

## C A S E R E P O R T

## An uncommon case of chronic myeloid leukemia with variant cytogenetics

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**Summary.** Chronic Myeloid Leukemia (CML) is myeloproliferative neoplasm characterized by Philadelphia chromosome which is a balanced translocation between chromosome 9 and 22 in 90% of cases. However, variant cytogenetic still happens in 5-10% of cases, the importance of which is controversial as well as its response to therapy, prognosis and progression to acute leukemias. Here we report a male patient with CML and variant cytogenetic who responded to low dose of Dasatinib (50 mg daily). ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** CML, variant cytogenetic, accelerated phase

### Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation. Majority of case are associated with BCR-ABL1 fusion gene, a result of reciprocal translocation between chromosomes 9 and 22, t(9;22)(q34;q11) (1). We present here an uncommon case of chronic myeloid leukemia with variant cytogenetics.

### Case presentation

A 52-year-old Eritrean man, known to have diabetes mellitus type 2 on oral medications, presented with a past history of upper abdominal pain of 4 months duration that became severe in the last 4 days before hospital admission. The pain was associated with 10 kilograms weight loss and fatigue. Physical examination revealed pallor, hepatomegaly and massive splenomegaly reaching up to the umbilicus.

Initial complete blood count (CBC): white blood cells (WBCs)  $37.3 \times 10^3/\mu\text{L}$  (normal values: 4.0-10.0), with basophilia (8.7%), hemoglobin (Hb) 11.9 gm/dL (normal values: 13.0-17.0), platelets count (Plts)  $128 \times 10^3/\mu\text{L}$  (normal values: 150-400). The abdominal ultrasound confirmed the markedly enlargement of spleen (longitudinal length: 24 centimeters) and liver (length: 18 centimeter).

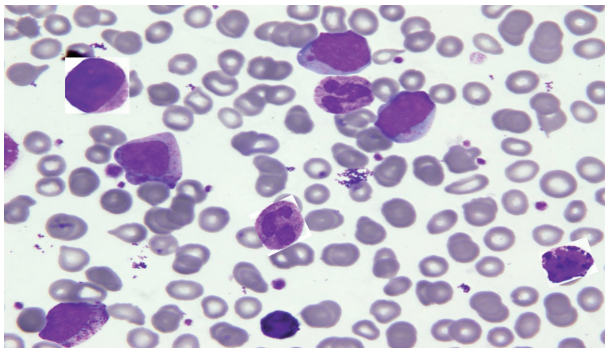
Complete blood picture revealed mild normocytic normochromic anemia (red blood cells (RBCs)  $3.7 \times 10^6/\mu\text{l}$  (4.5-5.5), mean corpuscular volume 85.5 fL (83-110) and mean corpuscular hemoglobin of 27.5 pg (27-32), with mild reticulocytosis of  $109.4 \times 10^6/\mu\text{l}$ . Peripheral smear (Figure 1) showed shift to the left with absolute basophilia and many circulating blasts medium to large in size with fine chromatin, some showing irregular nuclear contour and one or more nucleoli and some smaller in size with high nucleocytoplasmic ratio and showing cytoplasmic blebs. The differential count returned 16% blasts, 6% promyelocytes, 8% myelocytes, 9% metamyelocytes, 48% bands + segmented, 1% eosinophils, 10% basophils, 1% lymphocytes, 1% monocytes and 2% NRBCs/100WBCs.

Bone marrow aspirate smears (Figure 2) showed many unevenly distributed blast cells, granulocytic hyperplasia in full range of maturation and marked basophilia with occasional dwarf monolobated megakaryocytes spotted (probably because of hemodilution) with occasional erythroid precursors.

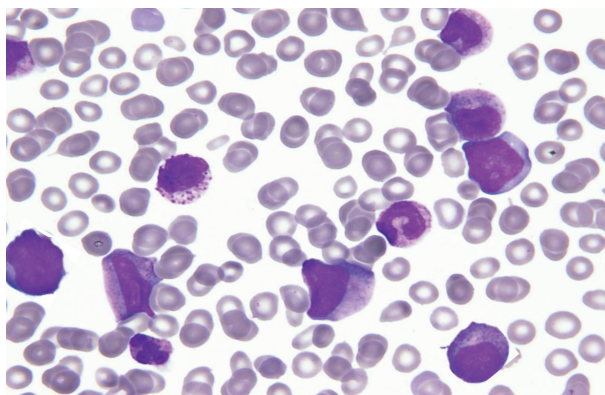
A 500-cell differential count revealed 15% blasts, 7% promyelocytes, 8% myelocytes, 13% metamyelocytes, 43% bands + segmented, 1% eosinophils, 7% basophils, 4% lymphocytes, 1% monocytes, 0% plasma cells and 1% erythroblasts. M/E is 79/1

Bone marrow core biopsy showed hypercellularity (90-95%) with marked granulocytic and megakaryocytic hyperplasia, depressed erythropoiesis and marked fibrosis. Megakaryocytes were seen in large clusters and sheets (Figure 3) with many dwarf/monolobated forms (Figure 4). Scattered immature cells were also noted.

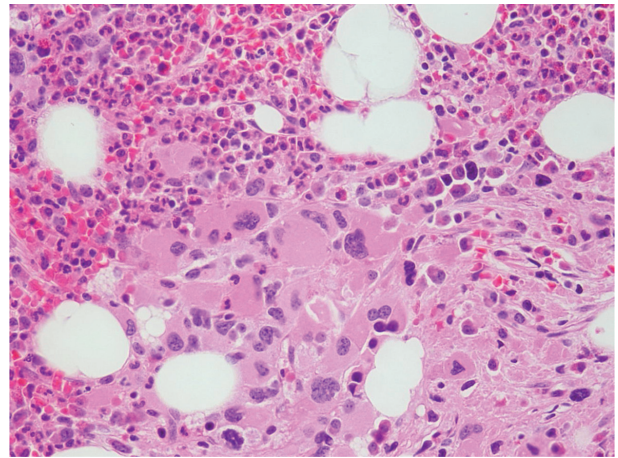
Reticulin stain showed increased fibrosis (Figure 5) and 2-3+ out of 3 with positive trichrome stain. Im-



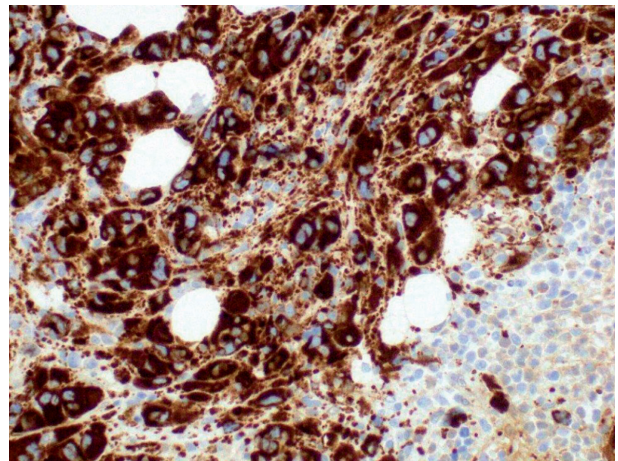
**Figure 1.** Peripheral blood, 100x, Wright stain showing 16% blasts and 10% b



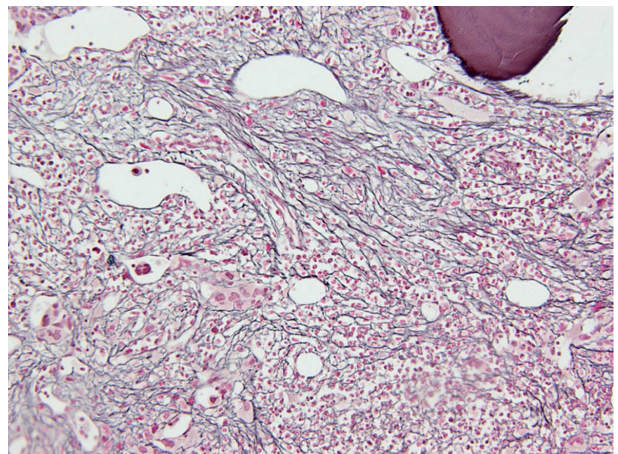
**Figure 2.** Bone marrow aspirate, 100X, Wright stain showing 15% blasts and 7% basophils



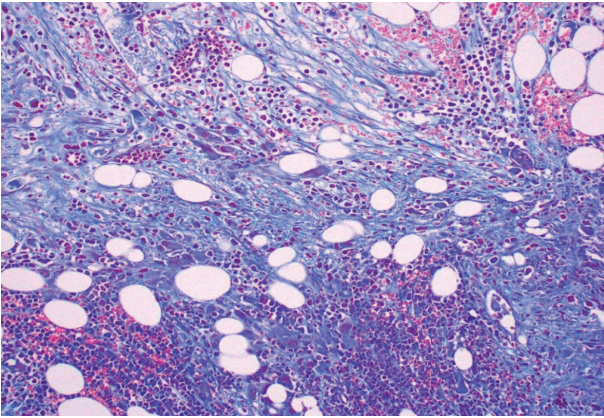
**Figure 3.** H&E, 40x: Megakaryocytes in large clusters and sheets



**Figure 4.** Bone marrow biopsy, vWF, 40x: Highlights large clusters and sheets of megakaryocytes with many small/hypolobated forms



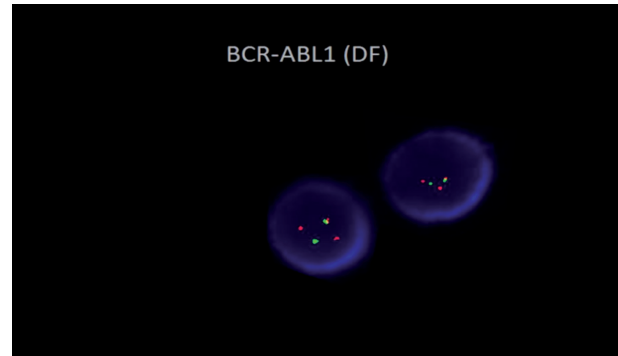
**Figure 5.** Bone marrow biopsy, Reticulin, 40x: Fibrosis 2-3/3



**Figure 6.** Bone marrow biopsy, Trichrome, 40x

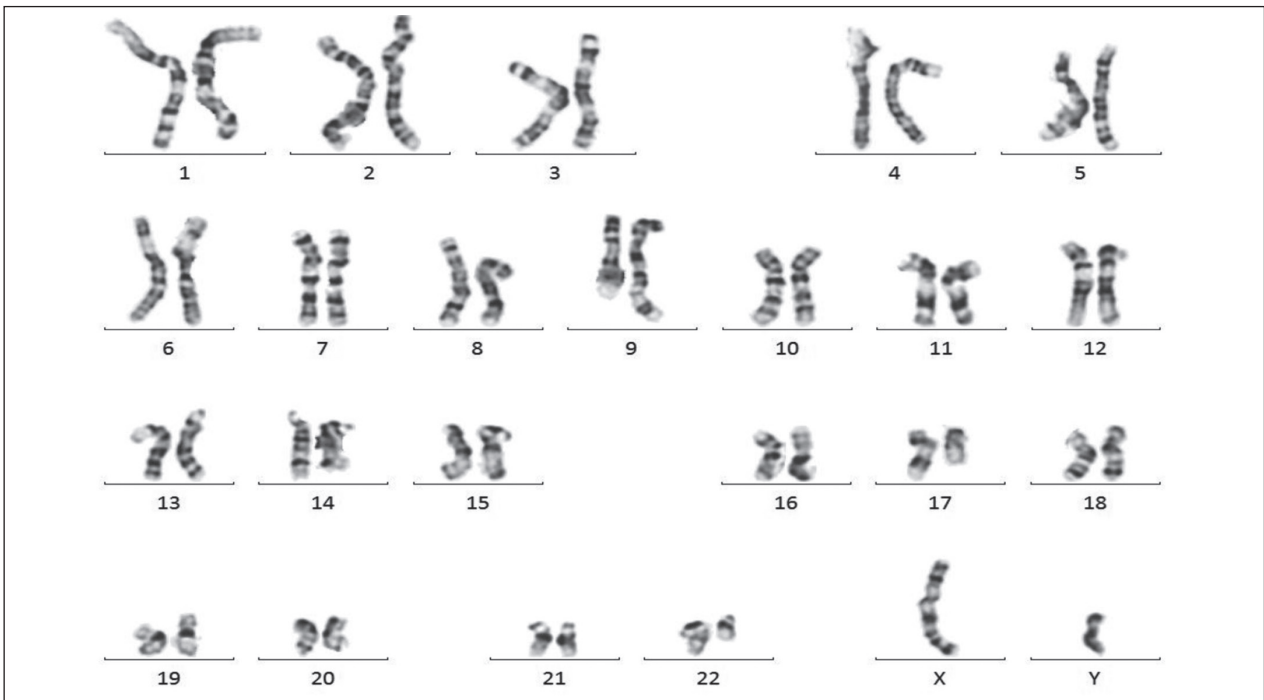
munohistochemical stains highlighted scattered and clusters of CD34-positive cells and large clusters and sheets of megakaryocytes with many dwarf/monolobated forms (Figure 6).

Fluorescence in situ hybridization (FISH) analysis was performed on interphase cells directly harvested from bone marrow sample. The probes used were ABL1 (red) and BCR (green) on cytogenetic bands



**Figure 7.** Interphase FISH on bone marrow cells using dual fusion BCR/ABL1 probe ISCN nomenclature: nuc ish(ABL1x3,BCRx2)(ABL1 con BCRx1)[197/200] variant BCR/ABL1 rearrangement, t(9;22)

9q34 and 22q11.2, respectively. The analysis revealed single fusion (yellow) (BCR/ABL1 Rearrangement, t(9;22), along with 2 red and one green singles emitted by normal chromosomes 9 and 22, respectively (Figure 7). Further, cytogenetic studies on metaphase cells from cultured bone marrow sample revealed a three way translocation involving chromosomes 9, 17 and 22 (Figure 8).



**Figure 8.** Karyotype bone marrow cell. ISCN nomenclature: 46,XY,t(9;22;17)(q34;q11.2;q21)[20]

## Discussion

CML is characterized by the presence of the Philadelphia chromosome (Ph), derivative chromosome 22 of the translocation  $t(9;22)(q34.1;q11.2)$  resulting in the *BCR-ABL1* fusion gene. Ph chromosome is detected in around 90% of CML patients among whom 5-10% may have variant types. Variant Ph chromosomes are characterized by the involvement of another chromosome in addition to chromosome 9 or 22. It can be a simple type of variant when only one additional chromosome is involved, or complex.

The most frequent form involves chromosome 17 followed by 1, 6, 11, 2, 10, 12 and 15 (2).

Studies reported contradicting outcomes regarding prognosis of variant Ph versus classical Ph. Several studies reported that prognostic significance of variant Ph chromosomes does not impact cytogenetic or molecular responses or even clinical outcome (3-6). However, other studies report poor clinical outcome with shorter overall survival (OS) and progression free survival (PFS) (7-10) and longer time to complete cytogenetic remission (CCR) and major molecular response (MMR) (9).

Current treatment guidelines don't include cytogenetic abnormalities in the choice of treatment but rather according to the phase. According to European LeukemiaNet (ELN) 2013 guidelines chronic phase and accelerated phase CML are treated with anyone of the tyrosine kinase inhibitors (TKIs): imatinib, nilotinib or dasatinib. Bosutinib can be used as second line. Ponatinib is used for patients with T315I mutation or as second line after failure of dasatinib as first line. Allogeneic stem cell transplant (AlloSCT) is reserved for patients who fail or don't tolerate second line TKI. Patients with CML in blast phase are treated with TKI plus chemotherapy to achieve remission followed by AlloSCT (11).

We started treatment with Dasatinib (70 mg twice daily); the dosage was reduced to 50 mg once a day due to some signs of toxicity. The lower dose of Dasatinib was found to be very well tolerated and the patient achieved a complete hematological and cytogenetic remission.

These data confirmed our previous observations in a subset group of patients with CML (12).

In conclusion, the data for CML with variant cytogenetics remain controversial with concerning the prognosis, the disease progression and the response to treatment. Therefore, further studies are needed to determine what is the best treatment for this group of patients.

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