PDGFRB-rearranged T-lymphoblastic leukemia/lymphoma occurring with myeloid neoplasms: the missing link supporting a stem cell origin

The 2008 WHO classification scheme of hematolymphoid neoplasms recognizes a category of myeloid and lymphoid neoplasms (MLNs) with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB*, or *FGFR1*.[1] The postulated cell of origin for *PDGFRA* or *FGFR1*-rearranged diseases is a pluripotent progenitor capable of giving rise to myeloid neoplasms (myeloproliferative neoplasms and acute leukemias) and to lymphoblastic leukemia/lymphoma. Historically, *PDGFRB* translocations have not been associated with malignancies of the lymphoid lineage. Myeloid neoplasms with abnormalities of *PDGFRB* have been described to have hematologic features of chronic myelomonocytic leukemia (CMML), sometimes with eosinophilia, or as various other myeloproliferative and/or myelodysplastic neoplasms.[2] In recognition of this distinction, the classification scheme designates specific categories of "MLNs" with *PDGFRA* and *FGFR1* rearrangement, but omits the word "lymphoid" from the *PDGFRB*-associated entity.[1] To call attention to the rare occurrence of lymphoid and mixed MLNs with abnormalities of PDGFRB, we present the clinical and pathological details of 2 cases.

Case 1: MLN, eosinophilia, and RABEP1-PDGFRB *fusion.*

A 64-year old man with splenomegaly and diffuse lymphadenopathy (supraclavicular, axillary, mediastinal, paraaortic, retroperitoneal, pelvic) was diagnosed with T-lymphoblastic lymphoma (T-LBL) on a left cervical lymph node (LN) biopsy. A complete blood count (CBC) showed anemia, thrombocytopenia and mild eosinophilia, but no blasts (Table 1). A staging bone marrow (BM) biopsy was abnormal, demonstrating features of a myeloid neoplasm with mixed myeloproliferative/myelodysplastic features but was not involved by T-LBL (Figure 1). He was treated with a vincristine/prednisone-based induction protocol for T-LBL. Following identification of a t(5;17)(q33;p13) in BM and confirmation of *PDGFRB* rearrangement in the LN and BM samples, imatinib 400 mg/day was added, but stopped after 18 days due to drug intolerance. Based on prior literature, fluorescence *in situ* hybridization (FISH) studies were subsequently performed that confirmed *RABEP1* as the partner gene (Figure 1).[3,4] Within three weeks after discontinuing imatinib, the patient developed increases in WBC count (18.9 x 10^9/L) and eosinophil count (8.69 x 10^9/L) that could not be attributed to an infection or medication, suggesting progression. He ultimately chose hospice care.

Case 2: MLN, eosinophilia, and novel C6orf204-PDGFRB *fusion.*

A 38-year old man with diffuse lymphadenopathy and mild splenomegaly was diagnosed with T-LBL on an LN biopsy. A CBC was significant for eosinophilia without leukocytosis (Table 1). Despite chemotherapy (methotrexate, cytarabine, cyclophosphamide, vincristine, doxorubicin, dexamethasone), over the next year, the patient suffered 2 additional relapses of T-LBL with intervening re-induction chemotherapy followed by additional treatment for residual lymphadenopathy (etoposide, cyclophosphamide, methotrexate, and high-dose cytarabine). At the time of his second T-LBL relapse, a CBC demonstrated a leukocytosis (WBC: 14.8 x 10^9/L) with eosinophilia (4.53 x 10^9/L) and a concurrent BM biopsy was carried out that showed a myeloid neoplasm with myeloproliferative features (Figure 2) without involvement by T-LBL. Karyotyping showed a t(5;6)(q33-34;q23) and subsequent kinase-targeted next generation sequencing demonstrated a novel *C6orf204-PDGFRB* fusion.[5] The identical translocation was also found in the initial LN biopsy involved by T-LBL. The patient responded well to imatinib 400 mg/day for seven days plus 2 cycles of nelarabine prior to allogeneic peripheral blood stem cell transplant. At the time of transplantation, the patient was not in complete molecular remission, with cytogenetic and FISH evidence of residual *PDGFRB* translocation (t(5;6) in 11 of 20 metaphases and FISH positive for *PDGFRB* in 32.5% of nuclei). Subsequent to transplantation, the patient has remained in clinical complete remission for more than three years with no molecular cytogenetic evidence of T-LBL or *PDGFRB* translocation on numerous biopsies.

Myeloid neoplasms with *PDGFRB* rearrangement are considered a specific entity in the WHO classification and are included as a single category within myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFRA* and *FGFR1*. *PDGFRA* and *FGFR1*-related disorders appear to arise from a common pluripotent (myeloid/lymphoid) stem cell since the genetic abnormalities are present in both the myeloid and lymphoid components. However, the *PDGFRB* category is thought to arise from a myeloid stem cell.

PDGFRB-rearrangements have previously been associated with a diverse group of myeloid neoplasms with eosinophilia.[1] Overall, *PDGFRB*-related diseases are rare. A study of 556 patients with myeloproliferative neoplasms detected *PDGFRB* rearrangements in 10 patients (1.8%), all with eosinophilia and all generally showing a complete response to imatinib therapy.[6] After the identification of *ETV6(TEL)-PDGFRB* in cases of CMML with t(5;12)(q33;p12) in 1994,[7] over 20 *PDGFRB* fusion partners have emerged.

PDGFRB encodes the β chain of the cell surface receptor for platelet-derived growth factor (PDGF), a tyrosine kinase (TK) that activates signaling pathways important to cell growth and differentiation.[8,9] Mutated PDGF signaling components have been identified in a number of neoplasms. Notably, a transgenic mouse model directing the *ETV6-PDGFRB* fusion protein to lymphoid cells demonstrated the development of B- and T-LBLs.[10] This shows that *PDGFRB* rearrangements have the ability to contribute to the genesis of lymphoid neoplasms in mice,

Table 1. Features of patients at presentation with *PDGFRB*-rearranged neoplasms with a T-lymphoblastic component and eosinophilia.

Case	Age/ sex	Lymphoid neoplasm	WBC x 10^9/L	Eosinophil count x 10^9/L	Staging-BM	Myeloid component	BM cellularity (%)	BM karyotype*
1	64 M	T-LBL	4.2	0.48	No T-LBL	MDS/MPN-U†	70-80	6,XY,t(5;17)(q33;p13)[9]/46,XY[1]
2	38 M	T-LBL	10.4	2.3	No T-LBL	MPN-U‡	80-90	46,XY,t(5;6)(q22;q21)[10]/46,XY[10]

*†Myelodysplastic syndrome/myeloproliferative neoplasm, unclassifiable. ‡Myeloproliferative neoplasm, unclassifiable. *PDGFRB rearrangement was confirmed by FISH in LN and BM samples for both patients.*

despite the rarity of such an observation in humans. Indeed, the recurring kinase-activating *EBF1-PDGFRB* fusion was identified in up to 8% of patients with *BCR-ABL1*-like B-lymphoblastic leukemia (as defined by gene expression profiling)[11] and remission with TK inhibitor therapy was documented.[12]

Although T-LBL in conjunction with a myeloproliferative process is not unusual in cases with abnormalities of *FGFR1* and/or *PDGFRA*, it had not been well documented with *PDGFRB* translocations. A single report of acute myeloid leukemia with t(5;12)(q33;p12) in BM with a concurrent T-LBL in an LN biopsy suggested that MLNs with *PDGFRB* fusion existed, but cytogenetic studies were not performed on the LN to confirm this.[13] To our knowledge, the first reported MLN with documented *PDGFRB* in both processes revealed a novel *C6orf204-PDGFRB* fusion in a patient using a systematic kinase fusion screen that involved capture of the tyrosine kinase regions, followed by next generation sequencing of the capture products. While the technical aspects related to the fusion detection were published, the clinical and pathological details of that case are described in detail for the first time in the current series (Case 2).[5] The myeloproliferative component of Case 2 is unlike the CMML-like presentation of most *PDGFRB*-associated disease, or even the chronic eosinophilic leukemia-like presentations of most *PDGFRA*-associated disease, but most resembles the presentation of *FGFR1* translocations involving 8p11. Moreover, the specific translocation (5;6)(q33-34;q23) had not been previously published. Recently, at least 2 other

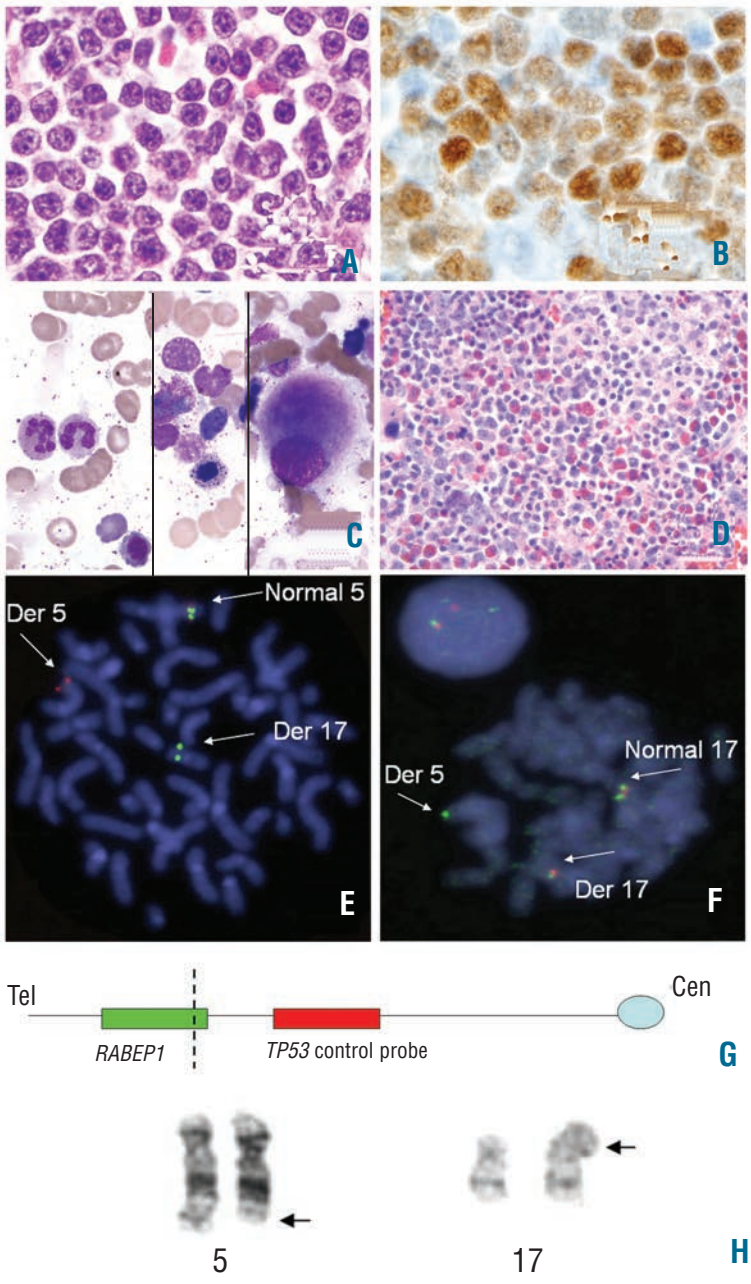

Figure 1. T-LBL and myeloid neoplasm in association with the *RABEP1-PDGFRB* fusion (Case 1). (A-B) High-magnification (1000x) images of T lymphoblasts, which by flow cytometry were positive for CD1a, CD2, CD3 (cytoplasmic), CD4 (dim, subset), CD5, CD7, CD8, CD10 (dim), CD38, and CD45 (*data not shown*), stained with H&E (A) and TdT immunohistochemistry (B). (C) Staging BM aspirate smear with abnormal granulocytic maturation (left), mild dyserythropoiesis (middle) and a subset of atypical, small megakaryocytes with hypolobated nuclei (right). Blasts were 1% of cellularity with an unremarkable myeloid phenotype (Wright stain, 1000x). (D) Hypercellular BM biopsy with megakaryocytic atypia, eosinophilia and histiocytic aggregates (H&E, 500x). Notably, immunostains (CD3, CD34, TdT) showed no evidence of T-LBL in the BM. Interstitial, atypical spindled mast cells highlighted by a tryptase stain represented 10% of cellularity (not shown), and allele-specific PCR for *KIT* D816V mutation was negative. (E) Metaphase fluorescence *in situ* hybridization (FISH) (T-LBL) with *PDGFRB* break apart probe showing split orange and green signals indicative of translocation (LPH031-A, CytoCell, Cambridge, UK). (F) Interphase FISH (T-LBL) with a probe encompassing the *RABEP1* locus (RP11-457I18, BlueGnome, Cambridge, UK) labeled in green and TP53 in orange showing split *RABEP1* and *TP53* signals (arrows) confirming disruption of *RABEP1* (17p13.2). FISH was negative for translocations of *PDGFRA* (*CHIC2* deletion probe, Abbott Molecular) and *FGFR1* (Abbott Molecular), not shown. (G) Schematic presentation of location of RP11-457I18 probe in relation to *RABEP1* locus (green) and adjacent *TP53* locus on chromosome 17. (H) Partial karyogram (BM) with balanced translocation at 5q33 and 17p13 (arrows), seen in both BM and LN samples.

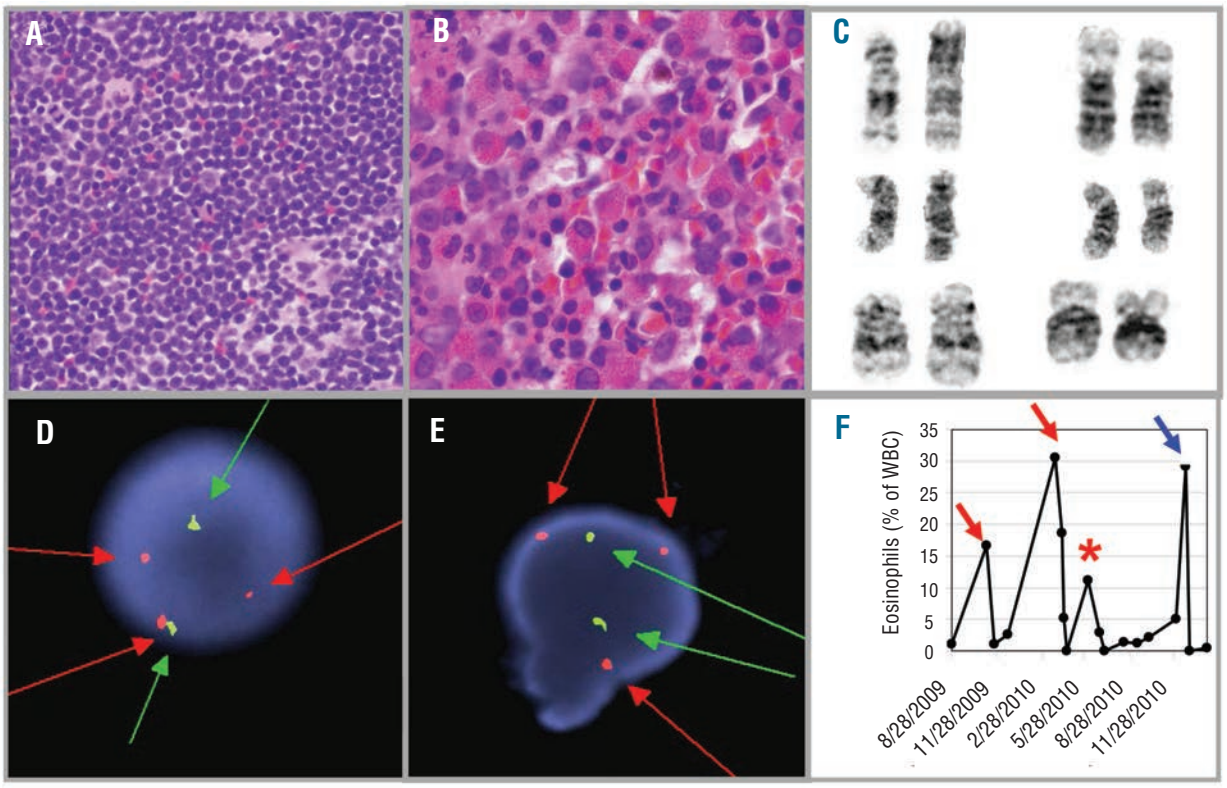

Figure 2. ***PDGFRB*-rearranged T-lymphoblastic lymphoma in a lymph node and myeloproliferative neoplasm with *PDGFRB* rearrangement in the bone marrow (Case 2).** (A) LN with T-LBL, positive for CD2, cytoplasmic CD3, CD4, CD38, CD43 and TdT and negative for surface CD3, CD10 and CD34 by flow cytometry (*data not shown)* (H&E, 400x). (B) Hypercellular bone marrow biopsy with eosinophilia, without morphological or immunophenotypic evidence of involvement by T-LBL (H&E, 1000x). (C) Bone marrow aspirate with 3 partial karyograms demonstrating a t(5;6) (chromosomes 5 on the left, chromosomes 6 on the right). (D) FISH of the bone marrow aspirate demonstrates 1 split red signal (*CSFIR-PDGFRB*) in 56% of cells, one normal red signal, and two normal green signals (D5S23), indicating a translocation involving *PDGFRB*. The partner gene was C6orf204, as previously reported.[5] (E) Fluorescence *in situ* hybridization (FISH) of the LN (performed retrospectively) demonstrates 1 split red signal (*CSFIR-PDGFRB*) in 87% of cells, one normal red signal, and two normal green signals (D5S23), indicating a translocation involving *PDGFRB* (Abbott Molecular). (F) Eosinophil percentage over time; red arrows, clinical recurrence of lymphoma; blue arrow, graft-*versus*-host disease; *stem cell transplant.

cases of *PDGFRB* rearranged lymphoid blast phase neoplasms have been reported as part of a larger series; however, no pathological details are available.[14]

The genetic abnormality t(5;17)(q33;p13) identified in both lymphoblastic and myeloproliferative components of Case 1 was discovered in a single reported case in which the novel *PDGFRB* translocation partner was identified as a gene encoding Rabaptin-5 by RACE-PCR. That patient had CMML and responded to imatinib therapy.[3,4] The *RABEP1-PDGFRB* fusion has not been previously described in a lymphoid neoplasm. The myeloid neoplasm evident in the BM in Case 1 was difficult to precisely classify until the cytogenetic and FISH results informed inclusion in the category of *PDGFRB*-rearranged neoplasms.

These cases serve to illustrate the dual lineage features of these types of fusions as well as the pathological spectrum of the myeloid components. From a diagnostic standpoint, recognition of an MLN when faced with only a T-lymphoblastic component requires a high index of suspicion (with attention to blood findings and staging marrow findings) and routine use of cytogenetics, since there are no reliable or specific morphological/immunophenotypic features. If an abnormality of 5q31-33 is detected by karyotyping, confirmatory FISH studies should be performed. In summary, this report documents the occurrence of MLNs with *PDGFRB* rearrangements and justifies the inclusion of *PDGFRB* in the list of genes associated with the WHO category of mixed MLNs.

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References

1. Bain BJ, Gilliland DG, Horny H-P, Vardiman JW. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1. In: Swerdlow S, Campo E, Harris N, et al. eds. WHO classification of tumours of haematopoietic and lymphoid tissues. Vol 1. 4th ed. 2008:68-9 pp. 70-3.
2. Holroyd A, Cross NC, Macdonald DH. The two faces of myeloproliferative neoplasms: Molecular events underlying lymphoid transformation. Leuk Res. 2011;35(10):1279-85.
3. Magnusson MK, Meade KE, Brown KE, Arthur DC, Krueger LA, Barrett AJ, et al. Rabaptin-5 is a novel fusion partner to platelet-derived growth factor beta receptor in chronic myelomonocytic leukemia. Blood. 2001;98(8):2518-25.
4. Magnusson MK, Meade KE, Nakamura R, Barrett J, Dunbar CE. Activity of STI571 in chronic myelomonocytic leukemia with a platelet-derived growth factor beta receptor fusion oncogene. Blood. 2002;100(3):1088-91.
5. Chmielecki J, Peifer M, Viale A, Hutchinson K, Giltnane J, Socci ND, et al. Systematic screen for tyrosine kinase rearrangements identifies a novel C6orf204-PDGFRB fusion in a patient with recurrent T-ALL and an associated myeloproliferative neoplasm. Genes Chromosomes Cancer. 2012;51(1):54-65.
6. 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;89(1):37-41.
7. Golub TR, Barker GF, Lovett M, Gilliland DG. Fusion of PDGF receptor beta to a novel ets-like gene, tel, in chronic myelomonocytic leukemia with t(5;12) chromosomal translocation. Cell. 1994;77(2):307-16.
8. Yu J, Ustach C, Kim HR. Platelet-derived growth factor signaling and human cancer. J Biochem Mol Biol. 2003;36(1):49-59.
9. Farooqi AA, Waseem S, Riaz AM, Dilawar BA, Mukhtar S, Minhaj S, et al. PDGF: The nuts and bolts of signalling toolbox. Tumour Biol. 2011;32(6):1057-70.
10. Tomasson MH, Williams IR, Hasserjian R, Udomsakdi C, McGrath SM, Schwaller J, et al. TEL/PDGFbetaR induces hematologic malignancies in mice that respond to a specific tyrosine kinase inhibitor. Blood. 1999;93(5):1707-14.
11. 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;22(2):153-66.
12. Weston BW, Hayden MA, Roberts KG, Bowyer S, Hsu J, Fedoriw G, et al. Tyrosine kinase inhibitor therapy induces remission in a patient with refractory EBF1-PDGFRB-positive acute lymphoblastic leukemia. J Clin Oncol. 2013;31(25):e413-6.
13. Chang H, Chuang WY, Sun CF, Barnard MR. Concurrent acute myeloid leukemia and T lymphoblastic lymphoma in a patient with rearranged PDGFRB genes. Diagn Pathol. 2012;7:19.
14. Metzgeroth G, Schwaab J, Gosenca D, Fabarius A, Haferlach C, Hochhaus A, et al. Long-term follow-up of treatment with imatinib in eosinophilia-associated myeloid/lymphoid neoplasms with PDGFR rearrangements in blast phase. Leukemia. 2013;27 (11):2254-6.