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PDGFR$^{\beta}$-Rearranged Myeloid Neoplasm with Marked Eosinophilia in a 37-Year-Old Man; And a Literature Review

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Conflict of interest: None declared

Patient: Male, 37
Final Diagnosis: PDGFR$^{\beta}$-rearranged myeloid neoplasm with eosinophilia
Symptoms: Night sweats • weight loss
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: PDGFR$^{\beta}$-positive myeloid neoplasms are rare. Marked leukocytosis (over 100×10^9/L) with marked eosinophilia (over 10%) has been rarely described in myeloid neoplasms associated with PDGFR$^{\beta}$ rearrangement.

Case report: We report a case of 37-year-old man with myeloid neoplasm associated with PDGFR$^{\beta}$ rearrangement who presented with marked eosinophilia of 13.3% and leukocytosis with WBC count of 189×10^9/L. He was found to have PDGFR$^{\beta}$ locus rearrangement at 5q32-33 by fluorescent *in situ* hybridization (FISH). He responded very well to low-dose imatinib therapy. To the best of our knowledge this degree of hypereosinophilia and leukocytosis in a young adult was reported only once previously. Using low dose therapy in treating this condition has rarely been reported and has not been clearly defined. Our case demonstrated that low dose imatinib therapy can be as effective as high dose imatinib therapy in treating PDGFR$^{\beta}$-positive myeloid neoplasms.

Conclusions: The patient presented with very high WBC and eosinophil count rarely reported in a young adult with PDGFR$^{\beta}$-rearranged myeloid neoplasm. The recognition of this rare presentation as a manifestation of PDGFR$^{\beta}$-gene translocation is important, and equally important that low-dose imatinib (100 mg/day) might have the same effect as higher dose imatinib (400 mg/day).

MeSH Keywords: Eosinophilia • Myeloid Neoplasm • PDGFR$^{\beta}$ Rearrangement

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/900623

Background

In 2008, a major revision of the World Health Organization (WHO) included a new molecular classification of myeloid malignancies; a subtype of myeloid neoplasms with eosinophilia (MLN-eo) and abnormalities of PDGFRa, PDGFRβ or FGFR1 were described [1]. The more recent 2016 revisions included a new provisional entity – myeloid neoplasm with t(8;9)(p22;q24.1) [2–4]. In particular, as we learned more about the heterogeneous of the clinical presentation of PDGFRβ-rearranged myeloproliferative neoplasms, genetic and molecular analysis becomes critical for appropriate diagnosis and management of eosinophilic myeloid neoplasms. Myeloid neoplasms and eosinophilia with rearrangement of PDGFRβ are more common among males, especially males aged 25 to 55 years. Elevated white blood cells (WBCs) with eosinophilia and splenomegaly are frequent features of this disease. A review of the literature found previously reported cases with marked leukocytosis and PDGFRβ-related eosinophilia were mainly in patients presenting at an older age (more than 50 years old) or very young patients. In this report, we present a case of a 37-year-old man with myeloid neoplasm associated with marked leukocytosis and eosinophilia with PDGFRβ locus rearrangement at 5q32-33 and complete hematologic response to low-dose imatinib. Recognizing this rare presentation with marked leukocytosis and eosinophilia secondary to PDGFRβ rearrangement is important, because effective treatments can be rendered.

Case report

A 37-year-old man was sent from his primary care provider to our emergency department (ED) for further management of abnormal blood work: leukocytosis (WBC 189×10^9/L, and absolute neutrophil count 149×10^9/L) with absolute eosinophilia. Complete blood count (CBC) showed red blood cell (RBC) count of 3.44×10^{12}/L, hemoglobin of 9.6 g/dL, hematocrit of 30.9%, MCV of 89.9 fL, and platelet count at 112×10^9/L. The peripheral blood eosinophils were 13.3% with an equivalent absolute eosinophil count (AEC) of 25×10^9/L, and monocytes were 4.5% with an absolute monocyte count (AMC) of 8.6×10^9/L. Patient history was significant for weight loss of 20–30 pounds in the previous three months, excessive night sweats, and family history of leukemia (his grandmother). Initial physical examination showed enlarged spleen with 3 cm below left costal margin. There was no lymphadenopathy or hepatomegaly. Further investigations revealed normal serum tryptase, IgE, and troponin. Laboratory results also showed elevated B12, ferritin of 858 ng/mL, LDH 3150, and slightly elevated uric acid and phosphorus. Peripheral blood smear (Figure 1A, 1B) showed marked leukocytosis with all stages of myeloid cells, eosinophilia and mild dysplasia in myeloid cells consistent with the diagnosis of atypical CML. No secondary etiology for eosinophilia was identified. Abdominal computerized tomography (CT) revealed an enlarged spleen with a span of 17.2 cm without any other abnormalities. The bone marrow (Figure 2A, 2B) was hypercellular (>95%) displaying immature and mature eosinophils up to 21% and left shift granulocytosis. Cytogenetic analysis showed normal karyotype 46,XY. There was no evidence of BCR-ABL fusion gene, nor PDGFRa or FGFR1 rearrangement by FISH, which were performed by the GenPath lab (NJ). Jak2V617F, MPL 515, CALR, and c-kit D816 V mutational analyses were negative. Negative cytogenetic, FISH, and RT-PCR studies did not support the diagnosis of chronic eosinophilic leukemia (CEL), chronic myeloid leukemia (BCR-ABL+ CML), myeloproliferative neoplasm with PDGFRβ rearrangement, myeloproliferative neoplasms (non-CML), or myelodysplastic syndrome (MDS). Subsequently, PDGFRβ FISH testing of bone

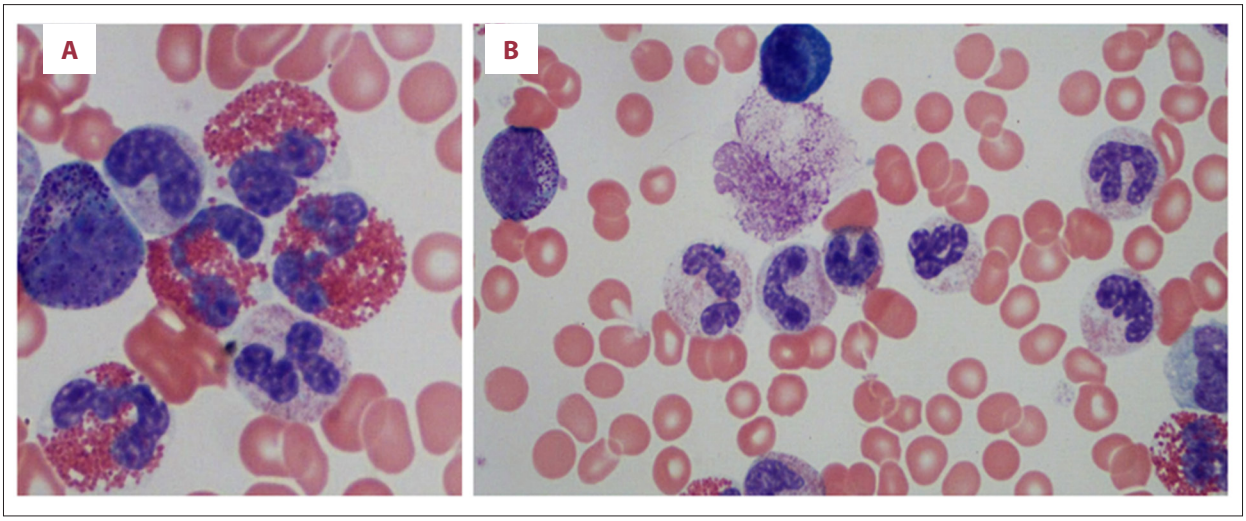

Figure 1. Wright's stain of peripheral blood cells shows increased eosinophil (**A**) and marked leukocytosis with granulocytes left shift and granulocytic dysplasia (**B**) (×100 magnification).

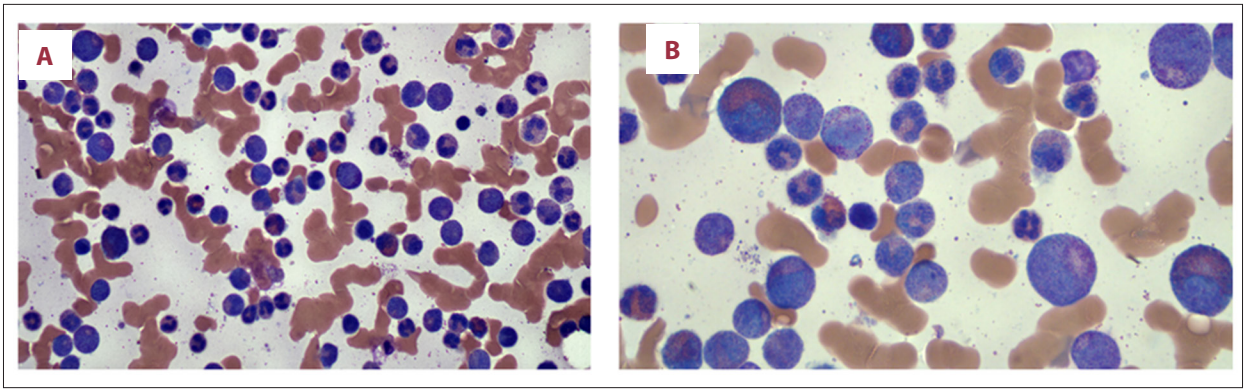

Figure 2. Bone marrow aspirate shows hypercelularity with maturing trilineage hematopoiesis (**A**) (×50 magnification) and prominent eosinophilia (**B**) (×100 magnification).

marrow cells was done by Vanderbilt University Medical Center using the probe developed by Vysis. It demonstrated abnormal rearrangement of the PDGFRβ locus at 5q32-33 in 81% of cells by FISH with no identified partner gene. Applying the current WHO-defined criteria (2015 update and 2016 revision) [3,4], the patient was diagnosed with myeloid neoplasm associated with eosinophilia with PDGFRβ abnormality.

While the aforementioned workup for myeloproliferative neoplasm (MPN) was in progress, given the patient's severe leukocytosis, he was started on hydroxyurea at 1 g/day, along with allopurinol for tumor lysis prevention. Because of persistently elevated WBC, his hydroxyurea was increased to 3 g/day and prednisone at1 mg/kg was added. Hematologic response was obtained two weeks after treatment was initiated: WBC 6.3×10^9/L with AEC 1.3×10^9/L. At this point, hydroxyurea was discontinued and imatinib 400 mg/day was initiated after PDGFRβ rearrangements was detected. Shortly thereafter (10 days), the patient developed leukopenia (WBC 2.5×10^9/L) and imatinib was temporary discontinued for approximately 14 days. Prednisone was slowly tapered over a five-week period and imatinib dose was reduced to 100 mg/day. The patient had close follow-up, with blood count monitoring on a weekly basis; medication dose adjustment was made based on blood counts as shown in Figure 3. The patient obtained sustained complete hematologic remission with resolution of leukocytosis and eosinophilia and normalization of spleen size in response to low-dose imatinib therapy for more seven months.

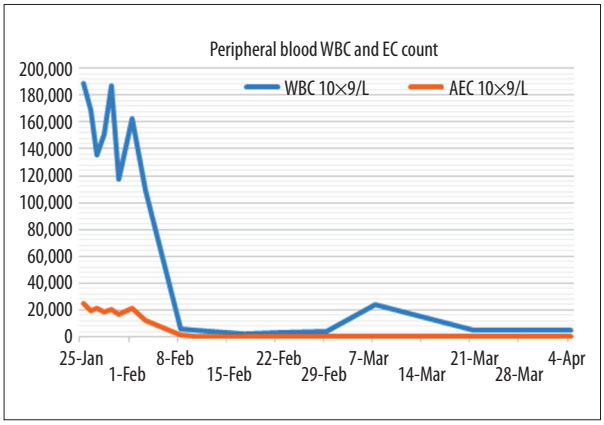

Figure 3. Peripheral blood white blood count (WBC) and absolute eosinophil count (AEC) response to therapy over 10-week duration.

Discussion

PDGFRβ positive eosinophilic disorders, as genotypically and phenotypically diverse neoplasms, are extremely rare. The discovery of this PDGFRβ rearrangement with molecular abnormality ETV6-PDGFRβ, t(5;12) (q33;p13) in 1994, prompted a more comprehensive molecular analysis [5]. Since that time, other translocations have been described and additional genes to PDGFRβ fusion transcript have been identified in the rearrangement of chromosome bands 5q31-q33 [6]. However, molecular identification of PDGFRβ fusion genes remains challenging due to the molecular heterogeneity of fusion partners and potential false-negative results by cytogenetic and/or FISH studies. Therefore, a combination of quantitative reverse transcriptase polymerase chain reaction (RT-PCR)-based approaches may be necessary to determine those rare genetic alterations [7–9].

"Myeloid neoplasms harboring PDGFRβ fusion" represent a small subset of myeloid neoplasms with eosinophilia that are included in the WHO classification. The revision to the WHO diagnostic criteria in 2008 based on molecular analysis included a different category of myeloid and lymphoid neoplasms with eosinophilia (MLN-eo) and abnormalities of PDGFRβ, PDGFRβ or FGFR1; there was no major change in the 2016 revision. Phenotypically, the most frequent morphologic presentations of myeloid neoplasms with abnormalities of PDGFRβ were: aCML, chronic myelomonocytic leukemia (CMML), myelofibrosis, acute leukemia, and chronic eosinophilic leukemia (CEL) [10–12] (Table 1). These spectrums of presentations, even

Table 1. Cases of myeloid neoplasm with eosinophilia and PDGFR^{b} abnormality.

Diagnosis	Age/Sex	WBC (×10^3/L)	Eosinophil (×10^3/L)	% Eosinophil	Reference
aCML	35 M	52,000	6,760	13	[36]
aCML	2/F	209,000	18,810	9	[23]
aCML	NA	NA	NA	NA	[21]
aCML	M	NA	NA	27	[35]
aCML	M	NA	NA	13	[35]
aCML	51/M	30,000	NA	5 to 25%	[25]
aCML	44/M	158,000	12,600	8	[19]
aCML	64/M	22,400	5,600	25	[14]
aCML	65/M	37,000	0	0	[14]
aCML	M	NA	NA	Eosinophilia	[35]
aCML	79/M	138,000	62,100	45	[51]
ALL and MPD	38/M	NA	Eosinophilia	NA	[46]
AML	36/M	3,100	NA	NA	[42]
AML relapsed-PDGFR$^{\beta}$ rearranged	NA	NA	Eosinophilia	NA	[31]
AML-M2	5/F	1,700	0	0	[14]
AML-M2	74/M	1,000	20	2	[14]
CEL	21/M	21,600	8,000	37	[39]
CEL	43/M	NA	NA	NA	[28]
CEL	70/M	55,900	17,900	32	[29]
CMML	29/M	173,000	NA	NA	[33]
CMML	35/F	386,000	15,400	4	[40]
CMML	54/M	NA	Eosinophilia	NA	[32]
CMML	NA	NA	NA	NA	[49]
CMML	17/M	NA	NA	NA	[30]
CMML.	57/M	181,000	7,240	4	[14]
CMML	NA	NA	NA	NA	[5]
CMML	29/M	59,200	NA	NA	[52]
CMML	77/M	12,000	120	1	[53]
JMML	18 months/M	25,400	2,790	11	[37]
JMML	18 months/M	NA	NA	NA	[47]
Leukocytosis	40/M	18,000	1,100	6.1	[28]
Leukocytosis	35/M	60,000	NA	NA	[28]
MDS	M	NA	NA	No Eosinophilia	[35]
MDS	63/F	1,000	20	NA	[14]

Table 1 continued. Cases of myeloid neoplasm with eosinophilia and PDGFR[b] abnormality.

Diagnosis	Age/Sex	WBC (×10³/L)	Eosinophil (×10³/L)	% Eosinophil	Reference
MDS	67/M	2,200	0	0	[14]
MDS/AML	M	NA	NA	8	[35]
MDS/AML	M	NA	NA	No eosinophilia	[35]
MDS/MPD	11 months/F	43.9	Marked esinophilia	NA	[34]
MMM	67/M	170,000	1700	1	[14]
MMM	67/M	5,700	57	1	[14]
MPN	32/M	80,000	7,820	10	[22]
MPN	50/M	52,000	4,800	9.2	[22]
MPN	68/M	41,000	1,640	4	[22]
MPN	6/M	9,300	4,100	44	[22]
MPN	M	NA	NA	NA	[35]
MPN	F	NA	NA	6	[35]
MPN	65/F	62,000	3,500	0.5	[43]
MPN	67/M	46,500	12,600	27	[43]
MPN	13 months/M	44,000	12,000	27	[43]
MPN	6/M	9300	4100	44	[43]
MPN	82/F	NA	NA	NA	[26]
MPN	8 patients – Median age 55 (21–78)	NA	NA	NA	[44]
MPN	34 weeks/M	37,600	5,600	14.8	[27]
MPN	4/M	15,600	3,900	25	[27]
MPN	26 patients with median age 50 (0.9–78)	Median 51,000 (4,000–138,000)	Median 3,500 (700–12,000)	NA	[15]
MPN	50/M	52,000	4,800	9.2	[24]
MPN	69/M	41,000	1,600	3.9	[24]
MPN	32/M	80,000	7,800	9.7	[24]
MPN	51/M	20,600	1,800	8.7	[24]
MPN	56/M	80,000	3,200	4	[24]
MPN	36/M	56,900	5,000	8.7	[24]
MPN	57/M	66,000	5,000	7.5	[24]
MPN	48/M	10,800	8,400	77	[24]
MPN	6/M	9,300	4,100	44	[24]
MPN	68/M	46,500	12,600	27	[24]

Table 1 continued. Cases of myeloid neoplasm with eosinophilia and PDGFR[b] abnormality.

Diagnosis	Age/Sex	WBC (×10³/L)	Eosinophil (×10³/L)	% Eosinophil	Reference
MPN	78/M	138,000	5,400	3.9	[24]
MPN	65/M	62,000	3,500	5.6	[24]
MPN	45/M	NA	1,100	NA	[41]
MPN	73/M	70,500	2,800	1.9	[41]
MPN	48/M	94,000	6,580	7	[20]
MPN	80/M	13,000	3,700	29	[48]
MPN	53/M	56,000	5,600	10	[48]
MPN	75/M	60,000	27,600	46	[48]
MPN	67/M	21,000	9,240	44	[8]
MPN	59/M	10,000	4,700	47	[8]
MPN	45/F	34,000	>6,800	20-40	[8]
Eos-MPN	40/M	19,000	1,800	9.4	[16]
MPN	45/M	15,100	4,700	31.1	[50]
MPN with thrombocytopenia	67/M	No leukocytosis	No	NA	[45]
MPN	F	NA	NA	2 to 16	[35]
MPN/CMMoL	42/M	64,900	3,245	5	[38]
Myeloma/MDS	74/M	1,100	22	2	[14]
MPN,34 cases (CMML, CEL, aCML)	Age 8–80 years	10.7–87,000	NA	9 to 42	[16]
RA	82/M	4,500	50	1.1	[14]

MPN – BCR-ABL negative myeloproliferative disorders; CMML – chronic myelogenous leukemia; CEL – chronic neutrophilic leukemia; MDS – myelodysplastic disease; AML – acute myelogenous leukemia; MMM – myelofibrosis, myeloid metaplasia; RA – refractory anemia.

though heterogeneous, have remarkable associations, particularly peripheral blood and bone marrow hypereosinophilia. The rarity of the condition requires us to know exactly how to diagnose this disease. After the secondary causes are excluded, the next step is to screen peripheral blood for the distinct driving molecular alterations of clonal eosinophilia. The most frequent recurrent aberration is the FIP1L1-PDGFR[a] fusion gene, detectable in 5–15% of all cases [13]. Molecular absence of FIP1L1-PDGFR[a] fusion gene indicates the need to evaluate for other rare abnormalities of PDGFR[β] given the critical therapeutic implications.

A comprehensive retrospective analysis of all cytogenetic studies performed at the Mayo Clinic over a 15-year period identified 25 cases of t(5;12) among 56,709 cytogenetic studies. The clinical and laboratory features were available for only 11 patients. Associated peripheral eosinophilia was found in three out of 11 patients, who were diagnosed as atypical chronic myelocytic disorder (aCMD), chronic myelomonocytic leukemia (CMMoL), and myelofibrosis with myelocytic metaplasia (MMM). Of note, all three patients were elderly (67, 64, and 57 years old). Two out of three patients presented with WBC >150×10^9/L; one out of three patients had 25% eosinophil count (diagnosed as aCMD); and all three patients displayed monocytosis (diagnosed as MMM, CMMoL) [14]. An updated and expended analysis of a cohort of 26 patients treated with imatinib was presented by Cheah et al. [15]. Most patients were males with median eosinophil count at diagnosis of 3,500×10^9/L that ranged from 0.7–12×10^9/L and PDGFR[β] fusion genes associated with translocations involving chromosome 5 confirmed on metaphase cytogenetic. Of note, all PDGFR[β] patients had 5q31-33 abnormalities and 78% had a t(5;12) translocation, emphasizing the need of cytogenetic analysis when clonal hypereosinophilia is suspected. Successful use of imatinib was demonstrated, with the most common starting dose of 400 mg. A 10-year overall survival rate of 90% was reported

and durable long-term remissions after a median follow-up of 10.2 years. As stated recently by Macaferri et al. [16], the optimal dose of imatinib in Eo-MPN with PDGRB rearrangement has not yet been clearly defined.

By reviewing the literature of case reports and case series, we observed that 400 mg/day imatinib was usually given and elicited durable hematologic and molecular remission. Although lower doses (100–300 mg/day) might be sufficient to achieve a molecular remission in some patients. However, this observation was based on a very small number of cases. More than 30 variants of PDGFRB fusion partners were identified and all appeared responsive to imatinib. The underlying detectable or undetectable fusion gene, patient's clinical features, prior therapy, and timing to start the therapy since diagnosis, all might influence the dose of imatinib. Thus, the optimal dose of imatinib that sustains a hematologic and molecular remission was not defined. Our case demonstrated a good hematologic response to low dose imatinib, suggesting that low dose can be equally as effective as high dose. The durability of response to imatinib obviates the need for allogeneic stem cell transplantation.

In addition to the t(5;12) translocation, several other cases with 5q31-5q33 translocations have been reported, with or without PDGFRβ involvement [17]. In one study, of the 34 patients with t(5;12) and PDGFRβ rearrangement, only five patients had eosinophils >20% and were diagnosed as CEL or CMML (one case with AML). All patients had a WBC <100×10^9/L and most of them were elderly. A remarkable feature of variant translocations involving 5q31-5q35, was a greater diversity of phenotype. The frequency of chromosomal changes in aCML was more variable, ranging from 20–88% [18]. To the best of our knowledge, as shown in Table 1, only one similar case of PDGFRβ-positive myeloid neoplasm with marked leukocytosis and eosinophilia in a young adult has been reported. The patient, a 44-year-old man had a significantly elevated WBC of 158×10^9/L with 8% eosinophil count [19]. Importantly, upon literature review, it was noticed that as opposed to young adults, pediatric and some elderly patients with PDGFRβ associated MPN are more likely to present with marked leukocytosis and eosinophilia (Table 1) [14,15,19–53]. However, our observation is still open to discussion given the rarity of these cases.

Conclusions

Our case report is relevant because of the rarity of marked leukocytosis and eosinophilia secondary to PDGFRβ rearrangement in young adults, with normal conventional cytogenetic analysis. To the best of our knowledge, this is the second case of PDGFRβ-positive myeloid neoplasm with marked eosinophilia in a young adult. Despite the rare frequency (<1%) of PDFRβ rearrangements, the rapid and durable response to imatinib highlights the importance of an accurate molecular workup in this entity. Importantly, the molecular pathophysiology and advances in standard therapy have changed the view of transplantation for this disease. Hence, we report the hematologic and molecular characteristics of a patient with PDGFRβ-associated marked eosinophilia. The challenge is to make an early diagnosis given the therapeutic implications of long-term observation of imatinib efficacy. One key unanswered question is the correlation of age and marked leukocytosis/eosinophilia; this is an area which deserves further investigation.

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