

# De Novo Complex Translocation 9; 22; 19 (Variant Philadelphia+) in Myelodysplastic Syndrome with Excess Blasts: A Case Report

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## Abstract

We report adult patients with myelodysplastic syndrome with excess blast (MDS) by the world health organization (WHO) 2016 revision for classification of myeloid neoplasm group. The case had clinical and hematological peculiarities, which had rarely reported and described yet. The cytogenetic alterations were complex translocation 9;22;19 (Variant Philadelphia+) of Philadelphia chromosomes which appeared at different moments of the disease. The patient showed the Ph chromosome with disease transformation at diagnosis and unfortunately, further workup could not be performed as the patient succumbed to her illness and expired. The complex characterization with multiple translocations and the presence of Ph could be a marker of this form of MDS. The association of clinical and hematological findings suggests the possibility of a new group of adult MDS.

**Keywords:** Myelodysplastic syndrome; Philadelphia chromosome; Cytogenetic; Complex translocation

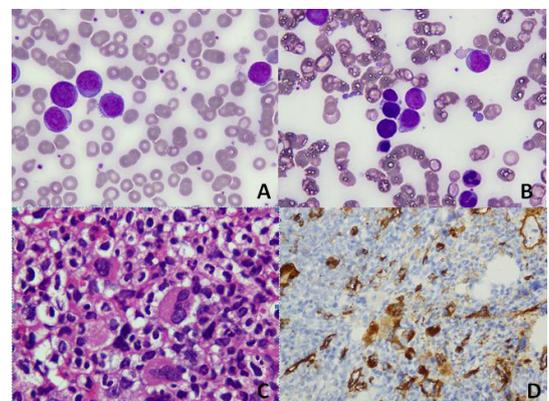
## Background

Myelodysplastic syndromes (MDS) are cytogenetically heterogeneous disorders that can transform to acute myeloid leukemia. The genetic profile of this syndrome is not well studied; however there is a link between genetic aberrations and defects in gene expression. An infrequent chromosome anomaly is the presence of the Philadelphia (Ph) chromosome in MDS. Clonal cytogenetic abnormalities are found in 30%–50% of primary MDS cases. The major types include monosomy 7, loss of the Y chromosome, del(5q), del(7q), del(11q), del(20q), and trisomy 8 [1]. There is a higher frequency of chromosomal aberrations in progressive stages of the disease, which indicates disease progression to a transformed stage. Various genetic aberrations occur during the clonal evolution of MDS; however, there are few reports of the appearance of the Philadelphia (Ph) chromosome [1]. The incidence rate of Ph chromosome has been reported to be approximately 20% of CML cases (adult cases), and 5% pediatric cases demonstrating acute lymphoblastic leukemia (ALL), and in 3% acute myeloblastic leukemia (AML) cases [2]. In MDS however, the Ph chromosome is rarely involved. In this case report we report a patient with Ph+ MDS in which the simultaneous emergence of t(9;22;19) of the Ph chromosome coincided with complex translocation to long arms (q) of 19 chromosomes.

## Case Description

A 47-year-old female was evaluated for 2 weeks history of generalized weakness, weight loss and bleeding from mouth. She had no significant past medical and surgical history except for packed red cell transfusion. Physical examination revealed pallor with no hepatosplenomegaly or lymphadenopathy. Laboratory findings were as follows: Hemoglobin (Hb) 9 g/dL, mean cell volume (MCV) 77.1 fL, mean cell hemoglobin (MCH) 22.7 pg, white blood cells (WBCs)  $47 \times 10^9/L$ , and absolute neutrophils count (ANC)  $21.6 \times 10^9/L$ , Platelets  $218 \times 10^9/L$  and corrected reticulocyte count 4.1%. There was no evidence of basophilia or monocytosis. Peripheral blood smear showed hypochromic microcytic anemia with anisocytosis, nucleated red blood cells, neutrophilia and 19% blast cells (Figure 1). Based on clinical history and complete blood count findings, bone marrow procedure was carried out for evaluation of Myelodysplastic/Myeloproliferative Neoplasm (MDS/MPN). Bone marrow aspirate was

a moderately cellular specimen exhibiting trilineage hematopoiesis with normoblastic erythropoiesis, and active myelopoiesis however with decreased myeloid to Erythroid ratio (1:1) and 17% myeloblasts. Adequate megakaryocytes were noted. Bone trephine biopsy revealed increased cellularity for age of around 80–85% and grade MF-2 reticulin fibrosis. Immunohistochemistry highlighted increased CD34 and Myeloperoxidase (MPO) positive blast cells (Figure 1). All these findings were consistent with myelodysplastic syndrome (excess blast-II). Conventional cytogenetic workup using Giemsa-Trypsin banding showed following karyotype: 46, XY, t(9;22;19)(q34;q11.2;q13.3)(20) (Figure 2). Estimated revised-International prognostic scoring system



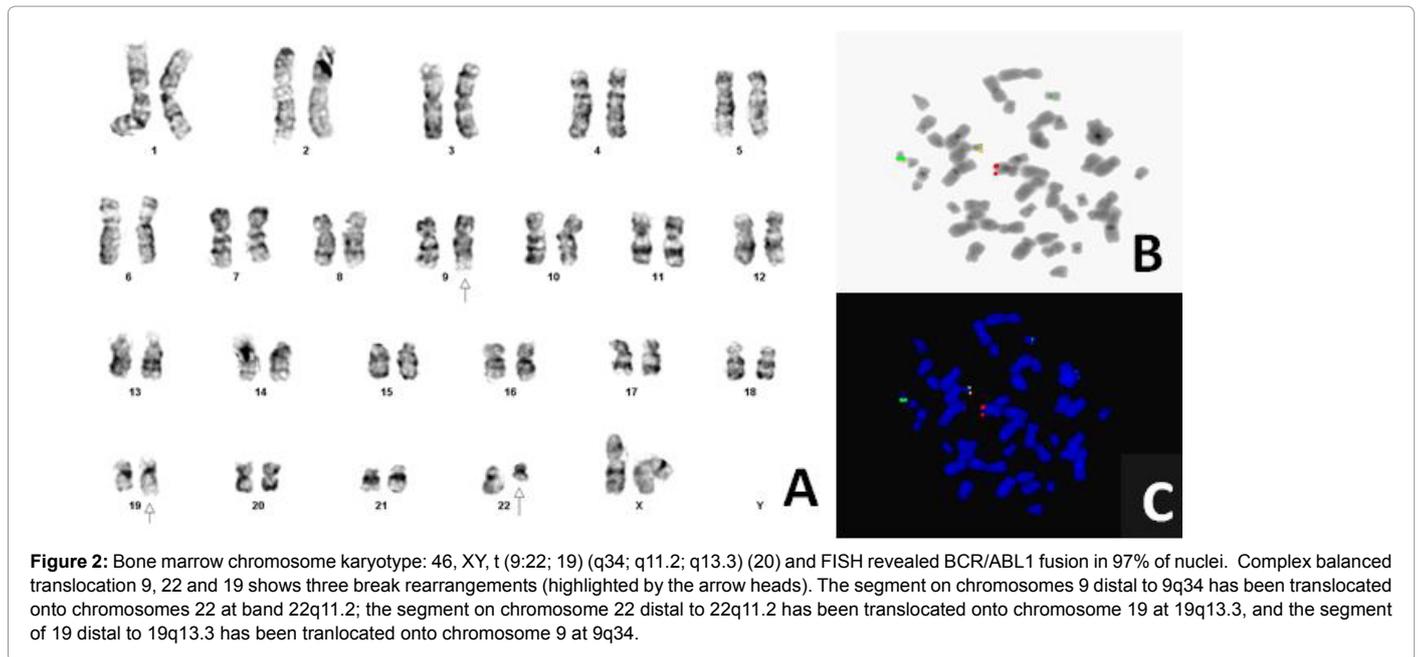
**Figure 1:** A: Peripheral blood film (at 100x), B: Bone marrow aspirate (at 100x), C: Bone trephine (H&E section at 100x), D: CD34 stain at 40x.

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Received February 21, 2018; Accepted March 20, 2018; Published March 28, 2018

**Citation:** Ahmed ZA, Shaikh MS, Khalid A, Moiz B, Moatter T (2018) De Novo Complex Translocation 9; 22; 19 (Variant Philadelphia+) in Myelodysplastic Syndrome with Excess Blasts: A Case Report. J Blood Lymph 8: 196. doi:10.4172/2165-7831.1000196

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(R-IPSS) score was 3. (Hemoglobin [9 g/dL]=1; platelets [218000/ $\mu$ L]=0; absolute neutrophil count [21600/ $\mu$ L]=0; cytogenetic=1; blast =[19%]=2). Trilineage hematopoiesis, with excess blasts but interestingly, without basophilia, karyotypic, and molecular clonal evidence for Ph+ disease. Unfortunately, further workup could not be performed as the patient succumbed to her illness and expired.

## Discussion

Myelodysplastic syndrome is cytogenetically heterogeneous presenting with karyotypic abnormalities in about 50% of the patients. Gains and somatic loss of tumor suppressor result in impaired differentiation [3,4]. Translocation (9;22) is frequently observed in chronic myeloid leukemia (CML). In a WHO report (2016) classification of myeloid neoplasm emphasizes that CML BCR-ABL1+ phenotype must include significant myeloproliferation. The translocation (9;22) is rarely associated with dysplastic hematopoiesis, suggesting that it may have antagonistic disease-initiating role. In this case case report, we have described a Ph+ MDS patient.

Keung et al reported three de novo Ph+MDS cases and reviewed 18 additional patients [5]. In contrast this case study was related to Ph+ treatment-related disease and CMML case. About 48% of patients lack Ph+ chromosomal abnormality and acquire translocation sequentially at disease progression. It is reported that 50% of patients present with t (9;22) as the only abnormality. This disease exhibits high-risk features characterized by complex karyotype and elevated proportion of blast and thrombocytopenia. Other studies have also demonstrated that thrombocytopenia adversely impacts MDS outcome [6] Neukirchen et al. specifically. It is possible that Ph+ MDS exhibits similar prognostic variables as those observed in Ph negative MDS. A short median time to AML transformation of 7 months suggests that Ph+ MDS is a highly aggressive disease, especially if it is associated with complex karyotype and thrombocytopenia. In Keung et al. study [5], median time to AML progression was reported as 13 months. Ph chromosome is infrequently seen during the course of MDS. Late emergence of the Ph chromosome during the progress of MDS has been described in some case reports and reviews [7-9] and is referred to as substantiation supporting multistep

leukemogenesis. The early event in leukemogenesis is ascribed to the clonal proliferation of stem cells, and the late acquisition of the Ph chromosome arises in neoplastic cells [10]. The element that few cases of Ph+ MDS have been reported to date is not conclusive evidence of low occurrence of this fusion in MDS patients.

FISH testing has accomplished to detect BCRABL fusion in MDS patients, lack of finding in normal karyotype study does not indicate definitive absence of this fusion [11,12]. Evaluation of reported cases shows that MDS patients concealing this chromosomal abnormality typically do not respond well to conventional treatments but do show a good response to imatinib therapy [13] Since imatinib is not consistently used in treatment of MDS patients, lack of Ph recognition in these patients may lead to improper treatment and thus put the patient's life at risk. Over-all, even if the findings of the studies specify the significance of Ph detection in MDS patients, they are not appropriate to illuminate the particular role of Ph in MDS patients. Hence, precise assessment of this chromosomal anomaly in MDS patients is suggested in future studies. Future directions should assess the role and probable appliance of action of TKIs in Ph+ MDS patients offering with low risk features.

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