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The Myeloproliferative Malignances at Campus Teaching Hospital of Lome (Togo)

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Abstract

Objective: To describe the epidemiological, clinical and biological profile of the myeloproliferatives syndromes (MPS) in Campus Teaching Hospital of Lomé (Togo)

Patients and methods:
This is a descriptive retrospective study of the records of patients followed from June 2003 to August 2015 is a period of 12 years. The search for the fusion protein BCR-ABL and / or JAK2 mutation was performed by RT-PCR in the hematology department of the Henri Mondor Hospital in Créteil (France).

Results:
Eighty-five patients of 3641 patients (or 2.33%) were received in consultation for MPS .63 (1.73%) for CML and 22 (0.60%) SMP Ph- (13 PV, 8 TE 1 SM). The annual prevalence of SMP is 7.08 new cases per year.

For CML, the sex ratio is 1.42% with a middle age of 39.63 ± 15.06 (range 9 -80ans). 87.3% had splenomegaly. Hepatomegaly was present in 55.56% of patients. The mean leukocyte count was 204.93 ± 137.23 g / l (43.8 and 971 g / l). The mean hemoglobin level was 95.74 ± 18.83 g / l (51 and 138 g / l) and the mean platelet count was 4662.06 ± 267,12G / L (108 and 1116 g / l). For PV, the average age was 46,7ans (31 to 65 years) a sex ratio of 2.25. The patient histories were mostly hypertension (53.8%). Headaches were the main clinical signs (69.2%). The V617F mutation of JAK2 is positive in 9 patients (69.2%). The average hematocrit, mean hemoglobin levels, average number of white cells and platelets in patients with JAK2 mutation positive and those with no mutation of JAK2 are respectively: 62.7 ± 4.4% (59, 0 ± 13.3%); 19,8g / l ± 4.4 d

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(17,9g / dl ± 13.3); 9.8 g / l ± 4.3 (7.5 g / l ± 4.2); 630,4G / l ± 367.4 (441,0G / l ± 564.7). In the TE, the annual prevalence of the disease is 0.66 new cases per year. The mean age was 48.4 ± 15.5 years (range 28 to 74) and a sex ratio of 0.33. The most identified clinical signs are headache (50%), paresthesia (50%). The JAK2 mutation was present in five patients (62.5%). In the presence of JAK2, the mean platelet count, hematocrit, hemoglobin and white blood cell counts were respectively 1618.2 G / L ± 402.7; 47.5% ± 15.9; 117g / L ± 42 and 11.2 g / L ± 5. As against those without the mutation JAK2, these values were respectively 1138G / L ± 570; 47.3% ± 15.3; 134g / L ± 10 and 7.6 g / L ± 1.4.

Conclusion: The mutation was diagnosed JAK2V617F interest in polycythemia vera and can even be systematic sub-Saharan Africa.

Keywords: myeloproliferative syndrome, bcr-abl mutation, JAK 2V617F, Lomé (Togo)

INTRODUCTION

Myeloproliferative malignances or disorders (MPD) are a group of diseases characterized by abnormal proliferation of myeloid lineage cells and sometimes connective tissue cells [1]. There is an abnormal proliferation of medullary cells to maturation without blocking. They include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [1].

CML is characterized by the Philadelphia chromosome (Ph1) translocation between the long arms of chromosomes 9 and 22 or its equivalent molecular transcript, bcr-abl fusion with tyrosine kinase activity [2-4]. CML accounts for 15% of leukemias in adults and about 600 new cases per year in France [5]. In Togo [6] a hospital study showed that of 849 myelograms performed on twelve years, CML represented 20% of hematological malignancies with an hospital annual incidence of 2.91 new cases. This frequency is increasing due to the current free treatment. The works of some authors have allowed epidemiologically classified CML as the most common leukemia after acute leukemia [7]. Outside the CML, other MPD are called Philadelphia chromosome negative (Ph).

The PV results from the clonal expansion of a pluripotent hematopoietic stem cell. Originally an unregulated proliferation of predominantly myeloid tissue on erythroid associated with increased of total globular volume [8]. It was described for the first time by a French doctor, Louis Henri vera (1860-1936). The exact nature of the disorder of hematopoiesis in the origin of the disease remains unknown. In Europe and America, there is a frequency of 1 case per 10,000 people per year. [1]

ET results from the clonal expansion of a pluripotent hematopoietic stem cell, causing unregulated proliferation of tissue on the predominant myeloid megakaryocyte lineage associated

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with an increase in the platelet count. [1] In Europe, an annual frequency varies between 0.1 and 2.4 new cases per 100 000 population per year.

MPD Ph- have seen their diagnosis changed by the discovery in 2005 of the JAK2 mutation that revolutionized understanding and diagnosis and prognosis [9]. This mutation has consequences for constitutive activation of JAK2, which is the initial key step in the activation of the signaling pathways of erythropoietin (EPO), leading to hypersensitivity to EPO cells carrying the mutation [4, 9,10]. This mutation is found in 95% of PV, ET 50% and 50% of MS [4,9-11]. In Togo studies were dedicated to certain pathologies of MPD [12] [13] but none was devoted to all MPD generally. The objective of this work is to study the epidemiological, clinical and biological profile of MPD in Campus Teaching Hospital of Lome.

MATERIAL AND METHOD

This is a retrospective study of the records of patients followed for MPD in Campus teaching Hospitalof Lome from June 2003 to August 2015. Were retained, the records of patients who benefited of brc-abl mutation research and / or the JAK2 mutation. Any record that does not meet these criteria is not retained for this study. The parameters studied were: epidemiological data (gender, age at diagnosis), clinical (signs of hyperviscosity, splenomegaly, hepatomegaly), biological (white bloodcell count, hemoglobin, hematocrit, platelet count, type of transcript). Serum erythropoietin was assayed in patients followed for PV. BCR-ABL and / or JAK2 mutation research wasperformed by RT-PCR in the hematology department of Henri Mondor Hospital at Créteil (France). The BCR-ABL was conducted in patients for the confirmation of CML. For SMP Ph-, all patients have benefited from the research of Jak2 and sometimes looking for the bcr-abl fusion was made for patients diagnosed with CML should be discarded before an atypical presentation isolated thrombocytosis (ET or CML) and in patients followed for PMF. The bone marrow biopsy (BOM) was performed with histological examination for suspected primary myelofibrosis.

Data analysis was performed by the Epi-info Version 7 and Excel 2013. The statistical tests used were: the Chi 2 for qualitative values and quantitative values for Anova (significant difference if $p<0,05$)

RESULTS

The hematology service of Campus teaching hospital follows a total of 3641 patients since 2003. Eighty-five of these patients as 2.33% were received in consultation for myeloproliferative disease in general which 63 (1.73%) were followed for CML and 22 (0.60%) for Ph negative myeloproliferative syndromes. Of these 22 patients there were 13 cases of polycythemia vera, 8 cases of essential thrombocythémie and 1 case of myelofibrosis. The annual prevalence of MPD is 7.08 new cases per year.

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Regarding CML, on 63 patients, 26 were female and 37 male, (sex ratio of 1.42.) The average age of patients was 39.63 ± 15.06 years with extremes of 9 and 80 years. The most affected patients were between 31 and 45 years. Clinically, 87.3% of patients had splenomegaly which 73% was significant (Type III to V). Hepatomegaly was present in 55.56% of patients and all patients had an associated hepatomegaly and splenomegaly. At diagnosis, the average leukocyte count was 204.93 ± 137.23 g / l (43.8 and 971 g / l). The average hemoglobin level was 95.74 ± 18.83 g / l (51 and 138 g / l) and the average platelet count was 4662.06 ± 267,12G / L (108 and 1116 g / l).

On the molecular level, 53.97% of patients were b3-a2 type and 46.03% of b2-a2 type. About polycythemia vera, annual prevalence was 1.91 new case. The average age of patients was 46,7ans (31 to 65 years). There were 9 male patients against 4 female or a sex ratio of 2.25. The slice of the most represented age was 50 years and over (5 cases) followed by the age groups of 40-49 years (4 cases) and 30-39 years (4 cases).

The patient histories were represented by hypertension (53.8%) followed by signs of hyperviscosity (46.2%), venous thrombosis and stroke with 23.1% each. The most identified clinical signs are headache (69.2%), paresthesia (30, 8%) and dizziness, tingling and numbness in 23.1% of cases each.

Biologically, the mutation of the JAK2 V617F is positive in 9 patients (69.2%) including 6 men and 3 women and negative in 4 patients (3 men and 1 woman). Eleven patients (84.6%) had a low serum erythropoietin levels. The average of hematocrit, hemoglobin levels, white cells and platelets numbers in patients with JAK2 mutation and those who haven't JAK2 mutation are respectively: 62.7 ± 4.4% (59, 0 ± 13.3%); 19,8g / l ± 4.4 d (17,9g / dl ± 13.3); 9.8 g / l ± 4.3 (7.5 g / l ± 4.2); 630,4G / l ± 367.4 (441,0G / l ± 564.7).

In the ET, the annual prevalence is 0.66 new cases per year. The average age was 48.4 years ± 15.5 years with extremes of 28 and 74 years. There were 6 women for two men or a sex ratio of 0.33. The slice of the most represented age was 50 years and over (4 cases) followed by the age groups of 30-39 years (2 cases). The patient histories were represented by respiratory failure and heart disease in 37.5% of cases for each followed signs of hyperviscosity and hypertension in 25% of cases each. The clinical signs are more identified by headache (50%), paresthesias (50%), pruritus in water (37.5%), splenomegaly (37.5%), dizziness (25%), the visual disturbances (25%). Biologically, the JAK2 mutation was present in 5 patients (62.5%). For patients with JAK2 mutation, the average of platelet count, hematocrit, hemoglobin level and white blood cell counts were respectively 1618.2 G / L ± 402.7; 47.5% ± 15.9; 117g / L ± 42 and 11.2 g / L ± 5againstthosewithout JAK2 mutation where values were respectively 1138G / L ±

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570; 47.3% ± 15.3; 134g / L ± 10 and 7.6 g / L ± 1.4. The patient monitored for PMF was 75 years old. He had type III Hackett splenomegaly. The hemoglobin level was 99g/L with a number of white blood cells at diagnosis at 28.0 G / L, platelets at 270 G / l. In blood, there was many dacryocytes and moderate myelemia made by myelocytes, promyelocytes metamyelocytes and some without basophilia. The bone marrow aspiration was unsuccessful with a white hard suction. The medullary bone biopsy showed marrow fibrosis with 77% of the sampled surface. The research for BCR - ABL was negative as well as the research for the JAK2 mutation.

DISCUSSION

The hematology unit of Campus teaching hospital, probably doesn't get all cases of MPD diagnosable in Togo. It arises in general first and foremost a problem of accessibility of patients to appropriate health facilities and secondarily a problem of adherence to long-term medical follow-Saharan Africa. However, this cross-sectional study showed that MPD are relatively frequent in hematology in Lome.

For CML:

The average age of our study population of 39.63 ± 15.06 years is similar to those of Sanogo and al in Ivory Coast[14], Nacoulma in Burkina Faso and al [15], who found respectively 39.05 years (range 24-62 years) 39.8 years (range 7-79 years). In France, Tardieu et al [16] found a higher average age (50 years). These results show that CML remains a disease of young adults. There is a male predominance (sex ratio 1.42) in our study. The same observation was made by Nacoulma [16]. As against Sanogo et al [14] reported a sex ratio of 0.9. Although some authors report a slight female predominance, the male is typically observed in the literature [17] and CML affects both sexes equally. [16]

Clinically, the number of patients with splenomegaly in our study (87.3%) is comparable to those reported by Mukiibi [17] (86.7% of cases). Sanogo [14] reported 100% of cases of splenomegaly. Some European authors [18-19] found a proportion of 95%. Hepatomegaly was present in 55.56% of our patients. Lean [19] found hepatomegaly in 50% of subjects. Lower prevalence have been found by Mukiibi [17] Sanogo [14] with 26% and 20% of cases. This difference in results may be explained by the fact that our study included all progressive forms of CML. Two types of transcript were found (53.97% of b3-a2 and b2-46.03% of a2). Segbena [13] et al in a first study in the same department reported that 56% of patients had b2-a2 type and 28% of cases of b3-a2 type. The hemoglobin level of our patients varies between 51 and 138g/L with an average of 95.74 ± 18,83g / l. Segbena [13] Sanogo et al [14] reported an average respectively of 105,7g / l and 109,3g / l. Mukiibi [17] in Zimbabwe reported that 57.3% of patients had a hemoglobin level lower to 94g / l with an average of 89g / l. The average leukocytosis was 204.93 ± 137.23 G / L (range 43.8 and 971 G / l). Nacoulma [15] has an

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average value of leukocytes of 214 G / L. The comparative study of our results with the data of European literature, allows to note that the average white cell count is less than that observed in our series. This could be explained by Guilhot [20] that the disease is more frequently diagnosed after a routine blood count in the case of a health check. In Africa in general and particularly in our series, the early forms are rare and could be explained by a delay in diagnosis. Platelet counts ranged from 108 to 1116G / L with a mean of 462.06 ± 267,12G / L in our patients. We noted thrombocytopenia in 3.17% of cases and thrombocytosis in 42.86% of cases. Sanogo [14] Mukiibi [17] reported a respective average of 360.8 G / L and 443 L / L and Mukiibi [17] observed a thrombocytosis in 44% of cases and a number of normal in 42% of wafer case For other MPD Ph-

The average age of patients followed for PV 46.7 years was low compared to that of 63 years reported in the literature [21,22]. Does the generally low life expectancy in sub-Saharan Africa may explain the early onset of SMP Ph-? However the average age at diagnosis of ET in our study of 48.4 years is relatively comparable to that reported in the literature varies between 50 and 60 years with nearly 25% of patients under 40 [23.24]. The male predominance (9 men and 4 women) of PV and the women (6 women 2 men) ET are supported by the literature [23-25]. The discovery during a routine blood count and thrombotic events such circumstances discovery of PV both in our study and in the literature [26] implies the importance of carrying out systematic blood count. This could also be explained as polycythemia remains an unknown disease in our communities.

The patients in our series followed for PV with JAK2 mutation, had a high level of hemoglobin, hematocrit and white blood cells from those who don't have JAK2. Patients followed for ET with positive JAK2 have a higher number of white blood cells. This is confirmed by the literature [4,9,10, 21-24], some studies incriminate their importance as prognostic criteria of severity.

The JAK2V617F mutation were positive in 14 patients of 22 or 9 out of 13 cases of PV, 4 of 8 patients followed for TE and negative in the patient monitoring to PMF. The proportion of JAK2 in the PV of our study (69.2%) is lower than the literature data. Indeed, in the PV, Ayad and al [27] in Egyp treported 81.4% positivity, whereas in Morocco Benmoussah and al [28] recorded 89.4% for the workforce of 246 and 88 cases of MPD. Apart from [29,30] Asian studies, the proportions of positivity are identical to those in North Africa, western series reported a positivity rate of 95% during the PV [4, from 9.21 to 23]. This difference can be explained by the small size of our series.

But the positivity of the JAK2 in the ET reported (50%) is comparable to the literature data [10, 11.21 to 23] where there are nearly 50% of positivity. The JAK2 mutation was negative in our patient monitoring for PMF while in the literature, the frequency varies from 30 to 46% [27,28]

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and can reach 50% positivity [4, 9, 27,28]. It would then compare random with respect to one case of our series.

The difference can be explained by poor selection of MPD Ph- patients before diagnostic confirmation in molecular biology including making a first or screening given the new WHO criteria [31] in the diagnosis of MPD. This should enable better diagnostic orientation for Molecular confirmation for an optimal management.

CONCLUSION

MPD is a reality in Togo. They saw their improved diagnosis through North-South cooperation which enabled the search bcr-abl transcript and JAK2V617F mutation. We encourage teams to deepen the application of molecular biology tests for diagnostic confirmation.

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