Hematolymphoid Neoplasms Associated With Rearrangements of PDGFRA, PDGFRB, and FGFR1

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Key Words: PDGFRA; PDGFRB; FGFR1; Eosinophilia; Tyrosine kinases

ABSTRACT

Objectives: This session of the 2013 Society for Hematopathology/European Association for Haematopathology Workshop was dedicated to tumors currently included in the World Health Organization (WHO) classification category of myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, and FGFR1.

Methods: We use the cases submitted to this session to review the clinicopathologic and genetic spectrum of these neoplasms, methods for their diagnosis, and issues related to the WHO classification terminology. Since many patients with these neoplasms have eosinophilia, we also briefly mention other causes of clonal eosinophilia.

Results: These neoplasms are the result of gene fusions involving any one of these three tyrosine kinase genes. A variety of gene fusion partners have been found consistently for each category of neoplasms. Diagnoses of these neoplasms are often highly challenging and require a high index of suspicion and a multidisciplinary approach.

Conclusions: Early recognition of these neoplasms is important because patients with neoplasms associated with PDGFRA or PDGFRB fusions often respond to tyrosine kinase inhibitor therapy, whereas patients with neoplasms associated with FGFR1 fusions usually do not respond.

This session of the workshop focused on the clinicopathologic, cytogenetic, and molecular features of the group of neoplasms defined in the 2008 World Health Organization (WHO) classification under the umbrella term “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, and FGFR1.” These rare neoplasms share in common a characteristic fusion gene encoding an aberrant tyrosine kinase and are frequently associated with peripheral blood or tissue eosinophilia. Each of these neoplasms is thought to a stem cell disorder in which the neoplastic cells share an underlying molecular abnormality, but affected patients often develop bilineal disease in which one component is lymphoid and the other is myeloid. These different disease components can manifest simultaneously or sequentially.

Platelet-derived growth factors (PDGFs) represent a family of mitogens that include five dimeric forms derived upon completion of this activity you will be able to:

• define the clinicopathologic and genetic features of disorders in the World Health Organization category of myeloid and lymphoid neoplasms with eosinophilia and rearrangements of PDGFRA, PDGFRB, or FGFR1.
• identify the hematologic and bone marrow features that should raise the suspicion for this category of neoplasms.
• list the diagnostic testing available to diagnose this category of neoplasms.

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from pairs of A, B, C, and D peptide chains: PDGF-AA, PDGF-AB, PDGF-BB, PDGF-CC, and PDGF-DD. PDGF dimers activate two specific receptors: PDGFRA, which binds the A, B, and C chains, and PDGFRB, which binds the B and D chains. PDGF receptors (PDGFRs) A and B are transmembrane glycoproteins that belong to the type III receptor tyrosine kinase family. This family also includes KIT, Flt3, and c-Fms.

Persistent high levels of PDGFs and PDGFRs have been detected in various cancers, including gliomas, Kaposi sarcoma, gastrointestinal stromal tumor, prostate and pancreatic carcinoma, and other tumors. Fibroblast growth factor receptor 1 is a member of the fibroblast growth factor receptor (FGFR) family of receptor tyrosine kinases that plays a role in embryonic development and wound repair by controlling growth, differentiation, and cell migration. The FGFR family is composed of 18 ligands that exert their actions through four highly conserved transmembrane tyrosine kinase receptors (FGFR1, FGFR2, FGFR3, and FGFR4). Activation of FGFR1 leads to downstream signaling via the PI3K/AKT and RAS/MAPK pathways, which are central to growth, survival migration, and angiogenesis in many cancers. Dysregulation of FGFR family signaling due to various mechanisms, such as amplification, translocation, and point mutations, has been described in a broad range of tumor types, including various sarcomas, plasma cell myeloma, and cancers of the breast, prostate, urinary bladder, lung, and endometrium.

### Overview of Submitted Cases

A total of 22 cases were submitted to this session. These cases included nine neoplasms associated with abnormalities of PDGFRA, three with abnormalities of PDGFRB, and seven with abnormalities of FGFR1. In addition, three cases were from patients with neoplasms that had clinical and pathologic features similar to hematolymphoid neoplasms associated with PDGFRA, PDGFRB, or FGFR1 but lacked these genetic abnormalities.

### Is the Current Terminology for These Neoplasms Adequate?

It is our opinion that the current terminology proposed by the 2008 WHO classification for this group of neoplasms has several drawbacks. First, although these neoplasms often share some unusual features, the grouping of these neoplasms in the 2008 WHO classification understates the fact that these neoplasms are biologically distinct and that they have unique clinical and pathologic characteristics.
these differences are associated with different therapies. Although patients with neoplasms associated with gene fusions involving PDGFRα or PDGFRβ often respond to tyrosine kinase therapy, patients with neoplasms associated with FGFR1 translocations usually do not respond.

Second, the designation “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ, and FGFR1” is not entirely accurate because “abnormality” conveys a spectrum of molecular or genetic changes beyond gene fusions or translocations, such as mutations or amplifications. The three diseases currently included in the WHO category, however, are limited to those associated with specific gene fusions as a result of translocations or interstitial deletion.

Third, we believe the designation “myeloid and lymphoid neoplasms with eosinophilia and abnormalities of PDGFRα, PDGFRβ, and FGFR1” is best considered an umbrella term that allows the inclusion of these rare diseases into an overall conceptual framework. However, we have observed other pathologists use this designation as a diagnosis in pathology reports, with resulting clinicians’ dissatisfaction. Perhaps this is not surprising since other headers of sections in the WHO classification can be used as a diagnosis. Nevertheless, we believe that the authors of this portion of the WHO classification did not foresee this term being used as a diagnosis since the designation is vague and incomplete.

Last, the variable manifestations of neoplasms associated with PDGFRα, PDGFRβ, and FGFR1 gene fusions suggest a need for nomenclature that incorporates the clinicopathologic features as well as the spectrum of genetic or molecular changes that may identify targets for therapy. Some examples of the terminology used by case submitters and the review panel to capture the complexity of these neoplasms include “myeloid and lymphoid neoplasm with FLIP1L1-PDGFRα rearrangement, presenting with T-lymphoblastic lymphoma and myeloproliferative neoplasm with eosinophilia” (case 265); “myeloid neoplasm with FLIP1L1-PDGFRα rearrangement, presenting as chronic eosinophilic leukemia (CEL)” (case 111); or “T-lymphoblastic lymphoma and myeloid neoplasm with eosinophilia associated with the RABEP1/PDGFRα fusion oncogene” (case 12).

**PDGFRα-Associated Hematolymphoid Neoplasms**

What Are the Clinicopathologic Features of Hematolymphoid Neoplasms Associated With PDGFRα Fusions?

Cools and colleagues identified the FIP1-like 1 (FIP1L1)–PDGFRα fusion gene in nine of 16 patients who were initially diagnosed with idiopathic hypereosinophilia or CEL. Since these patients responded to imatinib, Cools et al. played an important role in redefining the diagnostic and therapeutic approach to patients with eosinophilia.

Most patients with hematolymphoid neoplasms associated with FIP1L1-PDGFRα fusion are men, with a peak of incidence during the fourth decade. Pediatric cases are extremely rare, with only two cases reported to date. The disease is usually diagnosed at presentation as CEL, acute myeloid leukemia (AML), or acute lymphoblastic leukemia. Patients often have splenomegaly (~60%), anemia, thrombocytopenia, and neutropenia. Around 70% of patients have eosinophilia. Serum levels of tryptase and vitamin B₁₂ are increased in most patients. Symptoms related to release of eosinophilic granules occur, commonly skin rash and erythema and less frequently pulmonary, gastrointestinal tract, and/or cardiac manifestations. Endomyocardial fibrosis and restrictive cardiomyopathy may occur in patients who have this disease for a prolonged time interval.

In patients with CEL, the bone marrow (BM) is usually hypercellular with increased eosinophils, including eosinophilic precursors. Mast cells can be increased, but they are usually scattered and can express CD25. Increased reticulin fibers are frequently present. Erythropoiesis and megakaryopoiesis are usually normal. Dysplastic features and an excess of blasts are unusual.

The most common fusion gene partner for PDGFRα is FIP1L1. It has been estimated that around 10% to 20% of the patients with unexplained eosinophilia in developed countries carry the FIP1L1-PDGFRα fusion. The fusion gene is detected in eosinophils, neutrophils, mast cells, monocytes, and T and B lymphocytes, suggesting that the underlying genetic aberration occurs at the pluripotent hematopoietic progenitor cell stage.

What Are the Genetic Features and Consequences of FIP1L1-PDGFRα?

FIP1L1-PDGFRα was the first description of a gain-of-function fusion gene resulting from an interstitial deletion instead of a chromosomal translocation. In effect, the CHIC1 gene is lost as a consequence of an interstitial deletion of 800 kb (0.8 Mb) at chromosome 4q12, resulting in the fusion of the 5′ end of FIP1L1 with the 3′ end of PDGFRα. The breakpoints are variable in both genes and extend over a region of 40 kb in FIP1L1 and over a small region of exon 12 in PDGFRα. In contrast with other novel chimeric proteins, the activation of the PDGFRα kinase domain is not a consequence of oligomerization but instead the result of deletion of the inhibitory juxtamembrane domain, which normally keeps the kinase domain inactive. In addition, the chimeric protein seems to be stable, resistant to ubiquitination and proteosomal degradation, and its increased stability...
promotes cell proliferation.\textsuperscript{17} It has been shown in human CD34+ cells that expression of FIP1L1-PDGFRA induces cell proliferation and differentiation toward eosinophilic lineage in the absence of cytokines; these effects are mediated by the activation of nuclear factor (NF)-κB and STAT5.\textsuperscript{18}

Although FIP1L1 is the most common partner of PDGFRA, five other gene partners have been identified, including BCR, ETV6, KIF5B, STRN, and CDK5RAP2 (reviewed by Gotlib and Cools).\textsuperscript{14} The clinicopathologic features of cases with PDGFRA aberrations other than FIP1L1 have been reported in a very small number of cases and are apparently indistinguishable from those with FIP1L1-PDGFRA.\textsuperscript{19}

Activating PDGFRA point mutations have been described in a minority of patients with eosinophilia.\textsuperscript{20} Others have shown that some of these mutations result in phosphorylation of PDGFRA, STAT5, and clonogenic cell proliferation that responds to imatinib therapy.\textsuperscript{20}

What Are the Therapeutic Implications of Identifying FIP1L1-PDGFRA in Patients With a Hematolymphoid Neoplasm?

It appears that almost all patients with the FIP1L1-PDGFRA fusion are sensitive to tyrosine kinase inhibitors. Therefore, patients with hematolymphoid neoplasms associated with FIP1L1-PDGFRA should be treated with imatinib. Primary or secondary resistance to imatinib is unusual in these patients. However, the sensitivity to tyrosine kinase inhibitor rearrangements of PDGFRA with other gene partners or other abnormalities is uncertain at this time. Similarly, additional adjuvant therapy may be needed when patients have disease in the blast phase.

What Is the Most Reliable Technique to Diagnose Rearrangements of PDGFRA?

- The interstitial deletion of 800 kb that leads to FIP1L1-PDGFRA fusion is undetectable by conventional cytogenetics, a technique with a level of resolution estimated at 10 to 15 Mb. Therefore, conventional cytogenetics often shows a diploid karyotype in these cases. Routine detection of the 800-kb interstitial deletion in clinical practice is best achieved by interphase or metaphase fluorescence in situ hybridization (FISH) (Image 1). Since the CHIC2 gene is located in the deleted region, the FISH test to detect FIP1L1-PDGFRA gene fusion is often referred to as “CHIC2 deletion.” The fusion can be detected in peripheral blood, BM smears, or involved tissues. Similarly, the 800-kb deletion can be detected by array comparative genomic hybridization or single-nucleotide polymorphism arrays that, compared with conventional cytogenetics, have a much greater resolution for detecting gains or losses of chromosomal segments.\textsuperscript{21} The fusion gene also can be detected by nested reverse transcriptase polymerase chain reaction (RT-PCR).\textsuperscript{19} A screening method using a quantitative RT-PCR targeting the 3’ region of PDGFRA to detect increased levels of PDGFRA expression as a potential indicator of underlying fusion or overexpression of PDGFRA has been developed.\textsuperscript{19,22} Quantitative real-time PCR is an excellent method to monitor minimal residual disease.

- As stated above, rare patients with PDGFRA fusions arise as a result of fusions with other gene partners, rather than interstitial deletion of CHIC2. In these cases, chromosomal translocations involving the partner gene loci (BCR, ETV6, KIF5B, STRN, and CDK5RAP2) can be detected by conventional cytogenetics. The use of break-apart probes with FISH also can detect the presence of PDGFRA rearrangement but does not identify the gene partner. The use of RT-PCR methods using specific primer sets also can be used.

Workshop Cases of PDGFRA-Associated Hematolymphoid Neoplasms

A total of nine cases of hematolymphoid neoplasm associated with PDGFRA were submitted. The gene partner of
**Table 2**
Clinicopathologic, Cytogenetic, and Outcomes of Patients With PDGFRA, PDGFRB, and FGFR1 Rearrangements

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PDGFRA (n = 9)</th>
<th>PDGFRB (n = 3)</th>
<th>FGFR1 (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female, No.</td>
<td>8/1</td>
<td>3/0</td>
<td>4/3</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B symptoms</td>
<td>4/8</td>
<td>1/1</td>
<td>2/2</td>
</tr>
<tr>
<td>Others</td>
<td>3/8</td>
<td>1/1</td>
<td></td>
</tr>
<tr>
<td>Humoral</td>
<td>3/8</td>
<td>0/3</td>
<td>0/2</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilia &gt;1.5 × 10⁹/L</td>
<td>5/8</td>
<td>1/3</td>
<td>4/7</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>3/9</td>
<td>2/2</td>
<td>1/1</td>
</tr>
<tr>
<td>Nodal or extranodal</td>
<td>5/9</td>
<td>3/3</td>
<td>6/6</td>
</tr>
<tr>
<td>Nodal</td>
<td>3/9</td>
<td>2/3</td>
<td></td>
</tr>
<tr>
<td>T-LBL</td>
<td>1/9</td>
<td>3/3</td>
<td>6/6 (2/6 lymphoid/myeloid)</td>
</tr>
<tr>
<td>Extranodal</td>
<td>3/9 (paraspinal); 2/9 (myeloid sarcoma); 1/9 (T-LBL)</td>
<td>1/3 (kidney)</td>
<td>0/5</td>
</tr>
<tr>
<td>Bone marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPN</td>
<td>6/9; 5/9 (MPN Eo)</td>
<td>2/2; 1/1 (T-ALL)</td>
<td>7/7; 4/7 (MPN Eo)</td>
</tr>
<tr>
<td>AML</td>
<td>3/9</td>
<td>0/3</td>
<td>0/7</td>
</tr>
<tr>
<td>Karyotype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6/9</td>
<td>3/3</td>
<td>7/7</td>
</tr>
<tr>
<td>Diploid</td>
<td>4/4</td>
<td>1/3</td>
<td></td>
</tr>
<tr>
<td>Translocations</td>
<td>2/2</td>
<td>2/3</td>
<td>7/7 (trisomy 13 or 21)</td>
</tr>
<tr>
<td>FISH</td>
<td>7/7 (FIP1L1-PDGFRA); 2/2 (PDGFRB rearranged)</td>
<td>3/3 (PDGFRB rearranged)</td>
<td>5/5 (FGFR1 rearranged)</td>
</tr>
<tr>
<td>Gene partner</td>
<td>7/9 (FIP1L1); 1/9 (ETV6); 1/9 (STRN)</td>
<td>1 (RABEP1); 1 (c6orf204); 1 (unknown)</td>
<td>5/7 (ZMYM2); 1/7 (TRIM2); 1/7 (unknown)</td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>7/9</td>
<td>3/3</td>
<td>6/6</td>
</tr>
<tr>
<td>Imatinib therapy</td>
<td>6/9</td>
<td>2/3</td>
<td>0/6</td>
</tr>
<tr>
<td>Primary</td>
<td>3/9</td>
<td>0/2</td>
<td></td>
</tr>
<tr>
<td>Post induction</td>
<td>3/9</td>
<td>2/2</td>
<td></td>
</tr>
<tr>
<td>BMT (salvage)</td>
<td>2/7</td>
<td>1/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>6/9</td>
<td>1/2</td>
<td>3/6</td>
</tr>
<tr>
<td>DOD</td>
<td>2/8</td>
<td>0/2</td>
<td>2/6</td>
</tr>
<tr>
<td>AWD</td>
<td>1/8</td>
<td>1/2</td>
<td>1/6</td>
</tr>
<tr>
<td>Survival, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.1</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>Range</td>
<td>0.7-4</td>
<td>0.4-1.9</td>
<td>0.5-4</td>
</tr>
</tbody>
</table>

AML, acute myeloid leukemia; AWD, alive with disease; BMT, bone marrow transplant; CR, complete remission; DOD, dead of disease; Eo, eosinophilia; FISH, fluorescence in situ hybridization; MPN, myeloproliferative neoplasm; T-ALL, T-lymphoblastic leukemia/lymphoma; T-LBL, T-lymphoblastic lymphoma/leukemia.

*Values are presented as number/total number unless otherwise indicated.

**PDGFRA was FIP1L1** in seven cases, the partner was ETV6 in one case (case 93), and the partner was striatin (STRN) in one case (case 363). Eight patients were male and one was female; their ages ranged from 22 to 66 years (median, 48 years). **Table 2**. Four patients had B symptoms, two had pruritus (cases 111 and 202), three had splenomegaly (cases 90, 111, and 265), three had lymphadenopathy (cases 90, 111, and 265), and three had a paraspinal mass (cases 90, 184, and 275). Laboratory studies showed mild to moderate anemia in six, leukocytosis (ranging from 10.7 to 103.6 × 10⁹/L) in five, eosinophilia (>1.5 × 10⁹/L) in five (three of whom had abnormal circulating eosinophils), and thrombocytopenia in two patients.

Three patients had CEL (cases 111, 202, and 284), and all three patients responded well to imatinib and are in complete remission. Case 284 is a representative example. This 53-year-old man had features of CEL and symptoms of multisystemic organ damage. He had absolute eosinophilia Image 21, a hypercellular BM with myeloid predominance Image 31, and moderate reticulin fibrosis; no increased blasts were noted. FISH studies performed on the peripheral blood revealed 4q12 deletion suggestive of the presence of FIP1L1-PDGFRA fusion Image 41. The patient responded well to imatinib, with eosinophilia and systemic symptoms resolving in 1 month, and he went into complete remission.

Two patients had myeloproliferative neoplasm (MPN) and T-acute lymphoblastic leukemia (T-ALL) (cases 184 and 265). The role of imatinib therapy in patients with this presentation is not clear. Case 184 was from a 39-year-old woman who had a paraspinal mass involved by T-ALL,
and staging BM examination revealed MPN with eosinophilia. An increased number of mast cells were noted, a subset of which expressed CD25. The patient died of progressive disease in less than 1 year. Case 265 was from a 24-year-old man who developed simultaneously T-ALL involving the lymph node and MPN with eosinophilia involving the BM. The patient was treated with chemotherapy, experienced relapse as MPN in the BM, and then underwent an allogeneic BM transplant. He was in complete remission 4 years later. This patient was not treated with imatinib.

One patient had MPN and myeloid sarcoma (case 275) and one with AML in a background of MPN (case 90). Case 275 was from a 44-year-old man who had eosinophilia and a paraspinal mass that extended from C7 to T2. The paraspinal mass was a myeloid sarcoma with numerous eosinophilic precursors as well as Charcot-Leyden crystals. Subsequent BM examination showed MPN with eosinophilia. The patient went into complete remission with chemotherapy and is receiving maintenance with imatinib. Case 90 was from a man who had severe back pain, splenomegaly, and bilateral pelvic lymphadenopathy. A fine-needle aspiration of the lymph node showed myeloid sarcoma. A subsequent BM examination showed AML in a background of MPN with eosinophilia and reticulin fibrosis. He was treated with induction chemotherapy. Subsequently, the patient developed back pain, and a computed tomography scan showed an epidural/paraspinal tumor that extended from T5 to L5. Peripheral blood showed leukocytosis with absolute eosinophilia. A biopsy specimen of the epidural mass showed an MPN with eosinophilia and fibrosis. He was treated with imatinib, and the epidural mass completely regressed in 2 months, and he remains in complete remission while receiving maintenance on imatinib.

Two patients had AML (cases 93 and 363) with chromosomal translocations involving \textit{PDGFRA} but with partners different from \textit{FIP1L1}. Case 93 was from a patient with \textit{FIP1L1-PDGFR} (×1,000). (Case 284, courtesy of V. Alagiozian-Angelova, MD.)

Bone marrow core biopsy specimen of a patient with \textit{FIP1L1-PDGFR} shows hypercellularity and marked eosinophilia (×1,000). (Case 275, courtesy of S. A. Monaghan, MD.)

Fluorescence in situ hybridization (FISH) of a bone marrow specimen from a patient with \textit{FIP1L1-PDGFR} who had features of chronic eosinophilic leukemia. FISH shows a normal pattern of three probes in the bottom of the cell (arrowhead), whereas at the top it shows only two probes (one green and one aqua) (arrow), consistent with deletion of \textit{CHIC2}. (Case 90, courtesy of R. Juskevicius, MD.)
A 66-year-old man who had leukocytosis and circulating blasts (30%) and no eosinophilia. The blood smear and BM showed large blasts that had a monocytic appearance, and the BM had a background of trilineage dysplasia. Cytogenetic studies revealed the following karyotype: 46,XY, t(4;12)(q12;p13)[8]/46,idem,del(5)(q22q35)[12]. FISH studies confirmed the presence of PDGFRA and ETV6 at 12p13. FISH studies confirmed the involvement of PDGFRA and STRN (at 2p24). The patient failed to respond to induction chemotherapy and imatinib, and he died after infection complications following allogeneic BM transplant.

Case 363 was from a 70-year-old man who had weakness and fatigue. The BM revealed AML without increased eosinophils. Conventional cytogenetic studies showed 46,XY,t(2;4)(p11.2;q12[18])/46,XY[2]. FISH studies confirmed the involvement of PDGFRA and STRN (at 2p24). The patient was treated with chemotherapy and imatinib. The patient experienced several relapses for 3 years; the last follow up (4 years since the initial diagnosis) indicated that the patient had relapsed AML.

**Image 5** This patient who had a myeloproliferative neoplasm with eosinophilia developed lymphadenopathy, and a lymph node biopsy specimen showed T-lymphoblastic lymphoma. Fluorescence in situ hybridization demonstrated the presence of FIP1L1-PDGFRα. Low magnification (×10) shows effacement of the lymph node architecture (A). High magnification (×400) shows a diffuse infiltrate of blasts (B). Blasts express TdT (×400) (C). Neoplastic cells express CD3 (×400) (D). (Case 265, courtesy of T. C. Greiner, MD, PhD, and colleagues.)
What Are the Clinicopathologic Features of Hematolymphoid Neoplasms Associated With PDGFRB Fusions?

Gene fusions involving PDGFRB were first reported in 1994 by Golub and colleagues, who described the fusion of ETV6 (ets variant gene 6) at 12p13 and PDGFRB at 5q33 in a case of chronic myelomonocytic leukemia (CMML) with t(5;12)(q33;p13). Hematolymphoid neoplasms associated with PDGFRB gene fusions are rare, with a reported incidence of 1.8% of all myelodysplastic/myeloproliferative neoplasms (MDS/MPNs). These neoplasms are often classified as CMML, atypical chronic myelogenous leukemia, BCR-ABL1 negative, juvenile myelomonocytic leukemia, MDS, AML, or acute lymphoblastic leukemia. Most affected patients are adult men; the median age was 61 years in a recent series and 42 years in other studies. Children are rarely affected. Patients with PDGFRB gene fusions usually have anemia, leukocytosis, monocytosis, eosinophilia, and splenomegaly.

What Are the Genetic Features and Consequences of PDGFRB Fusions?

More than 20 different partners of PDGFRB have been identified in gene fusions. These gene fusions lead to the creation of chimeric proteins that have enhanced tyrosine kinase activity. The most common translocation is t(5;12)(q33;p13)/ETV6-PDGFRB. As a consequence of the t(5;12), the extracellular ligand binding domain of PDGFRB is replaced by the pointed domain (PNT, also called SAM or helix-loop-helix) of ETV6, resulting in enforced PDGFRB dimerization by the PNT domain. The chimeric protein ETV6-PDGFRB stimulates hematopoietic cell proliferation, leading to an MPN and eosinophilic proliferation. These effects are mediated by STAT5, NF-κB, and ERK signaling activation. In addition, as in the case of FIP1L1-PDGFR, the chimeric protein ETV6-PDGFRB is a stable protein.
resistant to ubiquitination and proteosomal degradation with increased stability that has been shown to promote cell proliferation.17

What Is the Most Reliable Technique to Diagnose Abnormalities of PDGFRB?

Since most neoplasms with rearrangements of PDGFRB have translocations, conventional cytogenetics is the best technique to identify involvement of PDGFRB at chromosome 5q33. The breakpoints in the long arm of the chromosome 5 are variable but usually have been assigned to the 5q31-33 region, whereas the many partners of PDGFRB reside at various chromosomal loci.

The presence of PDGFRB rearrangements can be detected using FISH with break-apart probes, but this approach does not identify the gene partner Image 8. With the existence of so many partners, it is not practical or cost-effective to identify the gene partner. If the partner of PDGFRB is known, RT-PCR methods using specific primer sets also can be used, and this approach is well suited to assess for minimal residual disease.

What Are the Therapeutic Implications of Identifying PDGFRB Rearrangements?

Most hematolymphoid neoplasms associated with translocations of PDGFRB are sensitive to tyrosine kinase inhibitors. Patients with these neoplasms respond well to imatinib therapy with excellent hematopoietic and molecular responses. Primary or secondary resistance to imatinib is very uncommon.25-29 Additional adjuvant therapy is needed when patients have or develop the blast phase of the disease.

Workshop Cases of PDGFRB-Associated Hematolymphoid Neoplasms

Three cases were submitted to this session. All were from men, ranging from 9 to 64 years (median, 37 years) (Table 2). Two patients had generalized lymphadenopathy and splenomegaly (cases 137 and 246), and one patient had cervical lymphadenopathy (case 12). Mild to moderate anemia was reported in two patients, eosinophilia (>1.5 × 10⁹/L) in one patient (case 137), leukocytosis (17.4 × 10⁹/L) in one (case 246), and thrombocytopenia in one. The reported gene partners of PDGFRB were RABEP1 (case 12) and c6orf204 (case 137). In case 246, the gene partner of PDGFRB was not identified.

All three patients had T-lymphoblastic lymphoma and MPN. Case 137 is representative of this group. This 38-year-old man presented initially with diffuse lymphadenopathy and splenomegaly. A lymph node biopsy specimen showed T-lymphoblastic lymphoma. The staging BM biopsy was performed on the BM and retrospectively in the lymph node confirmed PDGFRB gene rearrangements at both sites Image 10. Using a systemic screen for tyrosine kinase gene rearrangements, a novel C6orf204-PDGFRB fusion was identified in this patient. The patient was treated with chemotherapy and imatinib. He also received an allogeneic BM transplant and was in complete remission at last follow-up.

FGFR1-Associated Hematolymphoid Neoplasms

An association between the t(8;13) and the triad of T-cell lymphoblastic lymphoma/leukemia, eosinophilia, and myeloid malignancy was first reported in 1992.30 Subsequent studies confirmed the association31-33 and identified the fusion between ZNF198 (now known as ZMYM2) and FGFR1.34,36 The FGFR1 gene at chromosome 8p11 is a constant finding, and hence these neoplasms also have been of morphologic or immunophenotypic involvement by lymphoma. Subsequent BM examinations performed 2 months after completion of chemotherapy and after reinduction treatments showed a markedly hypercellular (95%) BM; there was left-shifted myeloid hyperplasia and eosinophilia. A karyotype showed t(5;6)(q33;q23), and FISH studies performed on the BM and retrospectively in the lymph node confirmed PDGFRB gene rearrangements for minimal residual disease.
Gene fusion results in constitutive activation of FGFR1 tyrosine kinase. Currently, there are 13 reported gene partners of FGFR1, 12 translocations and one rare insertion. The t(8;13)(p11;q12) is most common, in approximately 50% of the cases, followed by t(8;9) in around 15% and t(6;8) in around 10%.

Hematolymphoid neoplasms associated with FGFR1 fusions are rare and aggressive tumors. Patients usually have systemic symptoms, including fatigue, night sweats, weight loss, or fever. Lymphadenopathy and hepatosplenomegaly are common. Up to 20% of the patients are asymptomatic at the time of diagnosis. The BM is usually hypercellular with eosinophilia and features suggestive of MPN. These tumors frequently progress to AML, and around 15% of patients have acute leukemia.

Most patients with hematolymphoid neoplasms associated with FGFR1 fusions have acute leukemia. The disease equally affects males and females, with a reported male/female ratio of 1.2 to 1. The median age is 44 years (range, 3-84 years).
Other fusion genes appear to be associated with different neoplastic phenotypes, although very few patients with some of these abnormalities have been reported. Patients with t(8;22)(p11;q11)/BCR-FGFR1 have a higher median age (61 years) and often have neutrophilia and basophilia mimicking CML. A patient described with the t(1;8)(q25;p11.2) also had a CML-like disease. Tonsillar involvement and monocytosis (CMML-like) appear to correlate with t(8;9)(p11;q34), and patients with t(6;8)(q27;p11)/FGFR1OP2-FGFR1 may present with a polycytemia vera–like picture.\(^{34,39}\)

**What Are the Therapeutic Implications of Identifying FGFR1 Rearrangements?**

Patients with hematolymphoid neoplasms associated with FGFR1 fusions have aggressive disease that is usually not responsive to first-generation tyrosine kinase inhibitor (imatinib) therapy. Prognosis is poor, and aggressive chemotherapy and often stem cell transplantation are needed.

**What Is the Most Reliable Technique to Diagnose Rearrangements of FGFR1?**

Since most neoplasms with rearrangements of FGFR1 present with translocations, conventional cytogenetics is the best technique to identify involvement of FGFR1 at 8p11. The diagnosis is confirmed by using FISH with break-apart probes for FGFR1.\(^\text{Image 11}\) Since there are numerous partners of FGFR1, it is not practical or cost-effective to identify the gene partner. Commercial probes for MYM MYM MYM MYM MYM P

**Workshop Cases of FGFR1-Associated Hematolymphoid Neoplasms**

Seven cases were submitted to the workshop. The gene partner of FGFR1 was ZMYM2 in five cases and TRIM2 in one case (case 100), and the gene partner was not identified in one case (case 75).

Four patients were men and three were women, with a median age of 41 years (range, 16–65 years) (Table 2). Six patients had lymphadenopathy (cases 100, 217, 317, 341, 432, and 433). One of these patients also had a mediastinal mass (case 217) and another splenomegaly (case 75). Eosinophilia (>1.5 × 10\(^9\)/L) was reported in four patients (range, 1.6-3.5 × 10\(^9\)/L), basophilia in three (cases 75, 217, and 432), mild anemia in two, leukocytosis (range, 20.2-211 × 10\(^9\)/L) in four, and mild thrombocytopenia in two. Morphologic examination showed MPN involving BM in all patients and T-lymphoblastic lymphoma involving lymph nodes in six patients.

Six cases (100, 217, 317, 341, 432, and 433) had lymphadenopathy and BM with MPN, features that can be considered characteristic of FGFR1-associated hematolymphoid neoplasms. A representative example was
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Image 12 Lymph node with T lymphoblastic lymphoma in a patient with a mediastinal mass and eosinophilia. Karyotype revealed a t(8;13)(p11;q12), and fluorescence in situ hybridization demonstrated the presence of FGFR1 rearrangement. A, Neoplastic cells show a blastic chromatin (×1,000). The lymphoblasts were positive for CD1a (B, ×1,000) and were admixed with immature myeloid cells positive for myeloperoxidase (C, ×1,000). These features suggest the presence of a neoplasm associated with t(8;13) (p11;q12). (A, B, Case 217, courtesy of J. S. Sidhu, MD, and colleagues; C, Case 317, courtesy of S. Hu, MD, PhD, and colleagues.)

Image 13 Interphase fluorescence in situ hybridization from a patient with T lymphoblastic lymphoma/leukemia and t(8;13)(p11.2;q12). A normal cell on the left shows two fused signals. The abnormal cell on the right shows that the red and green probes are separated (break-apart), consistent with the presence of FGFR1 rearrangement. (Case 217, courtesy of J. S. Sidhu, MD, and colleagues.)

Image 14 Karyotype of bone marrow from a patient with myeloproliferative neoplasm demonstrates 47,XY,t(8;13)(p11;q12),+21, raising the suspicion of rearrangement of FGFR1 at 8p11. Arrows indicate translocations and trisomy 21. (Case 433, courtesy of L. Song, MD, and colleagues.)

case 217, from a 61-year-old woman who had a rapidly growing mediastinal mass and diffuse peripheral lymphadenopathy, while peripheral blood showed eosinophilia and basophilia. A lymph node biopsy specimen revealed a T-lymphoblastic lymphoma with a minor myeloid component (bilineal myeloid/lymphoma) Image 12, and BM examination showed an MPN with eosinophilia. Karyotyping and FISH studies performed in the BM and lymph node showed t(8;13)(p11.2;q12), and FISH testing with a break-apart probe demonstrated the presence of FGFR1 rearrangement Image 13. Six months later, the patient developed AML with t(8;13)(p11.2;q12), and she died of progressive disease.

An interesting and unusual case was a 28-year-old man with progressive diffuse lymphadenopathy (case 433). A lymph node biopsy specimen revealed T lymphoblastic lymphoma/leukemia. The BM was hypercellular with myeloid predominance and eosinophilia with only minimal involvement by T lymphoblastic lymphoma/leukemia. In addition, there were scattered and focally clustered spindled mast cells. The cardinal feature of this BM was the increased number of atypical spindle-shaped mast cells with focal cluster formation and mild eosinophilia. Serum tryptase level was elevated (38.9 µg/L; upper limit of reference range, 13.2 µg/L). Testing for KIT mutation was negative. Conventional cytogenetic studies performed on lymph node and BM showed 47,XY,t(8;13)(p11.2;q12),+21[20] Image 14. Analysis by FISH confirmed FGFR1 gene rearrangement in all samples. The patient was treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, and 1 month later, BM examination showed no evidence of
lymphoma/leukemia. In addition, the lymphadenopathy decreased, but the patient developed cardiomyopathy and died of progressive disease.

Case 75 in this session was of interest because the clinicopathologic presentation was similar to CML. This 54-year-old woman had left-shifted leukocytosis, mild basophilia, and massive splenomegaly. There was no significant eosinophilia or circulating blasts. BM was hypercellular with granulocytic predominance and left-shifted maturation. Conventional cytogenetic analysis showed 46,XX,t(8;17)(p12;q11.2)[20], and FISH studies confirmed the presence of FGFR1 rearrangement in all cells analyzed. There was no evidence of BCR-ABL1 fusion. A JAK2 (V617F) mutation was not detected. The t(8;17)(p12;q11.2) has not been reported previously.

Hematolymphoid Neoplasms With Eosinophilia but Lacking PDGFR, PDGFRB, or FGFR1 Rearrangement

Three cases (172, 237, and 393) submitted to this session exhibited some of the clinicopathologic features of hematolymphoid neoplasms associated with PDGFR, PDGFRB, or FGFR1 rearrangements, although these cases lacked these gene fusions.

Case 172 was from a 40-year-old woman with lymphadenopathy and leukocytosis in peripheral blood. A lymph node biopsy specimen showed
T-lymphoblastic lymphoma with a myeloid component (bilineal myeloid/lymphoma) **Image 15.** Conventional cytogenetic analysis revealed 46,XX,t(1;8)(q23;p11.2), but FISH studies and chromosome painting failed to detect FGFR1 rearrangement. A BM specimen was obtained that was aparatcular and inadequate for a morphologic diagnosis. The patient was treated with chemotherapy and BM transplant and was alive and in complete remission 2 years later.

Case 237 was from a 54-year-old man with a history of persistent eosinophilia who had massive splenomegaly. The peripheral blood smear showed mild neutrophilia and eosinophilia (7.0 × 10^9/L) and rare circulating blasts. Some of the neutrophils were hypolobated and hypogranular. The BM was hypercellular with granulocytic predominance, eosinophilia, and small and monolobated (“dwarf”) megakaryocytes. Blasts were not increased. Conventional cytogenetic studies showed 46,XY,t(9;12)(q34;p12–13),del(13)(q12–14q22–34) [9]/46,XY[2], and FISH confirmed the presence of ABL1 gene rearrangements. PCR studies failed to detect BCR-ABL1 or FIP1L1-PDGFRα fusion transcripts. A JAK2 (V617F) mutation was not detected. A diagnosis of MDS/MPN, unclassifiable with eosinophilia was rendered. The patient was treated with chemotherapy and BM transplant and was alive and in complete remission 2 years later.

Case 393 was from an 87-year-old man who sought treatment 2 years earlier for anemia and thrombocytopenia. The WBC count was 4.9 × 10^9/L. The peripheral blood smear showed neutrophils with significant dysplasia, and a diagnosis of MDS was rendered. Subsequent peripheral blood smears 1 year later and 2 years later showed leukocytosis (WBC, 29.6 × 10^9/L and 21.1 × 10^9/L, respectively), monocytosis, and eosinophilia. A BM was hypercellular with sheets of eosinophilic precursors and megakaryocytic dysplasia **Image 16.** Blasts were not increased. Cytogenetic studies (karyotyping and FISH) revealed trisomy 8. There was no evidence of t(9;22)/BCR-ABL1, t(15;17)/PML-RARA, t(8;21)/RUNX1-RUNX1T1, and inv(16) or t(16;16)/CBFB-MYH11 or rearrangements of PDGFRα, PDGFRβ, FGFR1, or MLL genes. There was no evidence of mutations involving CEBPA, FLT3, and NPM1. A diagnosis of MDS/MPN, unclassifiable with eosinophilia was rendered.

**What Are Other Causes of Clonal Eosinophilia?**

The term clonal eosinophilia is used for cases of eosinophilia associated with a monoclonal hematopoietic neoplasm. Three major groups of clonal eosinophilia are recognized in the WHO classification. This session focused on one major group. Other major groups in the WHO classification are (1) CEL, not otherwise specified and (2) core-binding factor AML (eg, AML with inv 16 or t(16;16) (p13.1;q22)/CBFB-MYH11 and AML with t(8;21)(q22;q22)/RUNX1-RUNX1T1).

In rare cases, clonal eosinophilia has been documented in patients with chronic myelogenous leukemia, CMML, MDS, MPN, MDS/MPN overlap syndromes, and a subset of patients with systemic mast cell disease.

**What Findings Suggest a Hematolymphoid Neoplasm Associated With PDGFRα, PDGFRβ, or FGFR1 Gene Fusions?**

A high index of suspicion is required to establish the diagnosis of these rare diseases. These neoplasms should be suspected in the presence of eosinophilia (>1.5 × 10^9/L), a finding that is detected in more than 70% of cases. Suspicion is heightened if the BM is hypercellular with eosinophilia and if the patient has concomitant or subsequent T-lymphoblastic lymphoma/leukemia or AML.


