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Case Report

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Concomitant Essential Thrombocythemia and Mature B -Lymphoproliferative Disorder in a Patient

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ABSTRACT

A-64-year old male presented with cough, weight loss, and maculopapular rash for 15-20 days. On examination, he was found to have cervical lymphadenopathy and splenomegaly. His leukocyte count was 62.1x10^9/L, platelets were 1169x10^9/L and LDH was 816 IU/L. Peripheral blood film showed a leukoerythroblastic picture with thrombocytosis. He was started on hydroxyurea and allopurinol. Subsequently, bone marrow evaluation was done which depicted increased lymphoid cells with an M:E ratio of 4:1. Cellular areas exhibited an increase in myeloid precursors along with prominent lymphoid cells and abundant megakaryocytes. Immunohistochemistry showed an increase in B-lymphocytes. Grade MF-2 reticulin fibrosis was noted. Overall findings suggested essential thrombocythemia (ET). On flow cytometry, CD45-positive lymphoid cells population was 31% and showed reactivity to Pan-B-markers with lambda light chain restriction. Janus Kinase 2 (JAK 2) mutation was detected while BCR-ABL1 translocation was negative. A diagnosis of ET progressing to myelofibrosis and mature B-lymphoproliferative disorder was made. Hydroxyurea and allopurinol were stopped while ruxolitinib was introduced and 2.5 years later he remains stable on this treatment.

Keywords: Essential thrombocythemia; Janus Kinase 2 (JAK2) V617F; Lymphoproliferative disorder

INTRODUCTION

Essential thrombocythemia (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by sustained thrombocytosis and increased number of large, mature megakaryocytes in the bone marrow. It can manifest with episodes of thrombosis or hemorrhage. Up to 40-50% of patients with ET harbor the Janus Kinase 2 V617F mutation. Janus Kinase 2 617F positive ET and B-lymphoproliferative disorders are considered 2 distinct, clonal hematologic entities [1]. Their coexistence in a single individual is exceedingly rare [1, 2]. Development of MPNs as a ramification of therapy in patients with various neoplasms has been well described in literature[3,4]. However, occurrence of MPN in treatment-naïve B-lymphoproliferative disorders in patients with MPN has been much less frequently reported. Here we describe the initial presentation, work up and management of an elderly gentleman who was diagnosed with both ET and B-lymphoproliferative disorder.

Case presentation

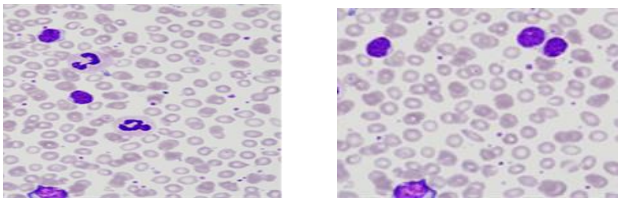
A 64-year-old male was admitted to our center with complaints of cough, weight loss and maculopapular rash on body. The rash was present on his face and trunk for 15-20 days and he had non-productive cough for the past two weeks. He denied any constitutional ''B" symptoms apart from weight loss. His past medical history was significant for hypertension and benign prostatic hyperplasia. On examination, he was found to have cervical

lymphadenopathy and splenomegaly (5cm below left costal margin). Upon workup, his blood counts were as follows: hemoglobin 10.8 g/dl, hematocrit 37.2%, RBC mass 5.34 $x10^{12}$/L, WBC 62.1$x10^9$/L, platelets 1169$x10^9$/L. LDH was found to be 816 IU/L (reference range: 208-378). Serum creatinine was 1.4 mg/dl and C-reactive protein was 2.43 mg/dl. Peripheral blood film showed anisocytosis, poikilocytosis, elliptical cells, teardrop cells, nucleated red blood cells, myelocytes and metamyelocytes (Figure A.1, A.2). Platelets were markedly increased on film. Leucoerythroblastic blood picture was noted. Suspecting a myeloproliferative disorder, additional investigations were sent while the patient was started on hydroxyurea 1gm daily and allopurinol 100 mg daily in addition to antibiotics. Ultrasound Abdomen showed enlarged spleen measuring 198.2x129.8mm while chest X-ray was within normal limits.

Bone marrow aspirate (Figure A.3, A.4) depicted increase in lymphoid cells that constituted around 35% of the total nucleated non-erythroid cell population. M:E ratio was 4:1. Bone trephine (Figure A.5, A.6) showed hypercellularity for age with overall cellularity of 90 to 95%. Cellular areas exhibited increase in myeloid precursors along with prominent lymphoid cells and abundant megakaryocytes. Pan-T (CD3) and Pan-B (CD20) marker by immunohistochemistry was applied on bone trephine biopsy specimen, which was interpreted as increase in B-lymphocytes. Reticulin stain showed grade MF-2 reticulin fibrosis. Overall findings were suggestive of essential thrombocythemia. In view of increased CD20 positive cells, immunophenotyping by flow cytometry was recommended. CD45 positive lymphoid cells population was 31%. This population showed reactivity to Pan-B-markers i.e. CD19 (26%), CD20 (27%), CD22 (26%), CD23 (11%) and cCD79a (30%) along with HLA-DR (12%) and CD45 (35%). Double bright positivity of CD19 and CD5 typical of chronic lymphocytic leukemia (CLL) was absent. This population also showed positivity to lambda light chains restriction (kappa 0%, lambda 13%). Results were consistent with mature-B-lymphoproliferative disorder (B-LPD). JAK2 mutation was detected by PCR while BCR-ABL1 translocation was not detected by fluorescence in situ hybridization (FISH).

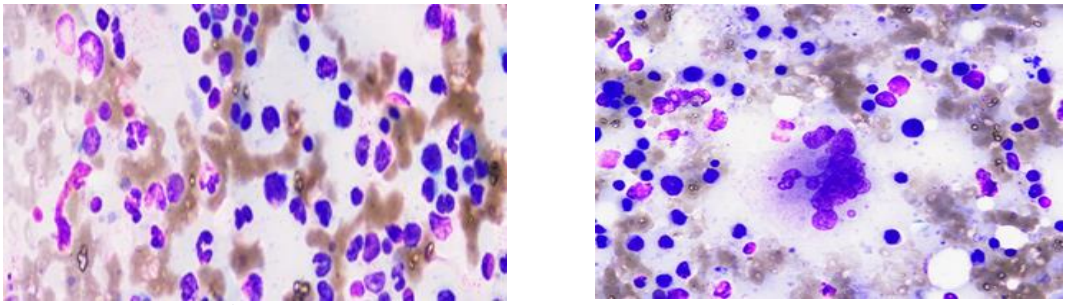
Since double bright positivity for CD19 and CD5 was absent along with absence of FMC7, a diagnosis of mature-B-lymphoproliferative disorder was made. Cyclin D1 was applied on bone trephine, which was negative, and the infiltration did not reveal a follicular pattern. Ki67 was approximately 30%. A diagnosis of essential thrombocythemia (ET) progressing to myelofibrosis and B-lymphoproliferative disorder was made.

Patient was discharged in a stable condition and followed up on an outpatient basis. Ruxolitinib therapy at a dose of 5mg twice daily was initiated while hydroxyurea was reduced to 500 mg daily and then later stopped. A wait and watch approach was adopted for the B-lymphoproliferative disorder. Ruxolitinib was later increased to 10mg twice daily. The platelet count decreased to 341$x10^9$/L, WBC to 33$x10^9$/L and hemoglobin to 9.7 g/dl. After a few months, ruxolitinib was switched to 15 mg daily with the counts remaining stable. The patient remains stable and asymptomatic two and half years after initial presentation. The most recent blood counts show hemoglobin at 10.9 g/dl, WBC 31.1$x10^9$/L, and platelets 445$x10^9$/L. The patient is followed up regularly on an outpatient basis.



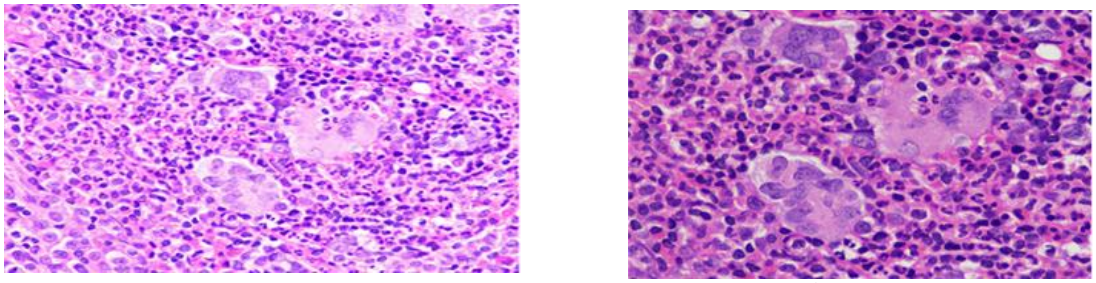
A1 A2

Figure A.1, A.2 Peripheral smear showing lymphocytosis and increased platelets



A3 A4

Figure A.3, A.4 Bone Marrow Aspirate showing infiltration with mature lymphoid cells



A5 A6

Figure A.5, A.6 Bone marrow biopsy revealing hypercellular bone marrow, increase in myeloid precursors along with prominent lymphoid cells and staghorn multinucleated megakaryocytes

DISCUSSION

In this report we have described the case of a 64-year-old gentleman with dual pathologies of essential thrombocythemia and mature B LPD. Janus Kinase 2 V617F positive ET and B-lymphoproliferative disorders e.g. B-CLL are two distinct, clonal hematologic malignancies with their concomitant existence in a single individual being exceedingly rare. The prevalence of CLL in the United States is 40 per 100,000 persons and that of MPN is 115 per 100,000 citizens, and the expected prevalence of the occurrence of both diseases in a single individual is 4.6×10^{-8} [5-7].

The pathophysiology in play behind concomitant development of a myeloproliferative disorder (MPD) and a lymphoid neoplasm remains unclear. One explanation is a “trigger hit” occurs in an early progenitor cell, which can differentiate into both lymphoid and myeloid cells. This can be followed by additional molecular events that cause genomic instability during lymphoid and myeloid neoplastic differentiation leading to two diseases that have the same origin but arise from different cellular lines [8-9]. If the JAK2 mutation occurs in pluripotent stem cells, both myeloid and lymphoid cells may harbor the mutation. However, only myeloid cells will possess the mutation if it succeeds lineage differentiation. Another postulate is that the lymphoid neoplasm and MPD may develop from different progenitor cells purely by chance. In this scenario, the JAK 2 mutation may be absent in lymphoid cells[10]. Another theory reasons that a MPN could lead to variations in cytokines that can be fibrogenic, osteogenic, angiogenic and leukemogenic. This results in a change in bone marrow environment caused by the MPN [1]. The possibility of clonal involvement of both

the B and T lymphocytes in primary myelofibrosis has been suggested. Although this has not been explored in other MPNs, but it is a possible mechanism [4].

Only a few reviews of patients developing both ET and LPD have been published. In 2012, Chintapatla et al reviewed all relevant case reports of concomitant ET and CLL published. It was found that ET preceded CLL or was diagnosed simultaneously in most cases (n=8) with CLL being the sole initial diagnosis in only one case. Most of the affected patients were male with ages ranging from 57-82 years. Secondary malignancy developed after an interval of 3-8 years [11].

The GIMEMA group presented the first systematic retrospective study in 2011. This study included 46 cases of concomitant CLL and MPNs diagnosed over a 25-year-period. Of these, 18 had essential thrombocythemia and 82% were stage A according to Rai classification of CLL, with no B or C stage being detected[12].

A study by Vannucchi et al. of 353 patients with polycythemia vera and 467 with essential thrombocythemia explored the risk of LPD in patients with MPNs. The review concluded that the cumulative risk of developing a LPN in MPN patients was 0.93% (95% confidence interval, 0.39-2.22) and 2.96% (95% confidence interval, 1.52-5.72), at 5 and 10 years respectively. Patients with a MPN were at a 3.44-fold increased risk of LPN compared with the general population, ranging from 2.86 for plasma cell disorder to 12.42 for chronic lymphocytic leukemia. The risk was particularly higher in JAK2V617F mutated patients (5.46-fold) and in males (4.52-fold)[13].

Rumi et al. conducted a study involving 1,915 consecutive patients with myeloproliferative neoplasms followed for a median time of 5.2 years (range 0-33.3) and found only 22 (1.1%) patients subsequently were afflicted by a lymphoid neoplasm over their lifetime. MPN patients had a 2.79-fold higher (95% CI, 1.80-4.33; P<0.001) risk of developing a LPN than that of the general Italian population. In Italy, the 10-year risk of lymphoid neoplasm in myeloproliferative neoplasm patients ranges from 0.7% to 2.96% [14]. Variation in the two Italian cohorts including age (55.6 years in the Rumi study and 59 years in the Vannucchi study) may account for these differences.

A more recent review, analyzing literature available from 2005-2016, found reports of 214 individuals harboring both MPN and LPD. Of these 44% had ET. Half of all patients developed a LPD after a median of 72 months after MPN diagnosis. However, LPD preceded or was simultaneously diagnosed with the MPN in 21% cases. Patients were mainly afflicted by indolent LPD, mostly CLL. CLL was associated with very high male-to-female ratio, as well as an older age at MPN diagnosis [15].

A study looking into pathobiological characteristics of cases of concomitant CLL and MPN evaluated the presence and significance of mutations of Janus kinase (JAK)-2 receptor, MPL and calreticulin (CALR). Two of the three ET cases had a CALR mutation while one was triple negative. Two patients received hydroxyurea therapy, with survival of 9.6 and 8.1 years while one was given lenalidomide and survived for 19.1 years. Polycythemia Vera (PV) and ET preceded CLL (P=0.001) and all PV and ET cases progressed to MF[16].

Studies have demonstrated a link between lymphocytes and development of marrow fibrosis with secondary marrow fibrosis occurring in 20%–30% of CLL patients. A case of CLL with secondary myelofibrosis was reported by Kimura et al. who confirmed that interleukin-1 alpha (IL-1α) secreted by the CLL cells served as a growth factor for fibroblasts[17]. In our patient, although it is unlikely that the myelofibrosis could be a repercussion of such an indolent lymphoproliferative disorder, it could possibly have accelerated the natural course of the ET, because it is known that ET is rarely leads to fibrosis.

Cases of rare, unrelated concomitant hematologic malignancies provide a diagnostic challenge. Myeloid proliferation in MPNs usually presents with leukocytosis and it is easy to miss a concurrent lymphocytosis due to B-lymphoproliferative disorders. LPD accompanied with MPD is usually indolent and mainly requires wait and watch approach.

CONCLUSION

We report a rare case of ET with concomitant B-LPD. The patient is stable on Ruxolitinib and maintaining platelet counts while he is on wait and watch approach for B-LPD.

CNFLICT OF INTERESTS

The authors disclose no conflict of interest.

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