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BCR–JAK2 fusion in a myeloproliferative neoplasm with associated eosinophilia

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Janus kinase 2 (JAK2) is located on chromosome 9 at band p24 and *JAK2*V617F is the most common mutation in Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-MPN). However, rearrangement of *JAK2* is a rare event. We report a case of myeloproliferative neoplasm, unclassifiable (MPN-U) with *BCR–JAK2* fusion confirmed by molecular studies. Conventional chromosome analysis (CC) revealed t(9;22)(p24;q11.2) and fluorescence *in situ* hybridization (FISH) showed a *JAK2* gene rearrangement in 88% of interphase nuclei. The *BCR–JAK2* fusion was confirmed by multiplex reverse transcriptase polymerase chain reaction (RT-PCR) and demonstrated two in-frame 5′*BCR*/3′*JAK2* transcripts with *BCR* exon 1 juxtaposed to *JAK2* exon 15 and exon 17, respectively. Our results, together with literature review, reveal *BCR–JAK2* fusions as oncogenic genetic alterations that are associated with myeloid or lymphoid neoplasms and are frequently characterized by eosinophilia. Further, patients with *BCR–JAK2* are candidates for JAK2 inhibitor therapy. Given the distinct clinical and pathological characteristics, we believe that hematological neoplasms harboring *BCR–JAK2* should be included as an additional distinct entity to the current WHO category of "myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR*", and testing for a *JAK2* fusion should be pursued in neoplasms with a karyotypic 9p24 abnormality.

Keywords JAK2, BCR–JAK2 fusion, myeloproliferative neoplasm, B-lymphoblastic leukemia/lymphoma, eosinophilia

Introduction

The Janus Kinase 2 (JAK2) protein belongs to the family of Janus non-receptor tyrosine kinases (JAK kinases) and associates with the cytoplasmic domain of receptors for several hematopoietic cytokines and growth factors. It is activated upon ligand binding, leading to activation of the downstream JAK-Signal Transducers and Activators of Transcriptions (STAT) pathway (1,2). The most common *JAK2* genetic alteration is *JAK2*V617F, which is highly prevalent in Ph-MPN, seen in ~95% of polycythemia vera and 50–60% of essential thrombocythemia and primary myelofibrosis patients (3–6). Two other rare *JAK2* genetic alterations reported are amplification and rearrangements (7). *JAK2* rearrangement partners include *PCM1*, *ETV6*, *BCR*, *PAX5*, *STRN3*, *SSBP2*, and *SEC31A* with the first three being more common. *JAK2*/partner rearrangements are associated with both myeloid and lymphoid malignancies, most commonly MPN and myelodysplastic/myeloproliferative neoplasms (MDS/MPN), but also include acute myeloid leukemia (AML), B-lymphoblastic leukemia (B-ALL) and rarely T-lymphoblastic lymphoma/leukemia (8). *BCR–JAK2* fusion is rare with only 14 cases described in the literature (9–22). Here we report a new case of *BCR–JAK2* fusion presenting as MPN-U and discuss the observed clinicopathological features and implications for disease classification of this rare genetic alteration.

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Materials and methods

Case report

A 36 year old woman presented with marked leukocytosis (60.1×10^9/L), mild anemia (Hb 9.1g/dL), and normal platelet count (340×10^9/L). Peripheral smear showed leukoerythroblastosis and eosinophilia with a white blood cell (WBC) differential of 54% neutrophils, 3% metamyelocytes, 19% myelocytes, 3% blasts, 11% eosinophils, 1% basophils, 2% monocytes, and 7% lymphocytes. Neutrophils revealed no dysplasia. Left shifted eosinophils and frequent large hypogranular platelets were present (Figure 1A and B). Bone marrow demonstrated morphological features of a Ph-MPN with marked hypercellularity, granulocytic hyperplasia, eosinophilia, slight erythroid hypoplasia and atypical megakaryocytic hyperplasia with clustering and large hyperlobated and pleomorphic hyperchromatic forms (Figure 1C). Focal grade 1–2 (of 3) reticulin fibrosis was seen. The patient was diagnosed with MPN-U and received cytotoxic chemotherapy after failing dasatinib and subsequently underwent allogenic stem cell transplantation at an outside institution. The patient remains in remission 18 months post transplantation.

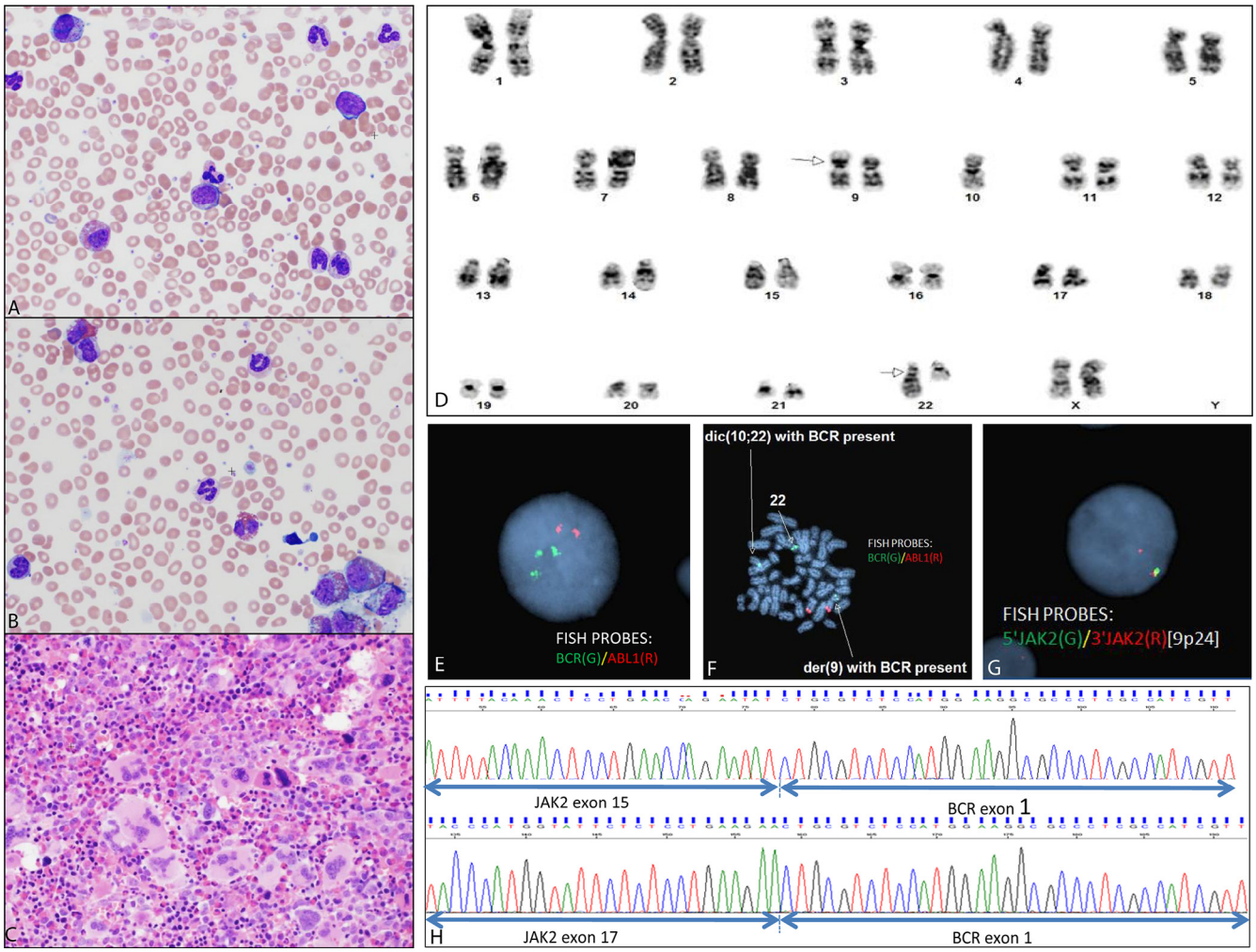

Figure 1 Peripheral blood smear showed left-shifted neutrophilia, eosinophilia and large hypogranular platelets (A and B). Marked hypercellularity, megakaryocytic clustering with large hyperlobated forms and pleomorphic hyperchromatic forms, granulocytic hyperplasia, and eosinophilia were seen on the bone marrow biopsy (C). Conventional chromosome analysis demonstrated a complex karyotype with multiple rearrangements involving chromosome 22, including a non-classical, unbalanced t(9;22) resulting in a derivative 9 (arrow) from a t(9;22) and a dicentric rearrangement involving chromosomes 22 and 10 (arrow) (D). No *BCR-ABL* fusion but 3 copies of the *BCR* signal (22q11.2) were observed in 88% of interphase nuclei by FISH analysis, using a double fusion probe strategy (*BCR*-green, *ABL1*-red) (E). Sequential metaphase FISH analysis demonstrated that the normal chromosome 22, derivative chromosome 22 from the dicentric (10;22), and the derivative 9p from the non-classical t(9;22) each contained a *BCR* signal (F). A *JAK2* break-apart probe set confirmed disruption of the *JAK2* gene region (at 9p24) in 88% of interphase nuclei (5′ *JAK2*-green, 3′ *JAK2*-red) (G). Targeted fusion transcript screen by multiplex RT-PCR detected two in-frame *BCR–JAK2* fusion transcripts, juxtaposing *BCR* exon 1 with *JAK2* exon 15 and exon 17, respectively (H). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)