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

Running head: *PDGFRB*-rearranged stem cell neoplasms

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The 2008 WHO classification scheme of hematolymphoid neoplasms recognizes a category of myeloid and lymphoid neoplasms (MLNs) with eosinophilia and abnormalities of PDGFRα, PDGFRβ, or FGFR1. The postulated cell of origin for PDGFRα- or FGFR1-rearranged diseases is a pluripotent progenitor giving rise to either MLNs, or both, including myeloproliferative neoplasms and acute leukemias of myeloid, T- and B-lymphoid lineages. Historically, PDGFRβ translocations have not been associated with malignancies of the lymphoid lineage. Myeloid neoplasms with abnormalities of PDGFRβ have been described to have haematological features of chronic myelomonocytic leukemia (CMML), sometimes with eosinophilia, or as various other myeloproliferative and/or myelodysplastic neoplasms. In recognition of this distinction, the classification scheme designates specific categories of “MLNs” with PDGFRα and FGFR1 rearrangement, but omits the word “lymphoid” from the PDGFRβ-associated entity. To call attention to the rare occurrence of lymphoid and mixed MLNs with abnormalities of PDGFRβ, we present the clinicopathologic details of two cases.

Case 1: MLN, eosinophilia, and RABEP1-PDGFRβ fusion
A 64 year-old man with splenomegaly and diffuse lymphadenopathy (supraclavicular, axillary, mediastinal, para-aortic, retroperitoneal, pelvic) was diagnosed with T-lymphoblastic lymphoma (T-LBL) on 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 PDGFRβ rearrangement in the LN and BM samples, imatinib 400mg/day was added, but stopped after 18 days due to drug intolerance. Based on prior literature, FISH studies were subsequently performed that confirmed RABEP1 as the partner gene (Figure 1). Within 3 weeks after discontinuing imatinib, the patient developed increases in the WBC count (18.9 x 10⁹/L) and eosinophil count (8.69 x 10⁹/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-PDGFRβ fusion
A 38 year-old man with splenomegaly and diffuse lymphadenopathy (supraclavicular, axillary, mediastinal, para-aortic, retroperitoneal, pelvic) was diagnosed with T-LBL on 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 10⁹/L)
with eosinophilia (4.53 x 10^9/L) and a concurrent BM biopsy was done 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.\textsuperscript{5} The identical translocation was also found in the initial T-LBL. The patient responded well to imatinib 400mg/day for 7 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 11/20 metaphases and FISH positive for PDGFRB in 32.5% of nuclei). Subsequent to transplantation, the patient has remained in clinical complete remission after transplantation for more than three years with no molecular cytogenetic evidence of T-LBL or PDGFRB translocation on numerous biopsies.

Discussion

Myeloid neoplasms with PDGFRB rearrangement are considered a specific entity in the WHO classification and are included in a single category alongside 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.\textsuperscript{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 generally showing complete response to imatinib therapy.\textsuperscript{6} After the identification of ETV6(TEL)-PDGFRB in cases of CMML with t(5;12)(q33;p12) in 1994,\textsuperscript{7} over 20 PDGFRB fusion partners have emerged.

PDGFRB encodes the beta chain of the cell surface receptor for platelet derived growth factor (PDGF), a tyrosine kinase (TK) which activates signaling pathways important to cell growth and differentiation.\textsuperscript{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.\textsuperscript{10} This demonstrates that PDGFRB rearrangements have the ability to contribute to the genesis of lymphoid neoplasms in mice, 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)\textsuperscript{11} and remission with TK inhibitor therapy was documented.\textsuperscript{12}
Although T-LBL in conjunction with a myeloproliferative process is not unusual in cases with abnormalities of FGFR1 and/or PDGFRα, 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 concurrent T-LBL in a LN biopsy suggested that MLNs with PDGFRB fusion existed, but cytogenetic studies were not performed on LN to confirm this. 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 clinicopathologic details of that case are described in detail for the first time in the current series (case 2). 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 PDGFRα-associated disease, but most resembles the presentation of FGFR translocations involving 8p11. Moreover, the specific translocation (5;6)(q33-34;q23) had not been previously published. Recently, at least 2 other cases of PDGFRB rearranged lymphoid blast phase neoplasms have been reported as part of a larger series; however, pathologic details are lacking.

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. 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 pathologic spectrum of the myeloid components. From a diagnostic standpoint, recognition of a 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 morphologic/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.
Authorship and Disclosures:

All authors were involved in drafting and editing substantial portions of the introduction and discussion. Case descriptions and figures were contributed by SLO, AGJ, ASM, JG, SS, MAS, AY, DH, MJ and EDH. There are no financial disclosures or conflicts of interest to report. Permission from the Institutional Review Boards was given for each collaborating institution.

References:


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

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Lymphoid Neoplasm</th>
<th>WBC x 10^9/L</th>
<th>Eosinophil Count x 10^9/L</th>
<th>Staging BM</th>
<th>Myeloid Component</th>
<th>BM Cellularity (%)</th>
<th>BM Karyotype‡</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>64 M</td>
<td>T-LBL</td>
<td>4.2</td>
<td>0.48</td>
<td>No T-LBL</td>
<td>MDS/MPN-U†</td>
<td>70-80</td>
<td>46,XY,t(5;17)(q33;p13)[9]/46,XY[1]</td>
</tr>
<tr>
<td>2</td>
<td>38 M</td>
<td>T-LBL</td>
<td>10.4</td>
<td>2.3</td>
<td>No T-LBL</td>
<td>MPN-U‡</td>
<td>80-90</td>
<td>46,XY,t(5;6)(q22;q21)[10]/46,XY[10]</td>
</tr>
</tbody>
</table>

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

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 megalakocytic 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 pictured), and allele-specific PCR for KIT D816V mutation was negative. (E) Metaphase 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 (RP11-457118, 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 PDGFRB (CHIC2 deletion probe, Abbott Molecular) and FGFR1 (Abbott Molecular), not pictured. (G) Schematic showing location of RP11-457118 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 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 morphologic or immunophenotypic evidence of involvement by T-LBL(H&E, 1000x). (C) Bone marrow aspirate 3 partial karyograms demonstrating a t(5;6) (chromosomes 5 on the left chromosomes 6 on the right). (D) FISH of 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) FISH of 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.