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Polyglobulia, as initial manifestation of BCR-ABL 1 positive chronic myeloid leukemia: a case report

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ABSTRACT SECTION

Introduction

WHO classification of chronic myeloproliferative disease encompass 8 entities of bone marrow neoplasms, amongst them the BCR-ABL1 positive chronic myelogenous leukemia and the polycythemia vera.

Polycythemia vera requires in the majority of cases (95%), the negativity of BCR-ABL1 rearrangement and the presence of Janus Kinase 2 (JAK2) mutations.

We report here on a case of polyglobulia, as primary manifestation of a chronic myeloid leukemia with the presence of Ph chromosome, BCR/ABL1 fusion gene and without JAK2 mutation.

Case Presentation

A 68-year-old Caucasian female, with a history of cigarette consumption and obstructive sleep apnoea syndrome needing CPAP has been investigated for fatigue and a hemoglobin (Hb) level of 18.6 g/l, with slight leukocytosis at 16 G/l and no other anomalies on complete blood cell count. Arterial blood gases found only a slight hypoxemia; erythropoietin and ferritin levels were very low and could not explain a secondary polyglobulia.

Further analyses revealed the absence of JAK2 mutation, thus excluding polycythemia vera. Together with a high vitamin B12 level, we asked for a BCR-ABL1 analysis and bone marrow cytogenetic analysis which returned positive leading to the diagnosis of CML.

Conclusion

To date, this case is the first description of a BCR-ABL1 positive chronic myelogenous leukemia with polyglobulia as initial manifestation, mimicking a JAK2 V617F negative polycythemia vera. The impressive response under imatinib therapy underscores the importance of not missing this diagnosis.

KEYWORDS

Polyglobulia, polycythemia vera, chronic myelogenous leukemia, BCR-ABL1, JAK2 V617F
INTRODUCTION

The WHO 2008 classification of myeloproliferative neoplasms (MPN) encompasses chronic myeloid leukemia, *BCR-ABL1* positive (CML), and 7 Philadelphia negative (Ph neg.) MPN.

The *BCR-ABL1* fusion gene is consistently found in CML. Conversely, *JAK2* mutations, especially *JAK2* V617F, are frequently encountered in Ph neg. MPN, particularly in polycythemia vera (> 95%) (1, 3), primary myelofibrosis (50%) (2), and in essential thrombocythemia (40-50%) (1). Other gain of function mutations in key proliferative genes, such as *MPL* W515K/L and, recently, in *CALR* gene have also been described in Ph neg. MPN (4). Although Ph neg. MPN requires evidence of absence of *BCR-ABL1*, CML may rarely harbor *JAK2* mutations, especially during evolution of the disease (4).

Neutrophilic leucocytosis is the initial major finding of CML, which is defined by the WHO as a myeloproliferative neoplasm that originates in an abnormal pluripotent bone marrow stem cell with *BCR-ABL1* fusion gene found in all myeloid lineages as well as in some lymphoid and endothelial cells (3).

Polyglobulia is usually the main feature of polycythemia vera and is considered, with one of the *JAK2* mutations, as a major criteria of this Ph neg. MPN. However, to our knowledge, it has never been reported so far as a manifestation of CML. In this case report, we describe a patient with isolated polyglobulia as the solely initial manifestation of *BCR-ABL1* positive CML.
CASE PRESENTATION

A 68-year-old Caucasian female, with active tabagism (40 pack-years), obstructive sleep apnoea syndrome needing CPAP via nasal mask and hypothyroidism secondary to partial thyroidectomy in 1979, has been investigated by her practitioner for fatigue in 2010.

Hemoglobin (Hb) level of 177 g/l was found, with slight leukocytosis at 12, 3 G/l, but there was no other abnormality on blood smear, especially no left deviation or myelemia. So it was initially interpreted as secondary polyglobulia.

In 2012 a raise in Hb was noted and the patient was seen in our institution for further investigations: Hb 180 g/l, leukocytes 16 G/l with normal differentiation, thrombocytes 294 G/l, reticulocytes 67 G/l. Arterial blood gases: PaO2 at 8.8 kPa, PaCO2 4.7 KPa, pH 7.42, Base excess -1.2mmol/l with oxygen saturation at 95%. The erythropoietin and ferritin values were low at 2, 3 U/l (normal value: 8-22 U/l) and 16 µg/l (NV: 30-300 µg/l), respectively. In this context, polycytaemia vera was suspected, but could not be confirmed by molecular biology analysis: The mutation JAK2 V617 F was negative. Interestingly, vitamin B12 level was very high 1703 pg/ml (NV: 185-1060).

The blood marrow biopsy revealed a slight hypercellularity with discrete hyperplasia and slight atypia of megakaryopoiesis, normal erythropoiesis with discrete signs of dyserythropoiesis without hyperplasia, and normal myelopoiesis. These abnormalities were aspecific and not suggestive for a MPN.

Based on hyperleukocytosis and a high vitamin B12 level, we searched for BCR-ABL1 fusion gene, which was surprisingly positive.

Bone marrow conventional cytogenetic revealed a female karyotype with the presence of the Philadelphia chromosome (t (9; 22) (q34; q11.2)) in 85% of metaphases.

The interphase FISH analysis confirmed the BCR-ABL1 rearrangement in 88, 5% interphases analyzed. In the light of these results we diagnosed a BCR-ABL1 positive CML, in chronic phase with low risk Sokal score (0.62).

We started on 13th April 2012 a therapy of imatinib mesylate (daily dose of 400 mg), with relatively good tolerance.
Under treatment, the patient obtained a complete hematological response at 3 months, including rapid disappearance of polyglobulia (see figures 1, 2), complete cytogenetic response and major molecular responses at 6 months and complete molecular response. These responses were considered optimal according to ELN criteria 2010 and 2013 (5).

DISCUSSION

Polyglobulia is usually associated with hypoxemia. In our patient, this was initially well explained by smoking and sleep apnoea syndrome. However, further analyses such as low erythropoietin and ferritin level, as well as high vitamin B12 levels, pointed the diagnosis to a MPN. In this situation further investigations are indicated: bone marrow analysis showing panmyelosis (hypercellularity of the three lineages) and molecular analysis, in particular of the JAK2 gene. In case of JAK2 negativity further investigation are needed such as cytogenetic of bone marrow.

To our knowledge, this is the first case reporting primary polyglobulia associated with negative JAK2 mutation, but presence of the BCR-ABL1 fusion gene. Based on the low EPO level and the molecular analysis results supporting the monoclonality of the red cells, as well as the excellent evolution of the polyglobulia under imatinib therapy (400 mg/day), we have to conclude that polyglobulia, without a high number of neutrophils, may be a feature of the disease with BCR-ABL1 fusion gene.

Conversely, have been some rare case reports on patients harboring both BCR-ABL1 fusion gene, as well as JAK2V617F mutation. However, the co-existence of both mutations appeared during the evolution of the disease (6).
CONCLUSION

To date, this case is the first description of a CML with polyglobulia as initial manifestation, mimicking a JAK2 V617F negative polycythaemia vera.

In such cases we proposed therefore to always test not only JAK2 V617F mutation but also BCR-ABL1 fusion transcript and to perform bone marrow cytogenetic.

CONSENT

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

COMPETING INTERESTS

The authors declare that they have no competing interests.
ABBREVIATIONS

**WHO**: World Health Organization

**MPN**: Myeloproliferative Neoplasms

**CML**: Chronic Myeloid Leukemia

**BCR-ABL1**: breakpoint cluster region- Abelson murine leukemia viral oncogene homolog 1

**JAK2**: Janus kinase 2

**CALR**: calreticulin

**Hb**: Hemoglobin

**Pa O2**: partial pressure of oxygen in the arterial blood

**Pa CO2**: partial pressure of carbon dioxide in the arterial blood

**t**: translocation

**ELN**: EuropeanLeukemia Net
Authors Contributions

MP (Mihaela I. Precup Cornea)

EL (Emmanuel Levrat)

PP (Paul Pugin)

DB (Daniel C Betticher)

MP wrote the manuscript. EL, PP, DB participates in the redaction of the manuscript.

MP, EL, PP, DB participated at discussion and decision of treatment at boards.

EL, PP have provided the clinical follow of the patient.

All authors read and approved the final manuscript.
References


Figure titles:

Figure 1- Evolution of Hemoglobin under imatinib mesylate therapy
Figure 2- Evolution of ANC under imatinib mesylate therapy
Figure 3- Molecular response under imatinib mesylate therapy