LETTERS TO THE EDITOR
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A Case of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia with Coexistence of *JAK2* V617F Clone

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To the Editor,

Essential thrombocythemia (ET) is one of the Philadelphia chromosome-negative(Ph^-) myeloproliferative neoplasms (MPNs). It usually presents with an indolent clinical course.Less than 5% of ET patients will transform into acute myeloid leukemia (AML). Studies have found that the probability of ET patients progressing to AML is 0.7%-3% in 10 years , and is 2.1%-5.3% in 15 years [1]. There are little reports about ET progressed to acute lymphoblastic leukemia (ALL) until now. Prithviraj Bose et al have reported 4 cases of ET progressed to ALL, only one of which progressed to Philadelphia chromosome-positive ALL (Ph^+-ALL).[2].

The index case was a 56-year-old man with a large hematoma in the left scapular region and fever. Routine blood tests showed white blood cell(WBC） 16.31×10^9/L and platelet(PLT) 2716×10^9/L. Bone marrow (BM) examination showed marked proliferation of mature megakaryocytes (Fig.1A). Karyotype analysis showed 46, XY [20]. The quantitative polymerase chain reaction(qPCR) analysis for the *JAK2* V617F point mutation was positive, and for the *BCR::ABL1* fusion gene was negative. This case fulfilled the clinical criteria for the diagnosis of ET. The patient received hydroxyurea (1.0 g twice daily) and IFN-α (3 million IU twice weekly) for two weeks, and the PLT count decreased to 839×10^9/L. But two months later, the patient discontinued treatment for unknown reasons, and was lost to follow-up.

Three years later, the patient revisited our hospital with the feeling of fatigue and dizziness. Routine blood tests showed WBC 100.42×10^9/L and PLT 20×10^9/L. BM examination showed hyperplasia of nucleated cells, and blasts accounted for 81.5%. 100% of these cells were peroxidase negative

(Fig.1A). The BM biopsy showed abundant blasts and no evidence of increased reticulin fibrosis (Fig.1B, Fig.2). Flow cytometry test revealed 86.63% of BM blasts that expressed HLA-DR, CD10 and CD19 (Fig.3). Karyotype analysis showed cytogenetic abnormalities with 46,XY,t(9;22)(q34;q11.2),add(14)(q32),del(20)(q13)×2[20] (Fig.4). The qPCR analysis for both the *JAK2* V617F point mutation and the *BCR::ABL1* fusion gene (e1a2 transcript) was positive. *JAK2* V617F missense mutation detected by next-generation sequencing (NGS) was also positive (Fig.5). Based on the results of BM examination, Ph^+-ALL was diagnosed for the patient. The patient received imatinib(600 mg once daily) and the standard VDCP regimen consisting of vincristine, daunorubicin, cyclophosphamide and prednisone.After primary induction therapy, BM assessment showed bone marrow remission (BMR) with 3% naive lymphocytes. And the patient achieved MRD negativity. An unexpected result is that the PLT count again increased to as high as 2419×10^9/L. And the patient were insensitive to hydroxyurea and imatinib. With 2 rounds of PLT apheresis and IFN-α (5 million IU daily) was treated, the PLT counts gradually decreased to $(300\text{-}400)\times10^9$/L. Another four courses of consolidation chemotherapies were administered and imatinib were replaced with dasatinib (70mg once daily) aiming to sustain deep remission. The qPCR analysis for *BCR::ABL1* was negative after the first consolidation therapy. The patient remained MRD negative after each chemotherapy treatment. The karyotype returned to normal. The qPCR analysis for *JAK2* V617F point mutation was always positive during the ALL diagnosis and treatment period. But *JAK2* V617F missense mutation was negative detected by NGS after the last chemotherapy treatment. And there were no signs of extramedullary leukmeia. The patient maintained a major molecular response(MMR) for 26 months from the diagnosis of Ph^+ -ALL.

The *JAK2* V617F mutation can be detected in most ET patients, and it is considered to be the driver mutation for these patients [3]. Only a small number of ET patients with *JAK2* V617F mutation progress or transform to ALL, the majority with AML[4]. There are a few of reports about ET patients with *JAK2* V617F mutation progressing or transforming to lymphoid malignancies, including non-Hodgkin's lymphoma and chronic lymphocytic leukemia(CLL), but fewer about ALL[5]. For this case, Ph^+-ALL was regarded as a second hematologic neoplasm that means disease progression not neoplastic transformation. The base for this conclusion is that *JAK2* V617F mutation and *BCR::ABL1* fusion gene coexist at the time of the diagnosis of Ph^+ -ALL, which suggests the existence of double clones. When Ph^+ -ALL achieved molecular remission, the platelet count significantly increased again and the *JAK2* V617F mutation still existed. That further confirm the above conclusion. There is a literature reported that the treatment with IFN-α for ET[5] has a high response rate [5]. To our patient, IFN-α was more effective in reducing platelets compared with hydroxyurea, implying that the features of clinical presentation and treatment response of ET were preserved during the leukemic phase.

Key words: Essential thrombocythemia; *JAK2* V617F mutation; Acute lymphoblastic leukemia; Philadelphia chromosome positive

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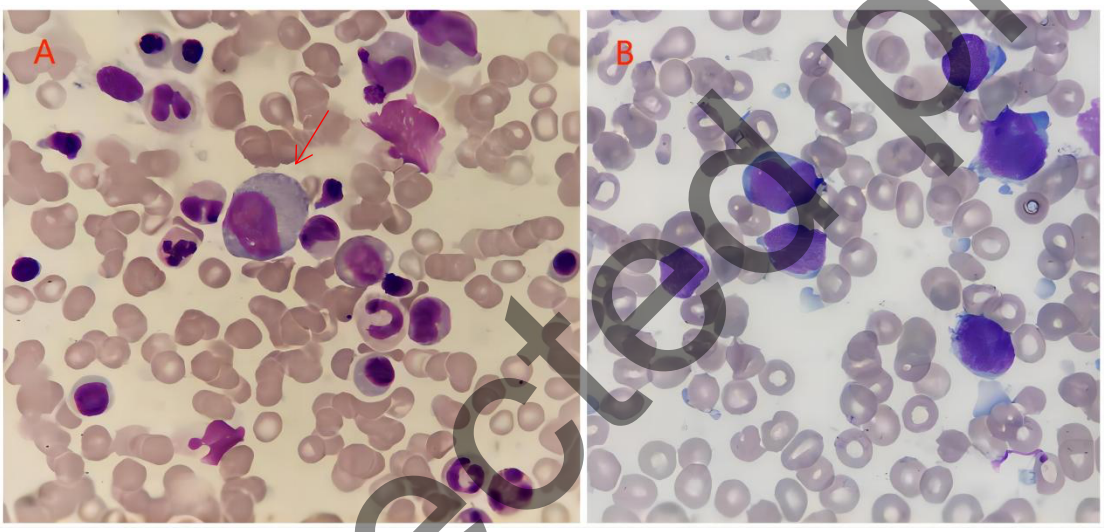

Fig.1A BM morphology of ET declared increased and enlarged megakaryocytes.(100×)(Red arrow)
Fig.1B BM morphology of ALL declared predominance of primitive and immature lymphocytes. (100×)

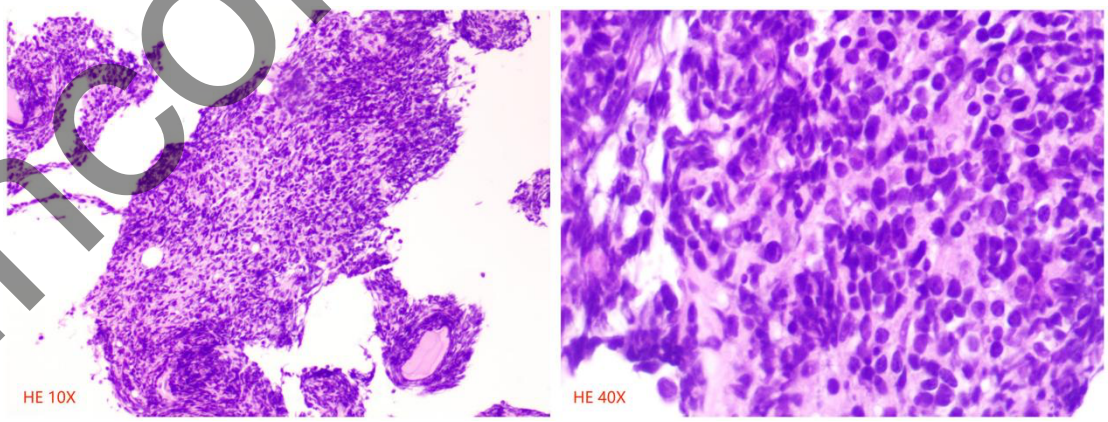

Fig.2 The BM biopsy showed active proliferation of nucleated cells, blasts were diffusely proliferated, and there was no collagen fiber hyperplasia in the stroma,

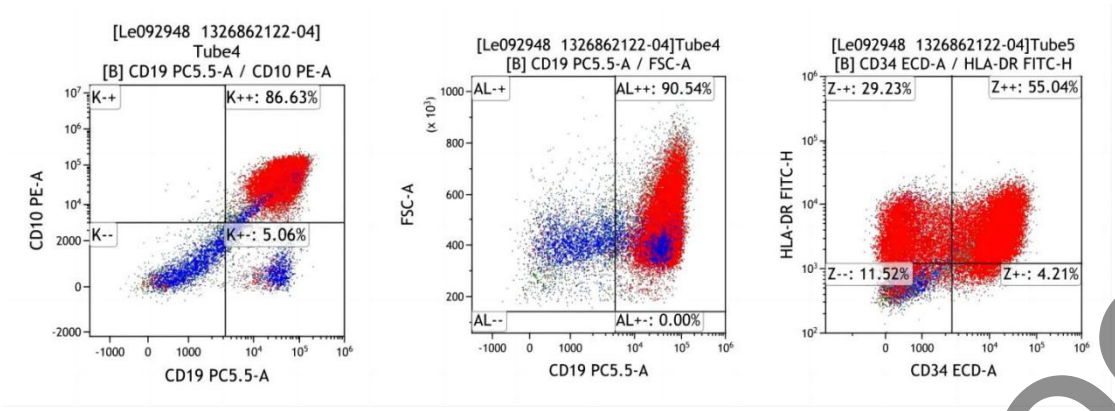

Fig.3 Immunophenotyping showed that: 86.63% of the nuclear cells were blast cells and expressed CD10, CD19, HLA-DR, and some expressed CD34.

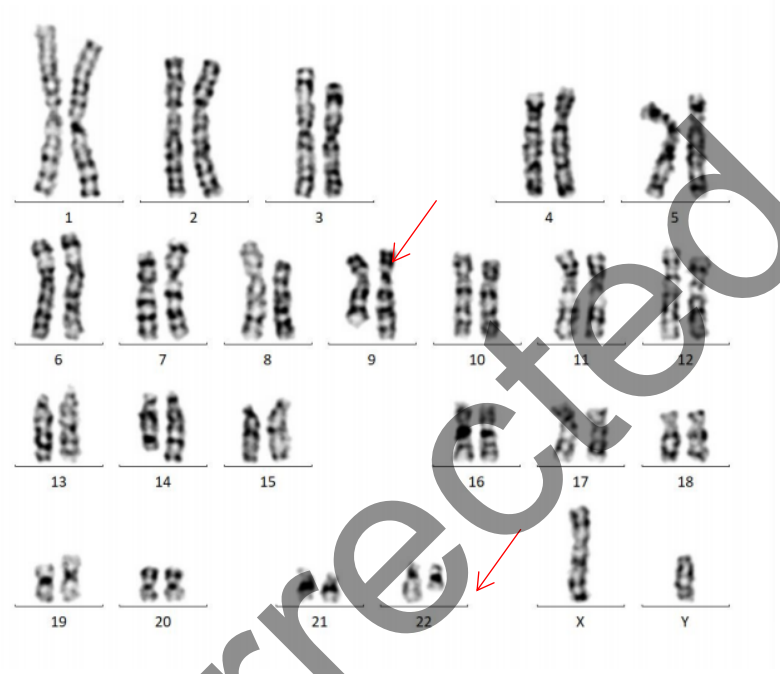

Fig.4 G-banded karyotype analysis showed 46,XY, t(9; 22)(q34; q11.2), add(14)(q32), del(20)(q13) ×2[20]. Arrows indicate translocations on chromosomes 9 and 22. (Red arrow).

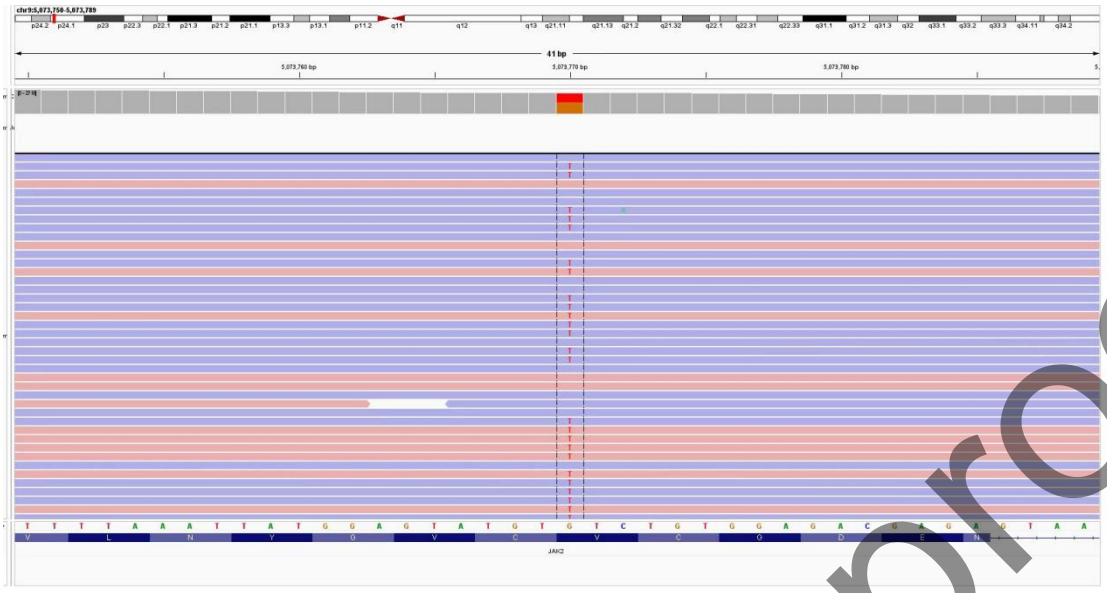

Fig.5 Next generation sequencing results.