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LETTER TO THE EDITOR

Response to interferon treatment in essential thrombocythemia with inv(3)(q21q26)

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Dear Editor,

Chromosomal inv(3)(q21q26)/t(3;3)(q21;q26) is a distinctive entity of acute myeloid leukemia (AML) with recurrent genetic abnormalities, occurring in about 2% of patients with AML [1]. It repositions a *GATA2* distal hematopoietic enhancer (G2DHE) into close proximity to ecotropic viral integration site 1 (EVI1) gene, which is a proto-oncogene, leading to leukemogenesis [2]. Patients with inv(3)/t(3;3) typically have poor response to chemotherapy, relapse early after hematopoietic stem cell transplant (HCT), and have worse clinical outcomes [3, 4]. We report a patient with essential thrombocythemia (ET) with inv(3), who achieved ongoing, prolonged hematologic remission and decreased inv(3)% with pegylated interferon-alfa 2a (IFN) treatment.

Our patient was a 57-year-old male with ET who was previously treated with hydroxyurea, and then anagrelide for 15 years, with normal platelet and leukocyte count, and hemoglobin ~ 11 gm%. Due to a decrease in hemoglobin to 9.5 gm%, a marrow examination was done and revealed 2+ fibrosis with increased megakaryocytes and a karyotype with inv(3)(q21q26). He was referred to our institution for further management. His only symptom was fatigue, he did not have splenomegaly or leukoerythroblastic picture, his leukocyte and platelet counts were normal, and his hemoglobin improved to 10.5 gm%. Repeat bone marrow showed variable cellularity of 30–70% with mild dysmegakaryopoiesis and moderate reticulin fibrosis of 2. He had a calreticulin mutation ($CALR^{MUT}$ type 1) and karyotype showed inv(3)(q21q26) in 60% of cells. Anagrelide was stopped and evaluation for allogeneic HCT ensued. Subsequently, his platelet count increased to 669 × 10^9/L and hemoglobin to ~ 13.5 gm%; leukocytes remained normal. Fluorescence in situ hybridization (FISH) performed with the RPN1(3q21) and MECOM(3q26) probes (Abbott Molecular) showed RPN1-MECOM fusion suggestive of inversion in 44.5% of cells. FISH on sorted T cells was negative, confirming that the mutation was acquired. He declined HCT and was enrolled in a clinical trial of IFN and achieved hematologic remission in 7 months. After 1 year of therapy, the percentage of cells in the bone marrow showing RPN1-MECOM fusion decreased to 18% (Fig. 1) with improvement in marrow fibrosis. His major symptom on IFN therapy was fatigue, and his IFN was discontinued after 3 years as the study completed. His platelet count increased within 6 weeks after discontinuation of IFN to 498 × 10^9/L, and the percentage of RPN1-MECOM fusion positive cells increased from 7 to 14% (Fig. 1). He was restarted at a lower dose of IFN and demonstrated continued response with hematologic remission and on FISH, and continuing presence of calreticulin mutation. This suggests that IFN induced an immune response against the malignant clone but did not eliminate it.

Inv(3) was previously reported in AML, aggressive myelodysplastic syndromes (MDS) and blastic phase of myeloproliferative neoplasms, mostly in patients with

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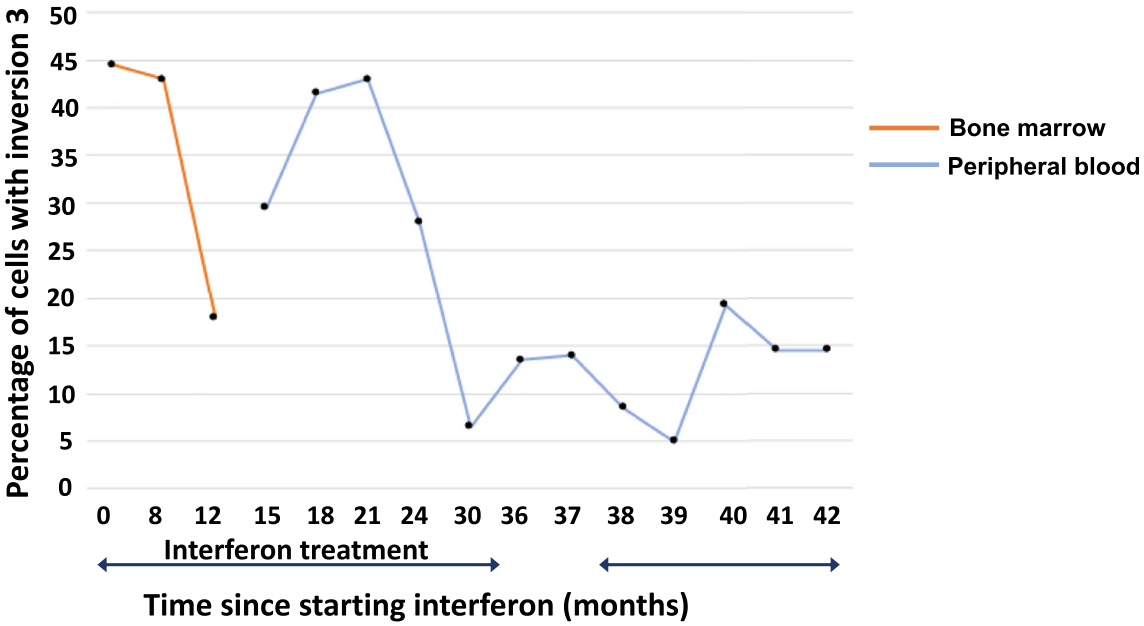

Fig. 1 Percentage of cells positive for inversion 3 after starting interferon

chronic myeloid leukemia. It was also reported in a patient with ET with normal karyotype, who, upon evolution to AML, developed inv(3), 9 years after the initial diagnosis [5]. Unlike the aggressive clinical course seen in reported patients with inv(3), our patient is doing exceptionally well with IFN treatment and continues to be in hematologic remission with persistence of the inv(3)(q21q26) clone. As these patients do not respond to the conventional treatments and have poor outcomes, investigation of better treatment options should be explored.

Authors' contributions RG has taken care of the patient and written the manuscript; AJC was consulted about the chromosomal abnormalities, reviewed material, and edited manuscript; and JTP treated the patient, organized studies, and has written the manuscript.

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Compliance with ethical standards

Ethical approval Ethics committee or IRB approval is not required for the publication of this single case report. Details that might disclose the identity of the patient are not included in this manuscript.

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