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Co-occurring systemic mastocytosis and T-lymphoblastic lymphoma driven by a novel cryptic *JAKMIP2::PDGFRB* rearrangement

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PDGFRB is a proto-oncogene that encodes the tyrosine kinase platelet-derived growth factor receptor (PDGFRB) which plays a crucial role in stimulating and regulating cell proliferation/differentiation.[1] Mutations involving *PDGFRB* have been implicated in various malignancies including breast cancers, glioblastomas, gastrointestinal tumours, and hematologic neoplasms often associated with eosinophilia. Generally, the activating mutation for these hematologic neoplasms is the fusion of the tyrosine kinase domain, causing deregulation of the kinase and activation without a ligand.[2,3] Since the discovery of the *ETV6*::*PDGFRB* fusion in 1994, over 40 fusion partners of *PDGFRB* have been identified in myeloid/lymphoid neoplasms with eosinophilia.[4] The detection of *PDGFRB* fusions has important clinical implications as these alterations are generally highly sensitive to imatinib therapy, however, conventional tools for detecting *PDGFRB* fusions, such as karyotype and fluorescence in situ hybridization (FISH), have relatively low resolution or evaluate a limited number of genomic targets. Technologies capable of more comprehensive high resolution genomic profiling, such as optical genome mapping (OGM) and long-read sequencing (LRS), could enable more reliable detection of Tyrosine Kinase (TK) fusion events but are not yet widely adopted in clinical practice.

The clinical presentation of myeloid/lymphoid neoplasms with *PDGFRB* fusions can be highly variable, with eosinophilia being common but not universal. Myeloproliferative and/or myelodysplastic features are frequent, while blast proliferations of greater than 20% in the bone marrow or peripheral blood (which may be myeloid or lymphoid) are less common and can occur at presentation or as a form of disease progression. Mast cell proliferations are also commonly identified, but generally without dense clustering or *KIT* driver mutations characteristic of systemic mastocytosis (SM). Rare cases with a concurrent TK-fusion, *KIT* driver mutation, and features of SM have been reported, yet their classification remains controversial, and their clinical behaviour is not well understood.[5] In this report (which conforms to guidance of the UBC Clinical Research Ethics Board and for which informed consent of the patient was obtained) we describe such a case harbouring a previously undescribed *PDGFRB* fusion.

A 64-year-old female with no history of hematologic disorder or malignancy presented to the emergency room with dysphonia and dyspnea due to an enlarging neck mass. She had experienced several months of enlarging cervical lymph nodes, fatigue, and weight loss with no fevers, night sweats, rash, or significant gastrointestinal symptoms. Physical examination revealed multiple enlarged lymph nodes in the cervical, axillary, and inguinal regions, along with stridor. Computed tomography scanning showed diffuse bilateral cervical lymphadenopathy (largest node ~5 cm) and smaller volume lymphadenopathy in the axillary and inguinal regions. The spleen and liver were normal. The patient's initial complete blood counts and LDH were within normal limits, including a normal eosinophil count.

A cervical lymph node biopsy was performed, showing near effacement by an infiltrate of blastic medium-sized cells (Figure 1A) which stained positively for CD3 (Figure 1B), CD4, CD5, TDT, and LMO2, with a high proliferation index (90%) by Ki-67, diagnostic of T-lymphoblastic lymphoma (T-LBL). A bone marrow biopsy was performed for staging which showed a normocellular-for-age (40%) marrow with orderly trilineage hematopoiesis throughout most of the sample and was negative for involvement by T-LBL. However, there were several large, dense aggregates of spindle-shaped mast cells associated with adjacent lymphoid aggregates

and interstitial eosinophilia (Figure 1C-D). Immunohistochemical staining showed the mast cells to be aberrantly positive for CD2 and CD25. Surprisingly, targeted molecular studies performed on the bone marrow aspirate were positive for a *KIT* codon D816V/F mutation, confirming a SM diagnosis. These findings were in keeping with an incidental diagnosis of systemic mastocytosis. A repeat CBC showed that the patient had developed mild neutrophilia and monocytosis, while further laboratory evaluation revealed an elevated tryptase level at 30.3 µg/L (reference range: <11.1 µg/L).

Banded chromosome analysis performed on the bone marrow sample showed a normal karyotype. FISH was requested to assess for selected TK-fusion drivers due to the unusual combination of mastocytosis and lymphoblastic lymphoma. FISH analysis showed no evidence of a *FIP1L1*::*PDGFRA* rearrangement, however, a *PDGFRB* break-apart probe set demonstrated two apparently normal fused signals and an extra 3'*PDGFRB* signal in 23% of interphase nuclei, consistent with a rearrangement of the *PDGFRB* locus (Figure 2A). Metaphase FISH localized the additional 3'*PDGFRB* signal to chromosome 5q, compatible with an intrachromosomal rearrangement (Figure 2B). The same *PDGFRB* rearrangement pattern was subsequently detected in the patient's lymph node biopsy containing T-LBL, demonstrating a clonal relationship between the patient's T-LBL and SM. The *KIT* mutation was not detectable in lymph node tissue.

OGM and Oxford Nanopore Technology LRS was performed to investigate the nature of the *PDGFRB* rearrangement. Results showed the presence of a duplicated insertion of *JAKMIP2* to the *PDGFRB* locus, resulting in fusion of the 5' portion of *JAKMIP2* (exons 1-18) to the 3' portion of *PDGFRB* (exons 11-23; Figure 2C-E).

The patient was initiated on standard induction multiagent chemotherapy for T-LBL which was supplemented with imatinib following identification of the *PDGFRB* rearrangement. The patient achieved a complete metabolic response of their T-LBL and their bone marrow showed no morphologic evidence of SM or T-LBL following induction chemotherapy (with 4.5% of cells remaining positive for *PDGFRB* rearrangement by FISH in bone marrow aspirate). Bone marrow complete cytogenetic remission, with no FISH evidence remaining of *PDGFRB* rearrangement, was achieved after consolidation treatment with imatinib only. The patient is currently experiencing ongoing remission (including normal tryptase levels) under the treatment of maintenance imatinib 100 mg PO daily.

TK fusions that drive myeloid/lymphoid neoplasms have critical diagnostic and therapeutic implications. Therefore, reliable identification of both expected and cryptic TK fusions is necessary for effective management of the disease. While FISH is a relatively reliable method for the detection of known TK rearrangements, the application of a limited panel of available probes that are generally incapable of providing coverage for all potentially relevant loci, and relatively low resolution, can lead to uncertainty in the diagnosis of a functional TK fusion.[6, 7] Conventional karyotyping, while providing a more global genomic evaluation, fails to detect submicroscopic rearrangements, and atypical fusion-forming rearrangements may go unrecognized.[7] Application of novel genomics technologies, such as OGM and ONT LRS, can overcome pitfalls associated with traditional standard-of-care methods. OGM, in which high molecular weight DNA is fluorescently labeled, imaged, and aligned against a reference genome, is a high resolution, whole genome approach capable of detecting complex and submicroscopic chromosome changes in an unbiased manner.[8] ONT LRS is a sequencing

platform in which long strands of DNA are passed through biological pores embedded in flow cells, generating characteristic electrical signals that are read and converted into sequences.[9] Here, ONT pinpointed the event at chromosome 5q32 spanning chr5:147,629,580-150,098,238 (hg38), a fusion of exon 10 of PDGFRB to exon 18 of JAKMIP2. In both methods, the cryptic fusion was effectively characterized, with ONT LRS operating at a higher, exon-level resolution.

The co-occurrence of bona fide systemic mastocytosis with a *PDGFRB*-rearranged myeloid/lymphoid neoplasm is exceptionally rare, and existing diagnostic frameworks, such as WHO 5th Edition and International Consensus Classification (ICC), disagree on its proper classification. Mast cell proliferation is fairly common in myeloid/lymphoid neoplasms with eosinophilia and TK fusions (particularly with *PDGFRA or PDGFRB* fusions), however, these cases almost always lack activating *KIT* mutations.[5] The ICC specifies that rare cases meeting criteria for SM with both a TK-fusion and *KIT* mutation should be classified as SM with an associated myeloid neoplasm. However, the WHO criteria proposes classifying these based on the TK-fusion regardless of *KIT* mutation status.[5,10] In our case, the *PDGFRB* fusion was present at a high burden in both the lymph node and bone marrow, whereas the *KIT* mutation was only identified in the marrow, suggesting that the *PDGFRB* fusion was the initial driver event. Interestingly, typical SM with the *KIT* D816V mutation does not respond well to imatinib,[11] whereas this patient has had a sustained remission of SM and T-LBL on single-agent maintenance imatinib. The clinical significance of having combined PDGFRB fusion and KIT mutation in the context of SM remains unclear, but when identified, a trial of imatinib is likely appropriate.

This is, to our knowledge, the first reported case of SM with a concurrent *PDGFRB* rearrangement and *KIT* mutation. It is also the first reported case that we are aware of with a *PDGFRB*-fusion presenting with both SM and T-LBL. This unusual case highlights some of the limitations of current diagnostic pathways and classification systems. The wider adoption of unbiased whole-genome profiling, such as OGM or LRS, for detecting TK fusions could play a critical role for the identification of cryptic clinically-relevant driver events, with the potential to improve biological understanding and patient outcomes in the current era of precision medicine.

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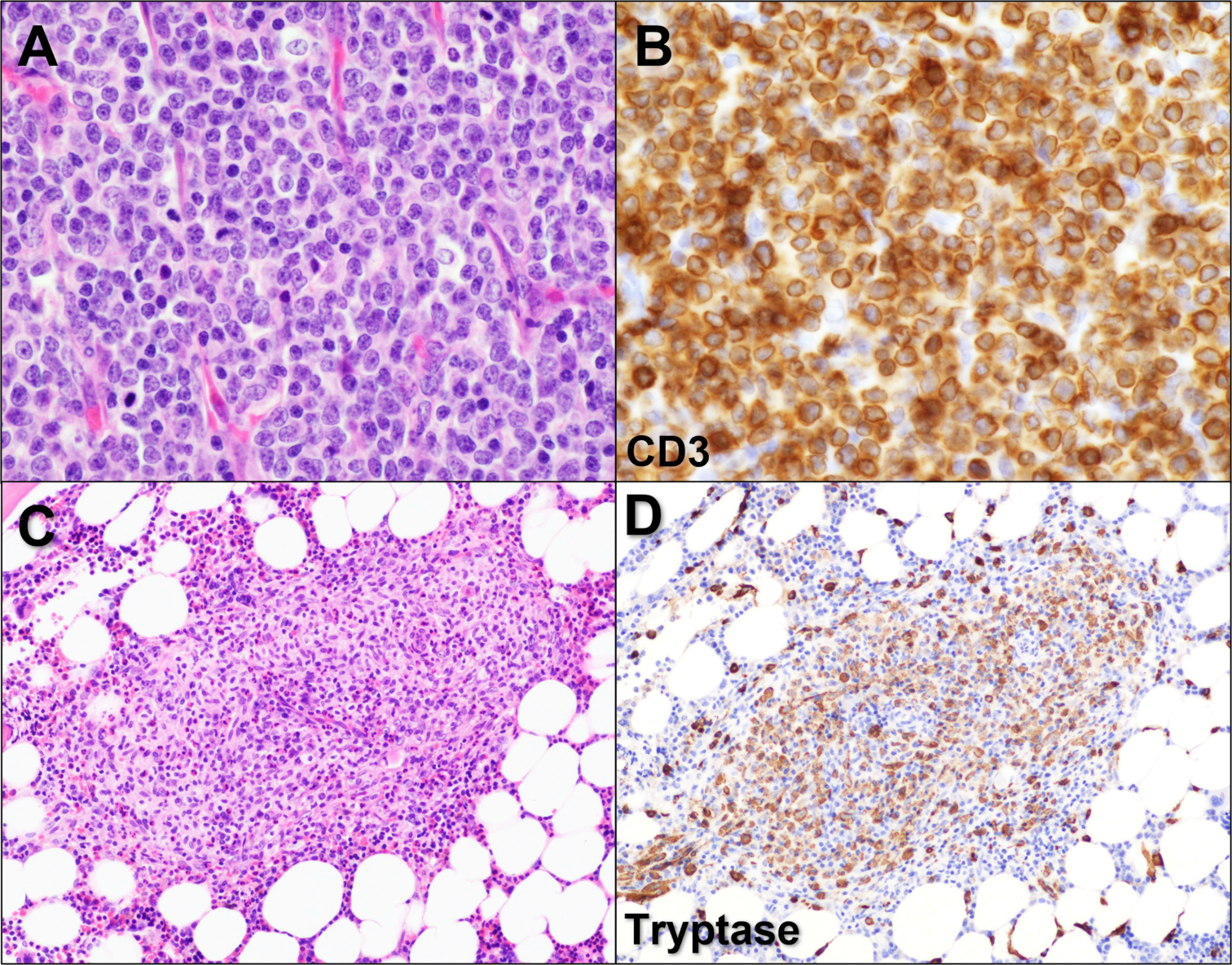
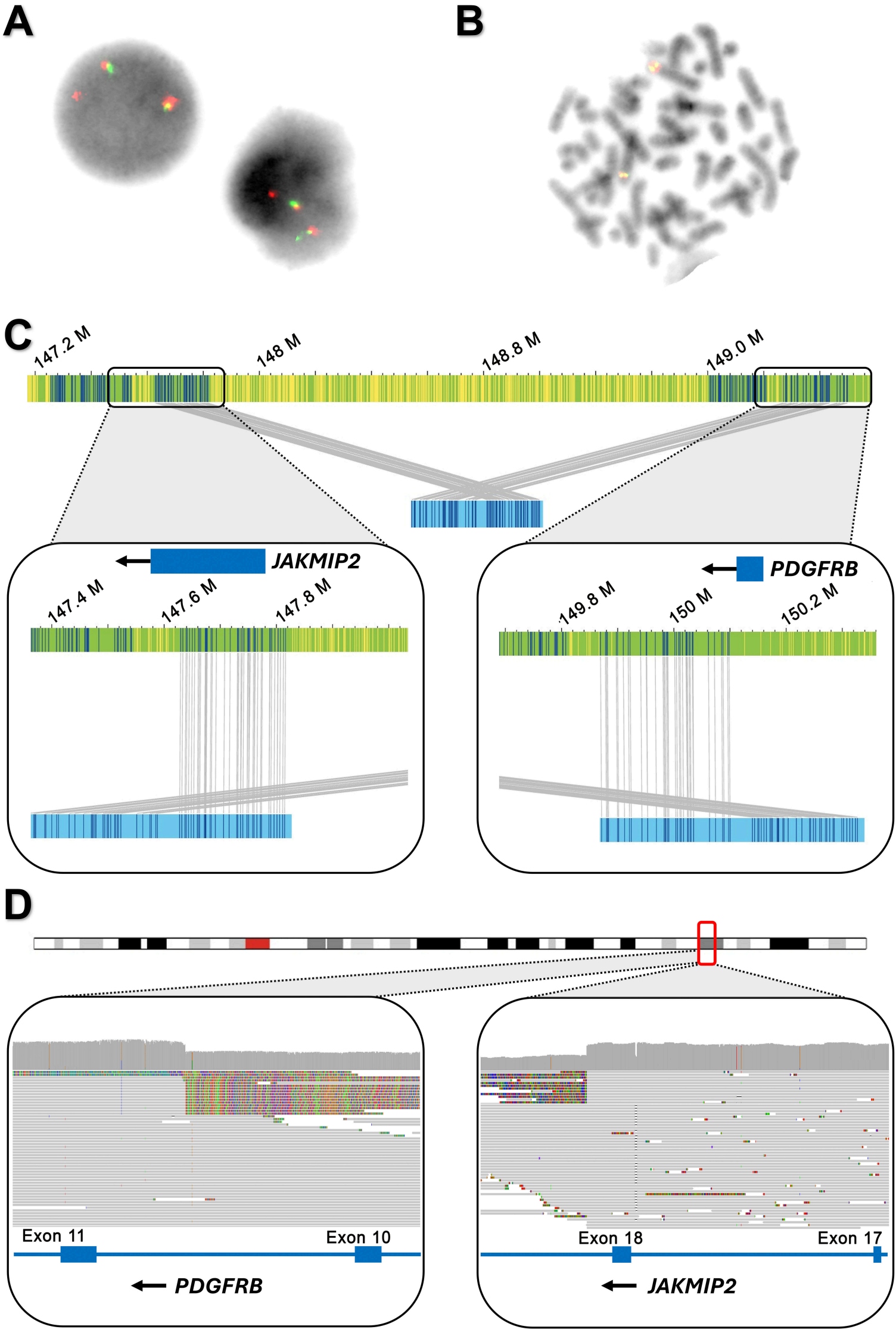
Figure 1. Lymph node and bone marrow tumour morphology. (A) Lymph node biopsy showing near effacement by an infiltrate of blastic medium-sized cells (hematoxylin and eosin, x60 objective). (B) Immunohistochemical analysis of the lymph node biopsy demonstrated the positive expression of CD3 (CD3 stain, x60 objective). (C,D) Large, dense aggregates of spindle-shaped mast cells associated with interstitial eosinophilia were scattered throughout the bone marrow (C: hematoxylin and eosin, x20 objective, D: tryptase stain, x20 objective).

Figure 2. Novel *PDGFRB* fusion detected in both bone marrow and cervical lymph nodes. (A) Interphase FISH was performed on the bone marrow with a *PDGFRB* break-apart probe. 23% of analyzed cells showed an additional 3'*PDGFRB* signal, consistent with the presence of a *PDGFRB* rearrangement. (B) Metaphase FISH was performed on the bone marrow with the same set of *PDGFRB* break apart probes. Metaphase FISH localized the additional 3'*PDGFRB* signal immediately adjacent to the intact signal at 5q32, compatible with an intrachromosomal rearrangement. (C,D) Optical genome mapping showed a duplicated insertion of *JAKMIP2* (exons 1-15~19) to the *PDGFRB* (exons 12-23:23) locus, resulting in fusion of the 5' portion of *JAKMIP2* to the 3' portion of *PDGFRB* (green and yellow bar: reference chromosome 5 map; blue bar: imaged DNA molecule; grey lines: alignment of imaged DNA to reference map). (E) Long-read sequencing resolved the breakpoints of the *PDGFRB* and *JAKMIP2* fusion event, demonstrating fusion of the exons 1-18 of *JAKMIP2* to exons 11-23 of *PDGFRB*.


A
B
CD3
C
D
Tryptase


A
B
C
147.2 M
148 M
148.8 M
149.0 M
JAKMIP2
147.4 M
147.6 M
147.8 M
PDGFRB
149.8 M
150 M
150.2 M
D
Exon 11
Exon 10
PDGFRB
Exon 18
Exon 17
JAKMIP2