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Detection of a *PDGFRB* fusion in refractory CMML without eosinophilia: A case for broad spectrum tumor profiling

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ABSTRACT

In this case report, we describe a refractory CMML case without eosinophilia harboring a *PDGFRB* re-arrangement leading to a favorable response with imatinib. We believe this case demonstrates the utility of broad spectrum genomic profiling in refractory CMML cases as an opportunity to uncover additional treatment options.

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Chronic Myelomonocytic Leukemia (CMML) with eosinophilia has been historically associated with rearrangements of *PDGFRA* or *B* [1,2]. Although this entity has now been reclassified as distinct from CMML by the World Health Organization (WHO) [3], clinicians reserve routine evaluation of *PDGFR* rearrangements in suspected CMML cases with eosinophilia because this genetic lesion predicts response to imatinib. A recent article by Cheah et al. report durable long-term remissions with the use of imatinib in a collection of patients with myeloid malignancies bearing *PDGFRB* fusions [4]. They confirm that the formation of *PDGFRB* fusion genes secondary to rearrangement of *PDGFRB* at 5q31-33 constitutively activates the *PDGFRB* receptor tyrosine kinase and are exquisitely sensitive to treatment with imatinib [1,5]. All patients in this report had eosinophilia at diagnosis which likely triggered the evaluation for a possible *PDGFRB* fusion. Given the limited armamentarium available for CMML, we perform broad spectrum genomic profiling to include analysis of *PDGFRB* in those cases that have failed standard therapies and have no clinical trial options. Using this strategy, we report a refractory CMML case for which a novel *PDGFRB* fusion was identified by next generation sequencing in a refractory CMML case without eosinophilia that achieved a favorable response with imatinib.

A 77-year-old woman was referred to our medical center for second opinion for refractory CMML-2. She had been incidentally found to have mild leukocytosis, anemia, and thrombocytosis on routine laboratory analysis. At diagnosis her white blood cell count (WBC) was $12 \times 10^9/L$, hemoglobin was 10.8 g/dL, and platelet

count was $420 \times 10^9/L$. Monocytes and eosinophils constituted 19% and 1% of total WBC, respectively. Bone marrow biopsy demonstrated hypercellularity, bone marrow dysplasia, and 14% blasts consistent with a diagnosis of CMML-2. Cytogenetics were 46,XX, del(7)(q22q32) and no other analysis to interrogate *PDGFR* rearrangements was performed at that time.

After two cycles of 5-azacitidine, the patient proceeded to undergo matched unrelated donor allogeneic hematopoietic stem cell transplantation but subsequently had graft failure and relapsed in a CMML-2 state. Post-transplant therapies included 5-azacitidine, induction chemotherapy, and decitabine for which she did not respond. Broad spectrum molecular profiling was performed using the clinically available FoundationOne[®]Heme assay which analyzes the complete coding DNA sequences of 405 genes, selected introns of 31 genes involved in rearrangements, and the RNA sequence of 265 commonly rearranged genes to identify gene fusions. Findings included mutations in *NRAS*, *RUNX1*, *ASXL1*, *IKZF1*, and a *SDPR*-*PDGFRB* rearrangement. *SDPR* is a gene that encodes a phospholipid-binding protein that has not been previously reported to partner with *PDGFRB* [4,6]. Given that *SDPR* is highly expressed in hematopoietic early progenitor cells (Fig. 1) [7,8], we hypothesized that the fusion of the *SDPR* promoter to the *PDGFRB* coding region would result in overexpression of *PDGFRB* as has been reported with other fusions. Her peripheral eosinophil count at the time of molecular profiling was 1.12 k/L and bone marrow biopsy was consistent with secondary AML with 36% blasts. The patient was started on 400 mg of imatinib and achieved a significant reduction in bone marrow blasts to 5%, consistent with a partial CR. Blood counts at time consisted of white blood cell count of 3 k/ μ L, platelets of 108 k/ μ L, hemoglobin of 8.5 g/dL and hematocrit of 25.9%. The duration of response using imatinib was approximately 4 months prior to disease progression

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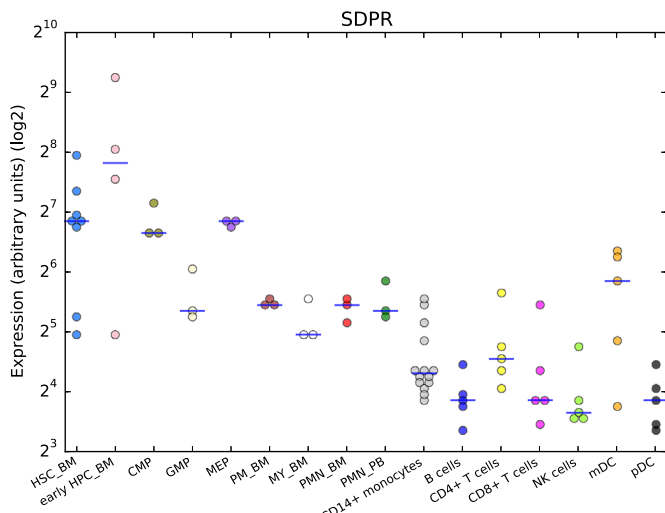


Fig. 1. SDPR expression for various hematopoietic cells. Each dot in the plot corresponds to the expression of SDPR in a microarray. Horizontal lines represent the median expression for each class of cells. Expression is given on y-axis on a log₂ scale. HSC_BM, Hematopoietic stem cells from bone marrow; early HPC_BM, Hematopoietic progenitor cells from bone marrow; CMP, Common myeloid progenitor cell; GMP, Granulocyte monocyte progenitors; MEP, Megakaryocyte-erythroid progenitor cell; PM_BM, Promyelocyte from bone marrow; MY_BM, Myelocyte from bone marrow; PMN_BM, Polymorphonuclear cells from bone marrow; PMN_PB, Polymorphonuclear cells from peripheral blood; CD14+ monocytes, CD14+ Monocytes; B cells, CD19+ B cells; CD4+ T cells, CD4+ T cells; CD8+ T cells, CD8+ T cells; NK cells, CD56+ natural killer cells; mDC, CD11c+ myeloid dendritic cells; pDC, CD123+ plasmacytoid dendritic cells.

after which the patient transitioned to best supportive care with hydroxyurea and expired 3.5 months later.

CMML remains a lethal malignancy with limited treatment options. The incidence of *PDGFRB* rearrangements in myeloproliferative neoplasms (MPNs) is low; a recent study reported only 1.8% of 556 patients evaluated [2]. While MPNs with *PDGFRB* rearrangements are phenotypically diverse, CMML with eosinophilia is a common morphologic diagnosis [2,4]. We report a case of a refractory CMML case *without* eosinophilia harboring a *PDGFRB*

rearrangement leading to a favorable response with imatinib. This case demonstrates the utility of broad spectrum genomic profiling in refractory CMML cases as an opportunity to uncover additional treatment options.

Contribution

G.C.B. and E.P. wrote the letter. Both authors gave final approval of the version to be published.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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