Myeloid Neoplasm with \textit{PCM1-PDGFRB} Transcript Responded to Low-Dose Imatinib: One Case Report with Literature Review

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Keywords
Myeloid/lymphoid neoplasms · Eosinophilia · Platelet-derived growth factor receptor beta rearrangement · Pericentriolar material 1 · RNA-seq

Abstract
Through an RNA-seq analysis of an adult patient with unclassifiable myelodysplastic/myeloproliferative neoplasms (MDS/MPN-U), we identified a rare \textit{PDGFRB} fusion partner gene, \textit{PCM1}. Conventional chromosome karyotype analysis showed abnormal clones of t(5;8)(q32;p22), and fluorescence in situ hybridization (FISH) confirmed rearrangement of the \textit{PDGFRB} gene. Reverse transcription PCR (RT-PCR) and Sanger sequencing further confirmed that exon 30 of the \textit{PCM1} gene was fused with exon 11 of \textit{PDGFRB} in frame, and the fusion event was accompanied by a 14 bp deletion of exon 11 of \textit{PDGFRB}. After low-dose imatinib treatment, the patient achieved complete molecular remission. This study not only broadens the understanding of myeloid/lymphoid neoplasms with \textit{PDGFRB} rearrangement but also reflects the vital role of RNA-seq in identifying \textit{PDGFRB} rearrangements.

Introduction
Chromosomal translocations involving band 5q31-33 result in rearrangement of the \textit{PDGFRB} gene, which is associated with diverse hematologic malignancies [1]. So far, more than 40 partner genes of \textit{PDGFRB} have been reported [2, 3], of which some partner genes (i.e., \textit{EBF1}, \textit{SSBP2}, \textit{TNIP1}, \textit{ZEB2}, \textit{ATF7IP}, and \textit{AGGF1}) were identified in patients with Ph-like acute lymphoblastic leukemia (Ph-like ALL) [4, 5]. Hematologic malignancies with \textit{PDGFRB} rearrangement are usually defined as “Myeloid/lymphoid neoplasms with eosinophilia and rearrangement of \textit{PDGFRB}, \textit{PDGFRB}, or \textit{FGFR1}, or with \textit{PCM1-JAK2}” within the World Health Organization category. Myeloid/lymphoid neoplasms with \textit{PDGFRB} rearrangement are often accompanied by eosinophilia and extramedullary involvement. Both the chronic phase and the blast phase are sensitive to tyrosine kinase inhibitors (TKIs) and rarely exhibit drug resistance [5, 6], so the diagnosis of \textit{PDGFRB} rearrangement is very important for the treatment and prognosis of these patients. The \textit{PCM1} gene at 8p22 encodes pericentriolar material 1 protein, which is a component of the centrosome satellite and...
contains multiple coiled-coil domains. It is essential for the accurate localization of several centrosomal proteins and the anchorage microtubules to the centrosome [7]. As a partner gene of JAK2, PCM1 has been reported many times in hematologic malignancies [8]. Here, we describe a patient with the PCM1/PDGFRB fusion gene and review the literature.

**Case Report**

A 28-year-old man presented in May 2021 with sternal pain and blood abnormalities. On physical examination, he presented spleen enlargement. The patient’s routine blood examination revealed hemoglobin 16 g/dL, platelet count 6.5 × 10⁴/μL, and white blood cell counts (WBCs) 4.253 × 10⁴/μL with neutrophils 3.598 × 10⁴/μL (84.5%), lymphocytes 1,130/μL (7.4%), monocytes 1,860/μL (3%), eosinophils 1,190/μL (2.8%), and basophils 370/μL (0.9%), no blasts. His abdominal ultrasound revealed an enlarged spleen measuring approximately 20.1 cm. A bone marrow (BM) smear showed an increased granulocytic proportion, a decrease in the erythroid line, no megakaryocytes, and <1% blasts (Fig. 1a). BM trephine biopsy showed increased cellularity with a prevalence of mature granulocytes, rarity of megakaryocytes, and grade MF-2 focal myelofibrosis (according to WHO grading myelofibrosis). Flow cytometry of BM cells revealed the decreased erythroid line, increased granulocytic line (87.58%), and highlighted eosinophil count (4.14%). Molecular tests were negative for major/minor BCR/ABL1 transcript as well as JAK2, MPL, and CALR mutations. The patient was initially diagnosed with unclassifiable myelodysplastic/myeloproliferative neoplasms based on clinical, morphological, and immunophenotypical features.

Chromosomal analysis of BM sample revealed a clonal translocation t(5;8)(q32;p22) in all 20 metaphases (Fig. 2a). We evaluated initial BM with next-generation sequencing (a panel of 175 genes, online suppl. Table 1; see www.karger.com/doi/10.1159/000524275 for all online suppl. material) to identify somatic mutations. The hotspot mutations involved CBL (p. C384R, mutation variant allele frequency, 3%) and CHD8 (p. Y1566* mutation, variant allele frequency, 1.8%). RNA-seq analysis of BM mononuclear cells revealed that exon 30 of PCM1 (NM_006197.4) fused to exon 11 of PDGFRB (NM_002609.4). To further verify the PDGFRB rearrangement, we performed fluorescence in situ hybridization (FISH) analysis using a PDGFRB dual-color fracture rearrangement probe (Vysis, Downers Grove, IL, USA) and showed detached signals in 95% (Fig. 2b). Agarose gel electrophoresis revealed a 374 bp reverse transcription PCR (RT-PCR) product (Fig. 2c), and Sanger sequencing confirmed the fusion between PCM1 exon 30 and PDGFRB exon 11 with a 14 bp deletion of exon 11 of PDGFRB (Fig. 2d). No reciprocal fusion transcript PDGFRB-PCM1 could be amplified. According to the 2016 WHO classification system, the patient facilitated a definitive diagnosis of myeloid/lymphoid neoplasms with PDGFRB rearrangement.

He was treated with hydroxyurea until the definite diagnosis was confirmed. After confirming the diagnosis, he was given imatinib therapy (100 mg/day). One month later, routine blood tests showed: WBCs 3,800/μL, hemoglobin 11.5 g/dL, and platelet count 6.0 × 10⁴/μL. After 3 months of treatment, he attained complete remission. Six months after admission, the patient’s chromosome karyotype returned to normal, and BM RNA-seq for minimal residual disease was negative. Abdominal ultrasound revealed that splenomegaly completely disappeared. The patient is being followed up regularly.

**Discussion**

The PCM1 protein plays an important role in centrosome assembly, microtubule anchoring, cell cycle division, cilia formation, and other processes [9]. The PDG-
FRB protein is members of the type III receptor tyrosine kinase family, which contains a split tyrosine kinase domain. The PDGFRB signaling pathways play an essential role in mitosis, cytoskeletal rearrangement, and chemotaxis [10]. If exon 30 of the PCM1 gene is fused directly to exon 11 of the PDGFRB gene, a stop codon would appear at position 7 after the fusion. In this case, exon 11 of the PDGFRB gene is lacking 14 bp, so the open reading frame is restored and fused to PCM1. It is expected to encode a chimeric protein containing 2,229 amino acids, including multiple coiled-coil domains encoded by PCM1 and tyrosine kinase domains encoded by PDGFRB. The coiled-coil domain is expected to induce ligand-independent dimerization of tyrosine kinases, resulting in activation of the kinase domain and continuous production of proliferation and antiapoptotic signals [11].

Myeloid/lymphoid neoplasms with PDGFRB rearrangement are heterogeneous. Extramedullary involvement is common, ranging from naive to maturity (e.g., myeloid sarcoma, lymphoblastic lymphoma, follicular lymphoma), usually accompanied by eosinophil infiltration [5]. Although eosinophilia is recurrent in this disease...
Myeloid Neoplasms Patient Expressing PCM1-PDGFRB

PDGFRB rearrangement is necessary for diagnosis, and the most common partner gene is ETV6 [5, 12]. PDGFRB rearrangement is often occult and may be missed by routine cytogenetic analysis [5]. However, in this case, conventional cytogenetic analysis revealed t(5;8)(q32;p22) in 20 of 20 metaphases. The patient went to the hospital due to sternum pain and had abnormally elevated WBCs (mainly naive and mature granulocytes), reduced platelets, eosinophilia, and splenomegaly, presenting the clinical features of myelodysplastic/myeloproliferative neoplasms. RNA-seq confirmed that the PCM1-PDGFRB fusion gene was positive, which was consistent with the abnormal clone of chromosome t(5;8)(q32;p22). FISH, RT-PCR, and Sanger sequencing further proved the rearrangement of PDGFRB. This case reflects the importance of RNA-seq to screen rare PDGFRB rearrangements in patients with eosinophilia, splenomegaly, and extramedullary invasion. However, the myeloid/lymphoid neoplasms with PDGFRB need to be diagnosed comprehensively, requiring a combination of FISH, RT-PCR, RNA-seq and other methods, each of which is not perfect. RNA-seq is often used as a supplement to conventional tests, for example, RNA-seq can identify the partner gene when FISH found PDGFRB rearrangement.

The rearrangement of the PDGFRB gene can lead to abnormal tyrosine kinase and overexpression of cytokine receptors. TKIs, such as imatinib and dasatinib, can inhibit the kinase activity of ABL, BCR-ABL, PDGFRB/B, and c-KIT. Clinical trials and case reports have confirmed that TKIs have a beneficial effect on patients with PDGFRB/rearranged MPNs. Through long-term follow-up, imatinib monotherapy can induce durable complete hematological and molecular remission in patients with myeloid/lymphoid neoplasms with PDGFRB/B rearrangement [6]. Several studies have shown that low-dose imatinib therapy can be as effective as high-dose imatinib therapy in the treatment of myeloid/lymphoid neoplasms with PDGFRB, especially in the chronic phase [13, 14]. The patient achieved complete molecular remission after 6 months of imatinib therapy. Previous literatures revealed 2 positive cases of PCM1-PDGFRB: one was clinically manifested as chronic myelomonocytic leukemia, and the other was initially diagnosed as myeloproliferative neoplasms (unclassified), both of whom achieved CR after TKI treatment and achieved long-term survival [15, 16]. Three patients with PCM1-PDGFRB rearrangements had different molecular and clinical characteristics, such as transcript type, clinical diagnosis, etc. (Table 1). This case is different in two points: (1) the PCM1-PDGFRB fusion transcript is a broken exon type fusion that the exon 11 of PDGFRB gene deletes 14 bp and (2) low-dose imatinib can also achieve a good response. The multiple types of PCM1-PDGFRB fusion gene may be associated with different clinical phenotype, however, all of these patients present with a chronic disease course. Myeloid/lymphoid neoplasms with PDGFRB rearrangement are very rare. Therefore, the case broadens the spectrum of this rare entity and highlights the importance of RNA-seq application in such patients.

### Statement of Ethics

This study protocol was reviewed and approved by the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences, approval number KT2020004-EC-2. The patient provided written informed consent to participate in this study and publish his case (including publication of images).

### Conflict of Interest Statement

The authors report no conflict of interest.
Funding Sources

This study was supported by the National Key Research and Development Program of China (2019YFC0840605).

Author Contributions

Conception and design: Z. Wang and Y.-C. Mi; development of methodology: Z. Wang, L. Wan, and Y.-C. Mi; data acquisition: Z. Wang, D. Lin, and Y.-C. Mi; analysis and interpretation of data: Z. Wang and Y.-C. Mi; writing, review, and/or revision of the manuscript: Z. Wang and Y.-C. Mi; administrative, technical, or material support: Z. Wang, L. Wan, C.-W. Li, and Z. Tian; study supervision: Y.-C. Mi.

Data Availability Statement

For the original data, please contact the corresponding author (ychmi@ihcams.ac.cn).

References

1. Alvarez RH, Kantarjian HM, Cortes JE. Biology of platelet-derived growth factor and its involvement in disease. Mayo Clin Proc. 2006 Sep;81(9):1241–57.
2. Arefi M, Garcia JL, Penarrubia MJ, Queizan JA, Hermosin L, Lopez-Corral L, et al. Incidence and clinical characteristics of myeloproliferative neoplasms displaying a PDGFRB rearrangement. Eur J Haematol. 2012 Jul;89(1):37–41.
3. Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. Am J Hematol. 2019 Oct;94(10):1149–67.
4. Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012 Aug;22(2):153–66.
5. Pozdnjakova O, Orazi A, Kelemen K, King R, Reichard KK, Craig FE, et al. Myeloid/lymphoid neoplasms associated with eosinophilia and rearrangements of PDGFRα, PDGFRβ, or FGFR1 or with PCM1-JAK2. Am J Clin Pathol. 2021 Feb;155(2):160–78.
6. Cheah CY, Burbury K, Apperley JF, Huget F, Pitini V, Gardembas M, et al. Patients with myeloid malignancies bearing PDGFRB fusion genes achieve durable long-term remissions with imatinib. Blood. 2014 Jun;123(23):3574–7.
7. Hames RS, Crookes RE, Straatman KR, Merdes A, Hayes MJ, Faragher AJ, et al. Dynamic recruitment of Nek2 kinase to the centrosome involves microtubules, PCM-1, and localized proteasomal degradation. Mol Biol Cell. 2005 Apr;16(4):1711–24.
8. Reiter A, Walz C, Watmore A, Schoch C, Blau I, Schlegelberger B, et al. The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2. Cancer Res. 2005 Apr;65(7):2662–7.
9. Hoang-Minh LB, Deleyrolle LP, Nakamura NS, Parker AK, Martuscello RT, Reynolds BA, et al. PCM1 depletion inhibits glioblastoma cell ciliogenesis and increases cell death and sensitivity to temozolomide. Transl Oncol. 2016 Oct;9(5):392–402.
10. Jones AV, Cross NC. Oncogenic derivatives of platelet-derived growth factor receptors. Cell Mol Life Sci. 2004 Dec;61(23):2912–23.
11. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev. 2008 May;22(10):1276–312.
12. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May;127(20):2391–405.
13. Di Giacomo D, Quintini M, Pierini V, Pelanera F, La Starza R, Gorello P, et al. Genomic and clinical findings in myeloid neoplasms with PDGFRB rearrangement. Ann Hematol. 2022 Feb;101(2):297–307.
14. Jawhar M, Naumann N, Schwaab J, Baurmann H, Casper J, Dang TA, et al. Imatinib in myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFRB in chronic or blast phase. Ann Hematol. 2017 Sep;96(9):1463–70.
15. Ghazaww M, Mehr V, Knut M, Brown L, Tapper W, Chase A, et al. A novel PCM1-PDGFRB fusion in a patient with a chronic myeloproliferative neoplasm and an ins(8;5). Acta Haematol. 2017;138(4):198–200.
16. Such E, Liquori A, Mora E, Marco-Ayala J, Avetisyan G, Regadera A, et al. RNA sequencing analysis for the identification of a PCM1-PDGFRB fusion gene responsive to imatinib. Acta Haematol. 2019;142(2):92–7.