Case Report

Co-existence of myeloproliferative neoplasias and β-thalassemia with IVS-2-654 mutation—a case report

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Abstract: Thalassemia and myeloproliferative neoplasias (MPNs) are recognized as two separate diseases. Thalassemia is a hemolytic disease caused by abnormal goblin genes, which results in the deficiency of globin chains. MPNs are clonal hematopoietic stem cell diseases characterized by the proliferation of multiple myeloid lineages. The coexistence of thalassemia and myeloproliferative neoplasia are rarely reported. We herein describe a case of a 24-year-old woman, previously diagnosed as β-thalassemia, with a lifelong history of thrombocytosis. She was subsequently diagnosed as low-risk essential thrombocythemia (ET), one of the MPNs. The patient was treated with folic acid supplementation and Iron-chelating therapy, without aspirin or cytoreductive therapy. Up to date, no thrombotic events or disease-related bleeding are happening to the patient, who remains in good health. Furthermore, we found three novel genes mutations EP300, CUX1, and FGFR3 after next-generation sequencing. We presume that the mutations of these genes in β-thalassemia might have an impact on the happening of ET and therefore need further investigations.

Keywords: β-thalassemia; case report; CUX1; EP300; myeloproliferative neoplasias (MPNs)

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Introduction

Beta-thalassemia (β-thalassemia) is characterized by abnormal synthesis of the hemoglobin subunit beta (hemoglobin beta chain), resulting in anemia in different degrees (1). Essential thrombocythemia (ET) is a kind of myeloproliferative neoplasias (MPNs), characterized by clonal proliferation of megakaryocytes in the bone marrow and high platelet counts in peripheral blood (2). The Janus kinase 2 gene (JAK2) mutation screening is a diagnostic strategy for ET recommended by the World Health Organization (WHO). The concomitancy of MPNs and β-thalassemia are exceptionally unusual. To date, only several cases of concurrent β-thalassemia and polycythemia vera (PV) were reported (3-5). ET in β-thalassaemic patients has not been previously described, as we have seen, it's the first time that coexistence of β-thalassemia and ET worldwide in clinical practice was reported. We present the following case in accordance with the CARE Guideline.

Case presentation

A 24-year-old female with a chipmunk face, presenting with slight weakness, previously was diagnosed as moderate β-thalassemia and underwent splenectomy in childhood. She was evaluated as a lifelong history of anemia and thrombocytosis. Data of genetic test was shown in *Table 1*, the mutant site of the beta-globin gene is in IVS-2-654. The hemogram of the patient showed moderate anemia with 3.61×10^{12} red cells per litre (normal female range, $3.8–5.1\times10^{12}$/L) and decreased hemoglobin level, 85 g/L (normal range, 115–150 g/L). The mean corpuscular volume was 78.6 fL (normal, 82–100 fL), and the mean hemoglobin mass was 23.7 pg (normal, 27–34 pg) in microcytosis. The density of white blood cells was about 9.6×10^9/L (normal, $3.5–9.5 \times10^9$/L) and the platelet

density was about 493×10^9/L (normal, 125–350 ×10^9/L). In the following days, her platelet count rose to 650×10^9/L. Erythrocyte sedimentation rate and C-reactive protein level were normal; no clinical infection was detected. Thus, it reminded us that the disease was possibly caused by myeloproliferative disorder. To confirm that, we performed a bone marrow biopsy. The result showed that megakaryocytes proliferated prominently, while neutrophil granulopoiesis and mild bone marrow reticulin fibrosis fluctuate at a normal level, as shown in *Figure 1*. Conventional cytogenetics revealed normal karyotype, and molecular analysis showed absence of BCR-ABL transcript and presence of JAK2^{V617F} mutation. It was diagnosed as the low-risk ET according to the 2016 WHO Diagnostic Criteria and the revised International Prognostic Score of Thrombosis for ET (IPSET-thrombosis). In addition, we found three novel genes mutations EP300 (c.1519A>G; p.S507G, 47.0%), CUX1 (c.328G>A; p.D110N, 51.1%), and FGFR3 (c.1738G>A; p.D580N, 47.0%) (*Table 2*) after screening 111 genes in next-generation sequencing.

The following detection showed that her hemoglobin maintained between 75 and 90 g/L, platelet counts ranged from 465×10^9/L to 750×10^9/L. Further detection showed the ferritin rose up to 3,501 μg/L, and the folic acid reduced to 1.03 μg/l. The patient was treated with folic acid supplementation and Iron-chelating therapy (deferasirox, 20 mg/kg). According to NCCN Guidelines, for the low-risk ET, it can just observation, does not need aspirin or cytoreductive therapy. Until now, there are no thrombotic events, or disease-related bleeding happening to the patient.

Table 1 Detection with liquid chip

Test object	Test result
α-globin gene deletion	Negative
α-globin gene mutation	Negative
β-globin gene mutation	IVS-2-654 heterozygous mutation

Detection 3 α- globin gene deletion: --SEA, -α3.7, -α4.2; Detection 3 α- globin gene mutation: WS122, QS125, CS142; Detection 17 β- globin gene mutation: CD41-42, IVS-2-654, CD17, -28, CD26, CD71-72, CD43, -29, Int, CD14-15, CD27-28, -32, -30, IVS-1-1, IVS-1-5, CD31, Cap.

Discussion

Mutation in IVS-2-654 was reported as a common characteristic of beta-thalassemia in Chinese (6). A research group investigated the status of thalassemia in Guangxi, China. The study showed that IVS-2-654 mutation accounted for 5.8% of β-thalassemia (7). Another study found Cd 41/42 (-TTCT) and IVS 2-654 (C-T) mutations were most prevalent in Chinese people (79.1%) (8).

The diagnosis of ET in a patient with β-thalassemia and splenectomy is a clinically challenge because some clinical features are overlapped between two diseases. Although the recognized complication of splenectomy is thrombocytosis, platelet number observed in reactive thrombocytosis generally is not as many as in primary thrombocytosis. From the viewpoint of increased thrombocytosis, bone marrow biopsy findings, and detection of JAK2^{V617F} mutation (approximately 57% occurrence rate) (9), we primarily diagnosed the possible disease as ET. The coexistence of ET and β-thalassemia in one patient is quite unusual. The potential relationship between these two diseases in the case is unknown. A study tried to detect the JAK2^{V617F} mutation in 20 patients with beta-thalassemia by RT-PCR , but the results were negative (10).

EP300 encodes a protein called p300, one of the three histone acetyltransferase (HAT) families. This protein plays an essential role in several fundamental biological processes, including cell growth and division, cell differentiation, cell cycle, and the DNA damage response. Mutations in the *EP300* prevent the gene from encoding a functional protein and contribute to the development of some cancers. Work by Gayther *et al.* provided the first evidence that *EP300* behaves as a classical tumour-suppressor gene, and showed that *EP300* was mutated in breast and colorectal cancers (11).

Table 2 Result after next-generation sequencing

Gene mutation	Transcript ID	Mutation site	Nucleotide	Amino acid	dbSNP	Mutation frequency
EP300	NM-001429	Exon6	c.1519A>G	p.S507G	Rs146242251	50.6%
FGFR3	NM-000142	Exon13	c.1738G>A	p.D580N		47.1%
CUX1	NM-181552	Exon5	c.328G>A	p.D110N		50.1%

Detection all exon regions of 111 genes with NGS, showing 3 types of gene mutation. NGS, Next generation sequencing.

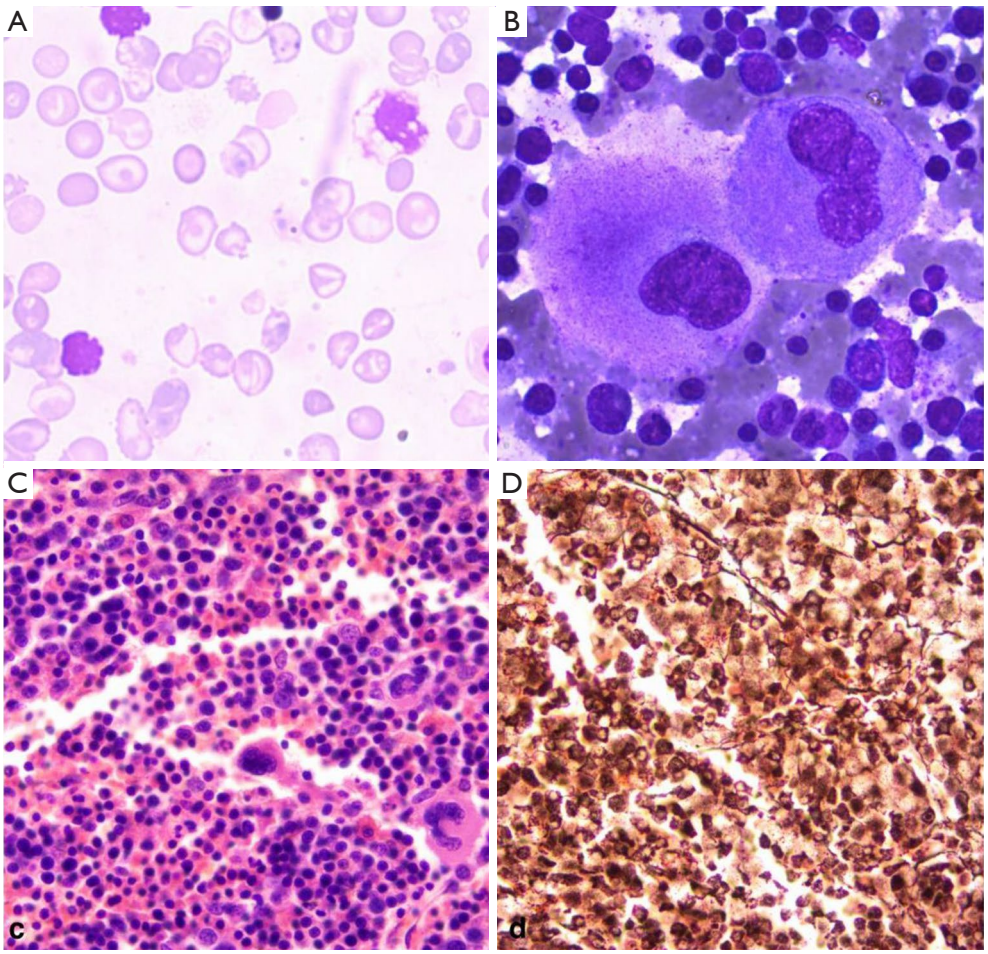

Figure 1 Morphological and histological features of this patient. (A) Bone marrow aspiration, beta-thalassemia showing anisopoikilocytosis, and basophilic stippling (H&E staining, ×1,000); (B) bone marrow aspiration, showing an increased number of mature, large megakaryocytes (H&E stain, ×1,000); (C) bone marrow biopsy, proliferation of megakaryocyte lineage (H&E staining, ×400); (D) bone marrow biopsy, grading of myelofibrosis, MF-I, with minimal increase in reticulin (reticular fiber staining, ×400).

More studies demonstrated that a series of solid tumors, including gastric, colorectal, hepatocellular and ovarian carcinomas detected the loss of heterozygosity (LOH) at the p300 or CBP (12-15). In our study, positive *EP300* mutation was detected in a β-thalassemia patient, which may contribute to the happening of MPNs. However, previous research showed that neither *CREEBP* nor *EP300* mutations were found in 56 MPNs patients after systematic screening (16).

CUX1 protein encoded by CUT-like home box 1 (*CUX1*) gene is a highly conserved hemeprotein, which acts as a transcriptional repressor, and plays an essential role in cell cycle progression, gene expression, and differentiation. It also affects tumorigenesis (17). A study showed that CUX1 expression was associated with the incidence of myelodysplastic syndrome (MDS). When the *CUX1* gene was knockdown in mice, it led to the exhaustion of hematopoietic stem cells, causing MDS (18). Only a few reports referred the CUX1 in MPNs; Thoennissen NH detected 15 post-MPN acute myeloid leukemia (AML) cases with aberrant chromosome 7 (-7 or 7q-), only one case with primary myelofibrosis (MF) had *CUX1* mutation (19). Another study investigated 408 MPNs samples for single gene mutation, (including *CUX1*) and chromosomal aberration. They found that the deletion of chromosome 7q was closely related to post-MPNs AML, but only one patient with aberration of chromosome 7q harbored a single gene deletion of *CUX1* (20).

Fibroblast growth factor receptor 3 (FGFR3) is one of the fibroblast growth factor receptors family. It plays a role in cell growth, proliferation, and angiogenesis. Nevertheless, its role in the development of MPN is still unknown.

There is no literature reporting β-thalassemia with *CUX1*, *EP300*, and *FGFR3* mutation and the potential roles they played in β-thalassemia.

In summary, this is the first report of the coexistence of β-thalassemia and ET. A timely diagnosis of an ET patient with β-thalassemia is important so that ET may be managed appropriately. Furthermore, we found three novel genes mutations, EP300, CUX1, and FGFR3, after next-generation sequencing. The acquired mutations of *CUX1*and *EP300* play roles in disease progression and transformation, especially the development of some cancers, which indicates that ET may have relationships with *CUX1* and *EP300* mutations. However, few studies have been reported. This single case, whether or not the mutations of *CUX1*, *EP300* and *FGFR3* in β-thalassemia are associated with the development of ET is still unconfirmed. More clinical data are required to identify the role of *CUX1*, *EP300* and *FGFR3* in the thrombocytosis, and the interaction mechanism between β-thalassemia and ET.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2020.01.48). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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