Multiple myeloma following essential thrombocytopenia

Myélome multiple survenant 6 ans après de diagnostic d’une thrombocytopénie essentielle

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Abstract. The association of essential thrombocytopenia and multiple myeloma is extremely rare, with only three patients previously treated with hydroxyurea reported in the literature until now. In this paper, we report the case of a 66 year old male who developed IgG-kappa M six years after the diagnosis of essential thrombocytopenia, for which he had received hydroxyurea. The possible etiological and pathogenic link between both these entities is here discussed.

Key words: essential thrombocytopenia, multiple myeloma, hydroxyurea

Résumé. L’association entre la thrombocytopénie essentielle et le myélome multiple est extrêmement rare, avec uniquement 3 cas traités par hydroxyurée rapportés par la littérature. Dans cet article, nous rapportons le cas d’un homme de 66 ans ayant développé un myélome multiple de type IgG kappa 6 ans après le diagnostic d’une thrombocytopénie pour laquelle il a été traité par hydroxyurée. À travers une revue de la littérature, nous discuterons l’étiopathogénie expliquant l’association de ces deux pathologies.

Mots clés : thrombocytopénie essentielle, myélome multiple, hydroxyurée

Essential thrombocytopenia (ET) is a chronic myeloproliferative neoplasm (CMN) that has been associated with transformation to acute leukemia, myelodysplastic syndrome, chronic lymphoblastic leukemia and other CMN especially primary myelofibrosis [1-4]. The association of multiple myeloma (MM), a lymphoproliferative neoplasm with ET, a myeloproliferative neoplasm is extremely rare. We present here a patient who developed MM six years after the diagnosis of ET, while he was receiving hydroxyurea (Hu) treatment.

Case report

A 66 year old Tunisian man with an history of hypertension treated by aspirin. He presented in October 2005 for thrombocytosis, he was asymptomatic and his physical examination was unremarkable with no palpable liver, spleen or lymph nodes. Complete blood cell count (CBC) showed marked thrombocytosis of 2770 G/L, normal hemoglobin (Hb=150 g/L), hematocrite concentration 44%, and hyperleukocytosis of 12.6 G/L. Results of serum analysis were within normal limits for ferritin, urea, creatinine, lactic deshydrogenase, C reactive protein (CRP) and protein electrophoresis. Abdominal ultrasound examination revealed moderate splenomegaly 15 cm sized. Bone marrow aspiration and biopsy were consistent with chronic CMPN-ET. Conventional cytogenetics revealed: 46,XY,?t(2;11)(p12;p13),?del(6)(q21;q24) [12] /46,XY [5]. JAK2/V617F mutation was positive. Therapy with Hu (1000-1500 mg/day) was initiated and continued for 6 years associated with aspirin, he was seen regularly when the platelet count was observed to be lower but not in the normal range. While on Hu therapy, he presented for asthenia and vomiting, serum creatinin level was elevated at 260 μmol/L. He was admitted in nephrology department for
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Figure 1. Bone marrow biopsy consistent with essential thrombocytopenia (A), or showing atypical plasma cell infiltration (B) (hematoxylin and eosin X).

Figure 2. Magnetic resonance imaging of that patient.

hemodialysis. Erythrocyte sedimentation rate (ESH) was 70 mm/h serum protein electrophoresis revealed a monoclonal peak; the albumin level was 29 g/L and an elevated total protein level of 84 g/L was noted, that was associated to a high globulin level at 16.4 g/L. A serum and urine immunofixation electrophoresis revealed IgG kappa clonality. Beta2 microglobuline was 2 mg/L (1.2-2.5 mg/L). The bone marrow aspiration and biopsy revealed atypical plasma cell infiltration of 20% (figure 1). MRI imaging showed vertebral lytic lesions (figure 2), so the diagnosis was a Durie Salmon stage IIIB and international staging system (ISS) stage I disease. A combination chemotherapy with melphalan-thalidomide and prednisone was started. After one course of chemotherapy, we noted normalization of creatinine levels at 60 μmol/L.

Discussion

Myeloproliferative neoplasms (MPN) including polycythemia vera (PV), ET and primary myelofibrosis (PMF), are rare disorders with an annual incidence rate of 2.1 per 100,000 person years. The course of MPN complicated mainly by vascular events and transformation to myelo-
brosis and leukemia, secondary malignancies may occur with a low incidence.

Rumi et al. [5] had noted that, among 1915 patients with MPN, 1.1% of patients developed lymphoid neoplasms over their life time chronic lymphocytic leukemia, T lymphoblastic lymphoma, chronic lymphoproliferative disorder, diffuse large B-cell lymphoma, myeloid leukemia, follicular lymphoma. . . . The most frequently associated MPN with MM is polycythemia vera; the association of ET with MM is infrequent and the reason of this association remains unclear [1]. An explanation for this association could be the treatment with busulfon and Hu for MPN [1, 6].

To our knowledge, our patient is the fourth case documented in the literature of patients who had received Hu alone for ET and then developed MM (table 1). Two cases of MM following ET [7, 8] and one case of plasma cell leukemia after ET [9] receiving Busulfon and Hu were reported in the literature. Cobo et al. [10] reported one case of MM following ET for which the patient had received alpha interferon and radioactive phosphore (32P). Another hypothesis that could explain the association of MM and ET is the existence of pluripotent stem cell with the capacity to differentiate into both lymphoid and myeloid cells [1, 6, 11].

MPNs are characterized by a state of chronic inflammation which is considered of major importance in the development of several cancers including certain hematologic neoplasms. They are also characterized by elevated inflammatory markers such as CRP, IL-6, fibrinogen, IL-7, IL-8, IL-6 is a potent human myeloma cell growth factor [12]. Elevated creatinine level may be due either MM and to myeloproliferative glomerulopathy. It was proposed that platelet-derived growth factor TGF-β might probably have an important role when considering that both cytokines are elevated in patients with ET and platelet derived growth factors is a very potent stimulus of mesangial cell proliferation and induces extracellular matrix production by mesangial cells. Chronic inflammation may facilitate renal dysfunction in MPN patients [12].

The JAK2-V617F mutation induces constitutive activation of downstream signaling pathways, including STAT3/STAT5 induction of cell proliferation (STAT5) and neutrophil activation (STAT3). By triggering The NF-KB and JAK pathways, STAT3 also activates the production of enzymes (metalloproteinases), cytokines (IL-6, IL-10, IL-7 and IL-23), and growth factors. Accordingly, STAT3 may be a key regulator of cancer associated inflammation in MPNs eliciting and sustaining angiogenesis (highly expressed in MM) in bone marrow [12].

### Conclusion

In the perspective that chronic inflammation and improved tumor immune surveillance may be important factor with the pathogenesis and progression of MPNs, it seems rational that JAK1-2 inhibitor with association of TNFα may be a rational approach with the potential of inhibiting clonal expansion and there by interruption the inflammation driven increase of several cytokines (TNFα, IL-6) [12].

### Conflicts of interest: to declare.

### References

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