 2009 and 2011.

In 2000, the patient developed shortness of breath and was evaluated with computed tomography (CT) scans of the chest, abdomen, and pelvis. CT scans revealed multiple bilateral pleural plaques consistent with his prior asbestos exposure, and he was diagnosed with pulmonary asbestosis. No lymphadenopathy or hepatosplenomegaly were noted on the CT scans. In 2006, the patient was noted to have an increased WBC of 16,500/µL with 41% granulocytes, 53% lymphocytes, and an absolute lymphocyte count of 8700/µL. Hematocrit and hemoglobin at that time were 10.7 gm/dL and 32.7% respectively, and the platelet count was 549,000/mL. A peripheral blood smear showed leukocytosis with a predominance of mature lymphocytes. Immunophenotyping of peripheral blood showed CD5+ CD10–, CD20+, CD22+, CD23+, and CD19+ B-cell lymphocytes with kappa light chain restriction. Peripheral blood polymerase chain reaction (PCR) for *BCR/ABL* was negative, and cytogenetic studies demonstrated a normal male karyotype. A diagnosis of Rai stage 0 CLL was made, and the patient was monitored by complete blood count (CBC) every 6 months. A subsequent bone marrow study in 2008 showed a hypercellular marrow with nodular lymphocytic infiltrates involving 30–40% of the marrow. Also noted was moderate reticulin fibrosis that was absent in 1994 at the time of diagnosis of ET (Figure 1). He received close follow-up, and his last WBC in 2011 was 16,200/µL with 30% granulocytes, 66% lymphocytes (absolute lymphocyte count of 10,700/µL; Figure 2), and a platelet count of 291,000/mL. He is now aged 74 and is essentially unchanged clinically since his diagnosis of CLL.

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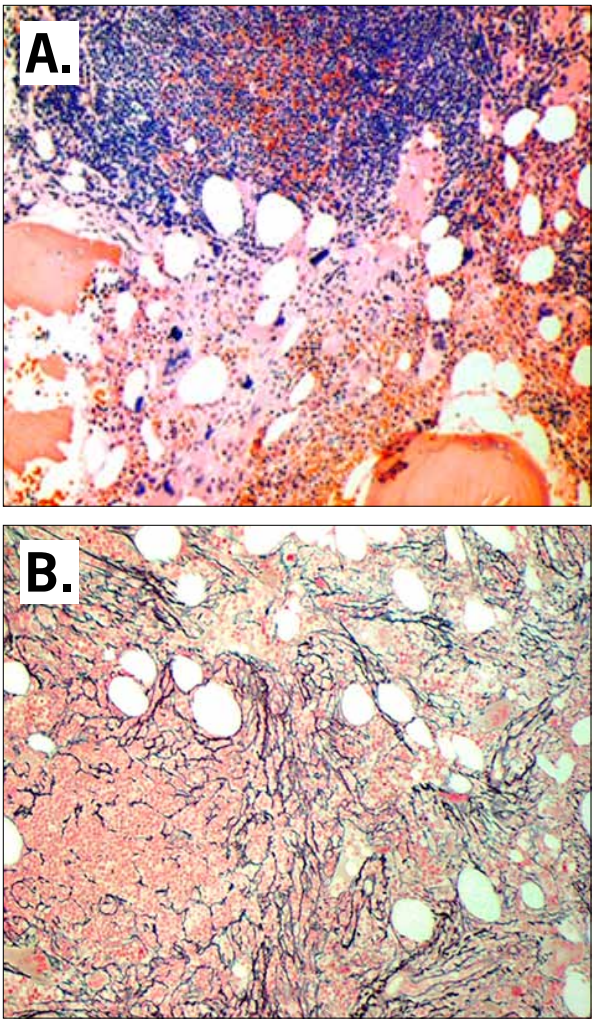

Figure 1. Bone marrow biopsy revealing: A) nodular and interstitial small lymphocytic infiltrate, dysplastic megakaryocytosis, and B) significant reticulin fibrosis (x 400).

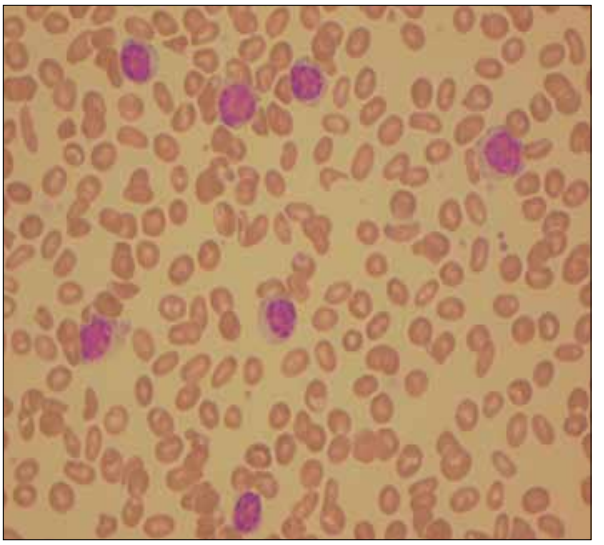

Figure 2. Peripheral smear showing atypical lymphocytosis 10 years after original diagnosis of essential thrombocythemia.

Table 1. Diagnostic Criteria For ET From the Polycythemia Vera Study Group

All of the following criteria must be met to establish a diagnosis of ET:
1. Platelet count >600,000/µL
2. Hematocrit <40% or normal RBC mass (men <36 mL/kg, women <32 mL/kg)
3. Stainable iron in bone marrow, or normal serum ferritin, or normal RBC mean corpuscular volume (and if iron-deficient, PV cannot be excluded unless iron therapy fails to increase RBC mass into polycythemia range)
4. Absence of the Philadelphia chromosome or *BCR/ABL* gene rearrangement
5. Collagen fibrosis of marrow either absent or less than one-third of biopsy area, without both marked splenomegaly and leukoerythroblastic reaction
6. No cytogenetic or morphologic evidence of myelodysplastic syndrome
7. No cause for reactive thrombocytosis

ET=essential thrombocythemia; PV=polycythemia vera; RBC=red blood cell.

Adapted from Murphy S et al. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. *Semin Hematol.* 1997;34:29-39.[30]

Discussion

Chronic myeloproliferative neoplasms are classified into several subgroups,[1] of which chronic myelogenous leukemia (CML), polycythemia vera (PV), ET, and primary myelofibrosis (PMF) are the more common.[2] ET is characterized by sustained megakaryocyte proliferation associated with thrombocytosis in the absence of any known cause of secondary thrombocytosis. Diagnostic criteria for ET are detailed in Table 1.

JAK2 V617F mutation is implicated in the pathogenesis of chronic myeloproliferative disorders and is present in approximately 80% of PV cases and in approximately half of ET cases at diagnosis.[3] Recent data have suggested that the incidences may be as high as 95–100% in PV and 60–70% in ET.[4] The JAK family of growth factors play a key role in the initiation of intracellular signaling cascades involving erythropoietin, thrombopoietin, interleukin-3, granulocyte colony-stimulating factor (G-CSF), and granulocyte–macrophage colony-stimulating factor (GM-CSF), and are involved in promoting cell survival, proliferation,

Table 2. Previously Described Cases of CLL and ET

Author (Publication Year)	Initial Diagnosis	Age (Years)	Sex	Interval (Years)	*JAK2/Zap-70* Status
Mir Madjlessi et al[19] (1986)	CLL	57	M	8	UK
Gabrail et al[13] (1991)	ET + CLL	70	M	NA	UK
Marcos Sanchez et al[14] (1995)	ET + CLL	UK	UK	NA	UK
Bizzaro[15] (1998)	ET	60	M	6	UK
Robak et al[12] (2003)	ET + CLL	77	F	NA	UK
Henry et al[18] (2007)	ET	58	F	5	*JAK2* positive in ET and negative in CLL. *Zap-70* not available
Tabaczewski et al[17] (2009)	ET + CLL	72	M	NA	Both positive
	ET	82	M	3	Both positive
Musolino et al[16] (2009)	ET	72	F	5	*JAK2* positive in ET and negative in CLL. *Zap-70* negative

CLL=chronic lymphocytic leukemia; ET=essential thrombocythemia; F=female; *JAK2*=Janus kinase 2; M=male; NA=not applicable; UK=unknown.

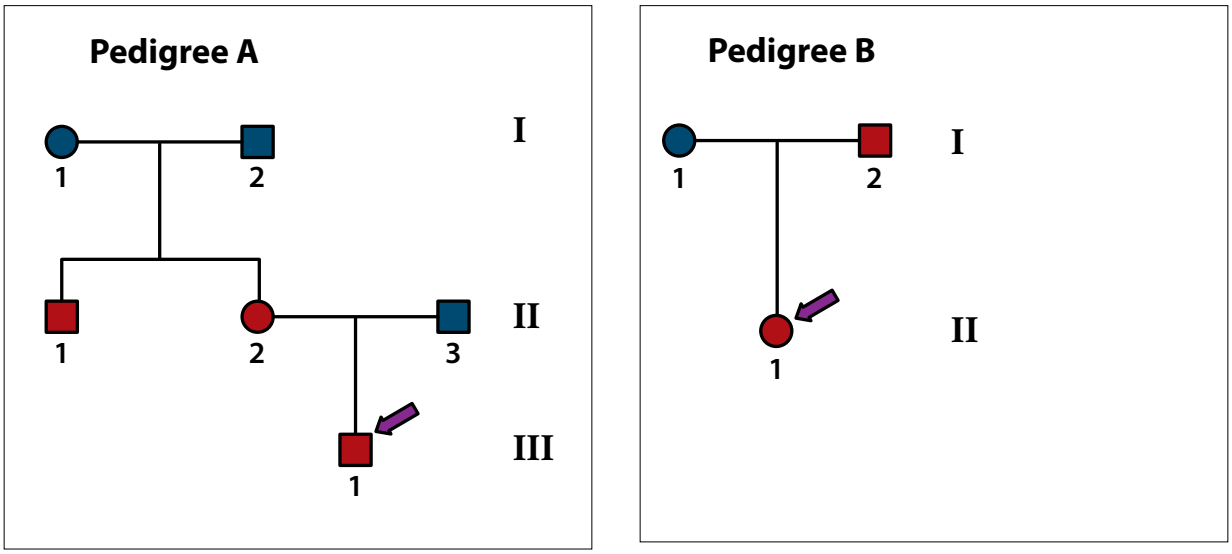

Figure 3. Pedigrees of families with B-cell neoplasms and essential thrombocythemia demonstrating anticipation, which suggests a genetic basis for the neoplasms.

and differentiation.[5] The *JAK2* mutation in the myeloproliferative disorders is an acquired mutation not present in the germline.[5] *JAK2* mutation in ET may increase the risk of thrombosis but appears to have no impact on leukemic transformation or overall survival.[6] The serum thrombopoietin level is often elevated in both ET and reactive thrombocytosis and has no diagnostic significance in ET.[7]

There is a long-term increased risk of lymphoid neoplasms in patients with chronic myeloproliferative disorders. The risk is more than 12-fold for CLL overall, with even greater risk in *JAK2 V617F*-mutated patients and in men.[8] There are multiple reports of disease transformation from ET to other hematologic conditions, including acute lymphocytic leukemia,[9] PV, or acute myeloid leukemia.[10] Some patients with disease transformation from ET to acute leukemia preserve their *JAK2* mutational status.[11] There are occasional reports of ET coexisting with CLL (Table 2) in the same patient, and it appears that both malignancies share a common etiopathogenesis.[12-19] Curiously, most of the reported patients with ET and CLL harbored the *JAK2* mutation in myeloid cells, but not in lymphoid cells. Tabaczewski and associates hypothesized the possibility of an initial "trigger hit" occurring in a pre-*JAK2* common early progenitor multipotential hematopoietic stem cell that can differentiate into both lymphoid and myeloid pathways and subsequent additional molecular events that could

promote myeloid and lymphoid differentiation, leading to the development of 2 diseases of likely identical origin but different lineages.[17] On occasion, B-cell malignancies occur in first-degree relatives of patients with ET, and in most of these cases, anticipation can be demonstrated (Figure 3).[20]

Asbestos exposure leads to chronic inflammation.[21] The possible mechanism of action may be related to DNA damage,[22] defective cell-mediated immunity, and hyperactive B-cell function.[23] In vitro studies using human cell lines have shown that asbestos complexes with immature B lymphocytes and stimulates cellular proliferation. Injection of animals with crystalline asbestos resulted in increased immune globulin levels,[21] which is not surprising considering the chronic antigenicity of asbestos. Various studies suggest an association between asbestos exposure and B-cell neoplasms, including CLL.[23,24] Bianchi and colleagues[25] examined necropsies of 169 patients from 215 total cases of malignant pleural mesothelioma identified at an Italian hospital and found coexisting second malignancies in 32 cases. These included 5 cases of non-Hodgkin lymphoma and CLL. Other malignancies included prostate, bladder carcinoma, kidney, large bowel, and liver cell cancers. Adiponectin is a well-known marker for inflammation, and low adiponectin levels are noted in morbid obesity, coronary artery disease, and diabetes.[26] Adiponectin induces caspase-mediated endothelial cell apoptosis and can inhibit primary tumor growth.[27] Avcu and coworkers[27] found that in patients with CLL and ET, the levels of plasma adiponectin were significantly low compared with healthy subjects or treated patients. These findings suggest a possible role for chronic inflammation in the etiopathogenesis of chronic myeloproliferative disorders and lymphoproliferative neoplasms.

Electricians are amongst those with a significant exposure to asbestos.[28] Mele and associates[29] studied various occupations and noted an increased risk of ET among electricians, although the exact mechanism is unknown. Our patient is an electrician and shipyard worker and has a significant asbestos exposure history, as evidenced by pulmonary asbestosis. The occurrence of ET and subsequently, CLL, in the setting of significant asbestos exposure may be related in part to chronic inflammation from the exposure. Further study of the relationship of asbestosis to ET and CLL will be required to establish whether or not a mechanism other than chance is operative in patients who demonstrate combinations of these entities.

References

1. Tefferi A, Thiele J, Vardiman JW. The 2008 World Health Organization classification system for myeloproliferative neoplasms: order out of chaos. *Cancer*. 2009;115:3842-3847.
2. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood*. 2008;112:45-52.
3. Vainchenker W, Constantinescu SN. A unique activating mutation in JAK2 (V617F) is at the origin of polycythemia vera and allows a new classification of myeloproliferative diseases. *Hematology Am Soc Hematol Educ Program*. 2005:195-200.
4. Pikman Y, Lee BH, Mercher T, et al. MPLW515L is a novel somatic activating mutation in myelofibrosis with myeloid metaplasia. *PLoS Med*. 2006;3:e270.
5. Campbell PJ, Green AR. The myeloproliferative disorders. *N Engl J Med*. 2006;355:2452-2466.
6. Chim CS, Sim JP, Chan CC, et al. Impact of JAK2V617F mutation on thrombosis and myeloid transformation in essential thrombocythemia: a multivariate analysis by Cox regression in 141 patients. *Hematology*. 2010;15:187-192.
7. Cerutti A, Custodi P, Duranti M, et al. Thrombopoietin levels in patients with primary and reactive thrombocytosis. *Br J Haematol*. 1997;99:281-284.
8. Vannucchi AM, Masala G, Antonioli E, et al. Increased risk of lymphoid neoplasms in patients with Philadelphia chromosome-negative myeloproliferative neoplasms. *Cancer Epidemiol Biomarkers Prev*. 2009;18:2068-2073.
9. Paietta E, Rosen N, Roberts M, et al. Philadelphia chromosome positive essential thrombocythemia evolving into lymphoid blast crisis. *Cancer Genet Cytogenet*. 1987;25:227-231.
10. Tefferi A, Fonseca R, Pereira DL, Hoagland HC. A long-term retrospective study of young women with essential thrombocythemia. *Mayo Clin Proc*. 2001;76:22-28.
11. Lopes da Silva R, Ribeiro P, Lourenco A, et al. What is the role of JAK2(V617F) mutation in leukemic transformation of myeloproliferative neoplasms? *Lab Hematol*. 2011;17:12-16.
12. Robak T, Urbanska-Rys H, Gora-Tybor J, et al. Coexistence of chronic lymphocytic leukemia and essential thrombocythemia. *Leuk Lymphoma*. 2003;44:1425-1431.
13. Gabrail NY, Martin TW. Coexistence of essential thrombocythemia and chronic lymphocytic leukemia. *Acta Haematol*. 1991;85:31-33.
14. Marcos Sanchez F, Juarez Ucelay F, Lobato de Blas C, et al. Simultaneous presentation of chronic lymphocytic leukosis and essential thrombocythemia. *An Med Interna*. 1995;12:566.
15. Bizzaro N. Chronic lymphocytic leukaemia in a patient with essential thrombocythaemia. *Clin Lab Haematol*. 1998;20:377-379.
16. Musolino C, Allegra A, Penna G, et al. Absence of the V617F JAK2 mutation in the lymphoid compartment in a patient with essential thrombocythemia and B-chronic lymphocytic leukemia and in two relatives with lymphoproliferative disorders. *Acta Haematol*. 2009;122:46-49.
17. Tabaczewski P, Nadesan S, Lim SH. Zap-70 positive chronic lymphocytic leukemia co-existing with Jak 2 V671F positive essential thrombocythemia: a common defective stem cell? *Leuk Res*. 2009;33:854-855.
18. Henry L, Carillo S, Jourdan E, et al. Association of essential thrombocythemia and chronic lymphocytic leukemia: absence of the V617F JAK2 mutation in the lymphoid compartment. *Am J Hematol*. 2007;82:500-501.
19. Mir Madjlessi SH, Farmer RG, Weick JK. Inflammatory bowel disease and leukemia. A report of seven cases of leukemia in ulcerative colitis and Crohn's disease and review of the literature. *Dig Dis Sci*. 1986;31:1025-1031.
20. Wiernik PH, Ashwin M, Hu XP, et al. Anticipation in familial chronic lymphocytic leukemia. *Br J Haematol*. 2001;113:407-414.
21. Rosenthal GJ, Corsini E, Simeonova P. Selected new developments in asbestos immunotoxicity. *Environ Health Perspect*. 1998;106(suppl 1):159-169.
22. Marczynski B, Czuppon AB, Marek W, et al. Increased incidence of DNA double-strand breaks and anti-ds DNA antibodies in blood of workers occupationally exposed to asbestos. *Hum Exp Toxicol*. 1994;13:3-9.
23. Kagan E, Jacobson RJ, Yeung KY, et al. Asbestos-associated neoplasms of B cell lineage. *Am J Med*. 1979;67:325-330.
24. Schwartz DA, Vaughan TL, Heyer NJ, et al. B cell neoplasms and occupational asbestos exposure. *Am J Ind Med*. 1988;14:661-671.
25. Bianchi C, Bianchi T, Ramani L. Malignant mesothelioma of the pleura and other malignancies in the same patient. *Tumori*. 2007;93:19-22.
26. Aprahamian TR, Sam F. Adiponectin in cardiovascular inflammation and obesity. *Int J Inflam*. 2011;2011:376909.
27. Avcu F, Ural AU, Yilmaz MI, et al. Association of plasma adiponectin concentrations with chronic lymphocytic leukemia and myeloproliferative diseases. *Int J Hematol*. 2006;83:254-258.
28. Hodgson MJ, Parkinson DK, Sabo S, et al. Asbestosis among electricians. *J Occup Med*. 1988;30:638-640.
29. Mele A, Visani G, Pulsoni A, et al. Risk factors for essential thrombocythemia: a case-control study. Italian Leukemia Study Group. *Cancer*. 1996;77:2157-2161.
30. Murphy S, Peterson P, Iland H, Laszlo J. Experience of the Polycythemia Vera Study Group with essential thrombocythemia: a final report on diagnostic criteria, survival, and leukemic transition by treatment. *Semin Hematol*. 1997;34:29-39.

Review

Association of Myeloproliferative and Lymphoproliferative Disorders

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Discussion

Chintapatla and associates[1] describe an interesting sequential association of essential thrombocythemia (ET) and chronic lymphocytic leukemia (CLL) in a patient exposed to asbestos. ET preceded CLL, and at the time of ET diagnosis, white blood cell (WBC) and differential counts were normal, as was the clinical examination. Subsequent testing for *JAK2 V617F* mutation, which was first described in 2005 as a marker of myeloproliferative disorders (MPD) and is observed in approximately 50% of ET cases, was negative.[2] The patient responded to treatment with anagrelide. A diagnosis of CLL was given 12 years later, based on lymphocytosis with B-cell phenotype, light chain restriction, and a nodular lymphocytic bone marrow infiltration. Lymphoproliferative disorder (LPD), evaluated as Rai stage 0 CLL, remains stable to date without treatment. This observation deserves several comments regarding the coexistence of MPD and LPD, its relation to genetic events, and the putative role of chronic inflammation.

Coexistence of Myeloproliferative and Lymphoproliferative Disorders

This case report reviews 9 previously published observations of patients with both ET and CLL. From a more general perspective, associations among all types of MPD and CLL have been reported. (Although it will not be further discussed here, chronic myeloid leukemia [CML] can transform into acute lymphoblastic leukemia [ALL] in approximately 30% of cases.) Among the large series involving true MPDs,[3,4] associations have been observed in multiple chronologic combinations, including simultaneous diagnosis, MPD preceding LPD, and vice versa. There does not seem to be a specific profile in patients who display such associations. CLL is mainly reported as indolent.

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Associated Genetic Events

A major improvement in the understanding of MPD pathophysiology occurred with the description of the *JAK2 V617F* mutation in 2005.[2] It is present in more than 90% of patients with polycythemia vera (PV) and in roughly half of patients with ET and myelofibrosis. Allelic burden varies in these different entities. The description of this mutation raised the question of its true role in MPD pathophysiology. If animal transfection models reproduce a disease comparable to human pathology, it now appears unlikely that this mutation can be the true transforming initial event.[5] From this point of view, the study of cases of familial MPD seems to be particularly relevant. Generally, the onset of the disease is independent from the presence of the mutation. Other proposed initial events, such as Tet-2 mutations[5] or the presence of specific SNPs,[6] have proven to be less sufficient. This finding is in line with the fact that the blast cell compartment is typically V617F-negative in acute transformation of MPDs.

There seems to be a genetic predisposition for developing LPD.[7] To date, however, there is no specific genetic marker for this predisposition, nor is there a common marker for predisposition to MPD and LPD.

Among published reports regarding the coexistence of MPD and LPD, *JAK2* mutational status is variable inside the lymphoid cells. There is an obvious technical concern as to whether the CLL compartment purification is sufficient to ascertain the lack or presence of *JAK2* mutations in lymphoid cells. Allele burden should be determined. Vannucchi and coworkers[4] recently reported a 12-fold increased risk of lymphoid neoplasms in patients with Philadelphia chromosome-negative MPDs.

Given that the *JAK2* mutation does not appear to be the initial event in MPD, and the fact that the *JAK2* mutation is related to a sole MPD phenotype, the putative link between MPD and LPD remains undetermined. The concept of genetic instability now plays a central role in the pathophysiology of MPD.[5] In Philadelphia (Ph) chromosome–positive MPD, additional chromosomal changes are often noted inside and outside the Ph1 clone. Mutational modifications in the *BCR/ABL* kinase domain are commonly detected, along with the presence of different clones and the variation of their relative proportion, even in early stages of disease. In Ph-negative MPDs, a similar instability occurs; coexistence of multiple mutations associated with these pathologies (eg, combined *V617F* and *exon12 JAK2* mutations or *JAK2* and thrombopoietin receptor [*cMPL*] mutations)

has been reported.[5] In CLL, genomic instability has been demonstrated in the unmutated forms.[8]

The Role of Chronic Inflammation

A common idea in the pathophysiology of LPDs is based on the promotion of a clonal population among a polyclonal background of activated lymphoid cells. This has been demonstrated in Burkitt's lymphoma and has been hypothesized in multiple myeloma. The determination of surface immunoglobulin idiotypes in CLL has provided interesting results in identifying several autoantigens or bacterial antigens.[9] If chronic inflammation is typically associated with a mild platelet count increase, no clear relationship has been reported between inflammation and MPD. Chintapatla and associates suggested that there may be value in the evaluation of adiponectin,[1] a marker of inflammation that has been shown to be lowered in such clinical conditions. However, this is not a demonstration of the role of inflammation in the pathophysiology of MPDs. Among the clinical conditions related to LPDs, asbestos exposure has been implied. That it provokes a chronic inflammation as well as DNA changes is well known.

Conclusion

MPDs and LPDs are fascinating models of malignant diseases. Their pathophysiology associates intrinsic genetic events, favored by genetic instability, as well as external interactions, including a probable selective competition between different clones. There is a logical and statistically demonstrated increased risk for the development of these 2 types of disease within the same patient. The above case report further supports this theory. Such rare observations deserve extensive investigations, as they may be the key to a better characterization of a general malignant process.

References

1. Chintapatla R, Battini R, Wiernik PH. Chronic lymphocytic leukemia with essential thrombocythemia: asbestos exposure association? *Clin Adv Hematol Oncol*. 2012;11:752-755.
2. James C, Ugo V, Le Couedic JP, et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythemia vera. *Nature*. 2005;434:1144-1148.
3. Laurenti L, Tarnani M, Nichele I, et al. The coexistence of chronic lymphocytic leukemia and myeloproliperative neoplasms: a retrospective multicentric GIMEMA experience. *Am J Hematol*. 2011:86:1007-1012.
4. Vannucchi AM, Masala G, Antonioli E, et al. Increased risk of lymphoid neoplasms in patients with Philadelphia chromosome-negative myeloproliferative neoplasms. *Cancer Epidemiol Biomarkers Prev*. 2009:18:2068-2073.
5. Cross NCP. Genetic and epigenetic complexity in myeloproliferative neoplasms. *Hematology Am Soc Hematol Educ Program*. 2011:208-214.
6. Olcaydu D, Harutyunyan A, Jäger R, et al. A common JAK2 haplotype confers susceptibility to myeloproliferative neoplasms. *Nat Genet*. 2009:41:450-454.
7. Goldin LR, Landgren O, Marti GE, Caporaso NE. Familial aspects of chronic lymphocytic leukemia, monoclonal B-cell lymphocytosis (MBL), and related lymphomas. *European J Clin Med Oncol*. 2010:2:119-126.
8. Stilgenbauer S, Sander S, Bullinger L, et al. Clonal evolution in chronic lymphocytic leukemia: acquisition of high-risk genomic aberrations associated with unmutated VH, resistance to therapy, and short survival. *Haematologica*. 2007:92:1242-1245.
9. Bühler A, Zenz T, Stilgenbauer S. Immunoglobulin heavy chain variable gene usage and (super)-antigen drive in chronic lymphocytic leukemia. *Clin Cancer Res*. 2010:16:373-375.