

**Case Report****A novel Germline JAK2 Splice-Site Variant Causing Exon 10 Skipping in a Patient with an ET-Like Thrombocytosis Phenotype and Early-Onset Tophaceous Gout**

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**Abstract.** Triple-negative essential thrombocythemia (ET) lacks canonical driver mutations, and its molecular basis remains largely undefined. A 26-year-old man presented with early-onset tophaceous gout and persistent thrombocytosis. Screening for JAK2 V617F, CALR and MPL was negative; extended sequencing identified a novel JAK2 splice-site variant (c.1326+2T>A), and RT-PCR confirmed complete exon 10 skipping, generating a truncated transcript predicted to retain the FERM domain—a configuration resembling recently reported germline JAK2 drivers of hereditary thrombocythemia.

**Keywords:** Germline JAK2 splice-site variant; Exon 10 skipping; Essential thrombocythemia; Tophaceous gout.

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**Introduction.** Gout is a common inflammatory arthritis typically associated with chronic hyperuricemia, and tophaceous gout is uncommon in young adults.<sup>1</sup> While myeloproliferative neoplasms (MPNs), including essential thrombocythemia (ET), can cause hyperuricemia through increased cell turnover, gout as a manifestation of ET is exceedingly rare.<sup>2</sup> In addition, the contribution of MPN-associated inflammation to gout pathogenesis, particularly in patients without canonical driver mutations, remains poorly understood. Here we report a 25-year-old man with an ET-like thrombocytosis phenotype and early-onset tophaceous gout who carried a novel germline JAK2 splice-site variant with experimentally confirmed exon 10 skipping,

and whose joint symptoms improved during pegylated interferon- $\alpha$ 2b therapy while serum uric acid remained elevated.

**Case Presentation.** A 25-year-old man presented in November 2025 with a 4-year history of recurrent inflammatory polyarthritis that developed after undergoing posterior lumbar spondylolysis repair in July 2021 at another medical institution. Before this lumbar surgery, he was diagnosed with glial fibrillary acidic protein antibody-associated autoimmune encephalitis in 2020. Preoperative evaluation revealed thrombocytosis, with a peak platelet count of  $817 \times 10^9/L$ , right calf muscular venous thrombosis, and

hyperuricemia (serum uric acid [SUA], 698  $\mu\text{mol/L}$ ). He denied any history of hepatitis, tuberculosis, or other infectious diseases. He had been smoking 6 cigarettes per day for 5 years and reported occasional alcohol consumption. There was no reported family history of hereditary disorders, hematological malignancies, myeloproliferative neoplasms, thromboembolic events, or gout.

Postoperatively, he developed bilateral knee pain and swelling, as well as swelling over the left fourth proximal interphalangeal (PIP) joint. Thrombocytosis persisted, and initial bone marrow aspiration showed hypercellular marrow with increased megakaryocytes and platelet clusters. Screening for canonical driver mutations was negative. A presumptive diagnosis of reactive arthritis was made, but treatment with iguratimod and an interleukin-2-based regimen produced limited benefit.

Several months later, reevaluation confirmed marked hyperuricemia (SUA 815.5  $\mu\text{mol/L}$ ), and a  $1 \times 1$  cm mass was noted over the left fourth PIP joint. The diagnosis was revised to gouty arthritis. Despite urate-lowering therapy, the patient experienced insufficient improvement in gout-related symptoms, which contributed to poor long-term treatment adherence.

Recurrent gout flares and thrombocytosis persisted over the following years, culminating in presentation to our hospital with a 1-week history of intermittent fever (peak  $39^\circ\text{C}$ ), progressive left lower-extremity swelling and worsening polyarticular pain. Physical examination revealed visible gouty tophi involving multiple PIP joints, with the largest tophus measuring  $1.5 \times 1.5$  cm. No hepatosplenomegaly was noted. Laboratory testing showed thrombocytosis ( $489 \times 10^9/\text{L}$ ), marked systemic inflammation (hsCRP 129.7 mg/L; ESR 60 mm/h; fibrinogen 6.40 g/L; D-dimer 1200 ng/mL FEU), and hyperuricemia (588  $\mu\text{mol/L}$ ).

By January 2026, after the acute episode had resolved, hsCRP had fallen more than tenfold to 11.21 mg/L, with decreases in fibrinogen (4.60 g/L), ESR (54 mm/h), and D-dimer (790 ng/mL FEU), whereas the platelet count had risen further to  $542 \times 10^9/\text{L}$  and SUA remained elevated (536.3  $\mu\text{mol/L}$ ). This dissociation between platelet count and acute-phase response argued against a purely reactive thrombocytosis. The peripheral blood smear showed giant platelets and platelet aggregation. Both bone marrow aspiration and trephine biopsy were formally evaluated. The trephine core ( $1.1 \times 0.2$  cm) showed approximately 60 vol% cellularity with trilineage hematopoiesis and normal granulocytic and erythroid maturation; megakaryocytes numbered 0–4 per high-power field, were dispersed rather than clustered, and showed no significant variation in size or nuclear atypia. Reticulin was graded MF-0, although the grading system was not specified in the pathology report. The evaluable core did not show features supportive of

prefibrotic primary myelofibrosis, although interpretation was limited by the small core size; flow cytometry revealed no abnormal blast population. Representative marrow morphology is shown in Supplementary Figure 1. The aspirate was hypercellular (58.5% granulocytic and 23.5% erythroid cells; granulocyte-to-erythroid ratio, 2.49:1), with 349 megakaryocytes on the whole smear. Of 25 classified megakaryocytes, 1 was promegakaryocytic, 5 granular, and 19 platelet-producing; platelets were increased, scattered, and clustered.

Conventional testing for JAK2 V617F, CALR, MPL, and BCR::ABL1 remained negative. Because canonical driver mutations were absent, we performed targeted next-generation sequencing, which identified a JAK2 splice-site variant in intron 10 (c.1326+2T>A, VAF 51.4%) and a KMT2A variant in exon 3 (c.1474G>C, VAF 50.3%). Sequencing of buccal epithelial cells, collected with precautions to minimize leukocyte contamination, detected both variants at comparable allele fractions (48.10% and 47.40%), establishing their germline origin. Family segregation testing was offered but declined. Neither variant had a ClinVar entry. The JAK2 variant was absent from gnomAD v2.1.1, and the KMT2A c.1474G>C, p.(Ala492Pro) variant was extremely rare (gnomAD allele frequency  $3.99 \times 10^{-6}$ ; rs782462364). Both were classified as germline variants of uncertain significance under an ACMG/AMP-style assessment; for JAK2, PVS1 was not applied because loss of function is not an established mechanism of JAK2-related thrombocytosis, and PS3 was not applied because no protein or signaling consequence was demonstrated. The KMT2A variant had no established association with thrombocytosis or gout and was not interpreted as an acquired clonal marker. Criterion-level assessments are provided in **Supplementary Table 1**. Reverse transcription PCR and Sanger sequencing confirmed complete skipping of exon 10 in mature mRNA, corresponding to a 112-nt deletion (c.1215\_1326del, **Figure 1**). The aberrant transcript was predicted to induce a frameshift and premature stop codon, potentially producing a truncated JAK2 protein without the JH2 and JH1 domains, which are the core structures mediating the activation of STAT5 signaling. Expression of this protein and its effect on JAK/STAT signaling were not assessed.

Based on sustained thrombocytosis over more than 4 years (platelet counts repeatedly  $>450 \times 10^9/\text{L}$ , peak  $817 \times 10^9/\text{L}$ , without cytoreductive therapy), increased megakaryocytes on bone marrow aspiration, the absence of canonical JAK2 V617F, CALR, and MPL driver mutations, and no identified secondary cause, the patient was considered to have an ET-like thrombocytosis phenotype with concomitant gout and was clinically managed as ET. Under this management framework, he was categorized as high thrombotic risk per the revised International Prognostic Score for Thrombosis in

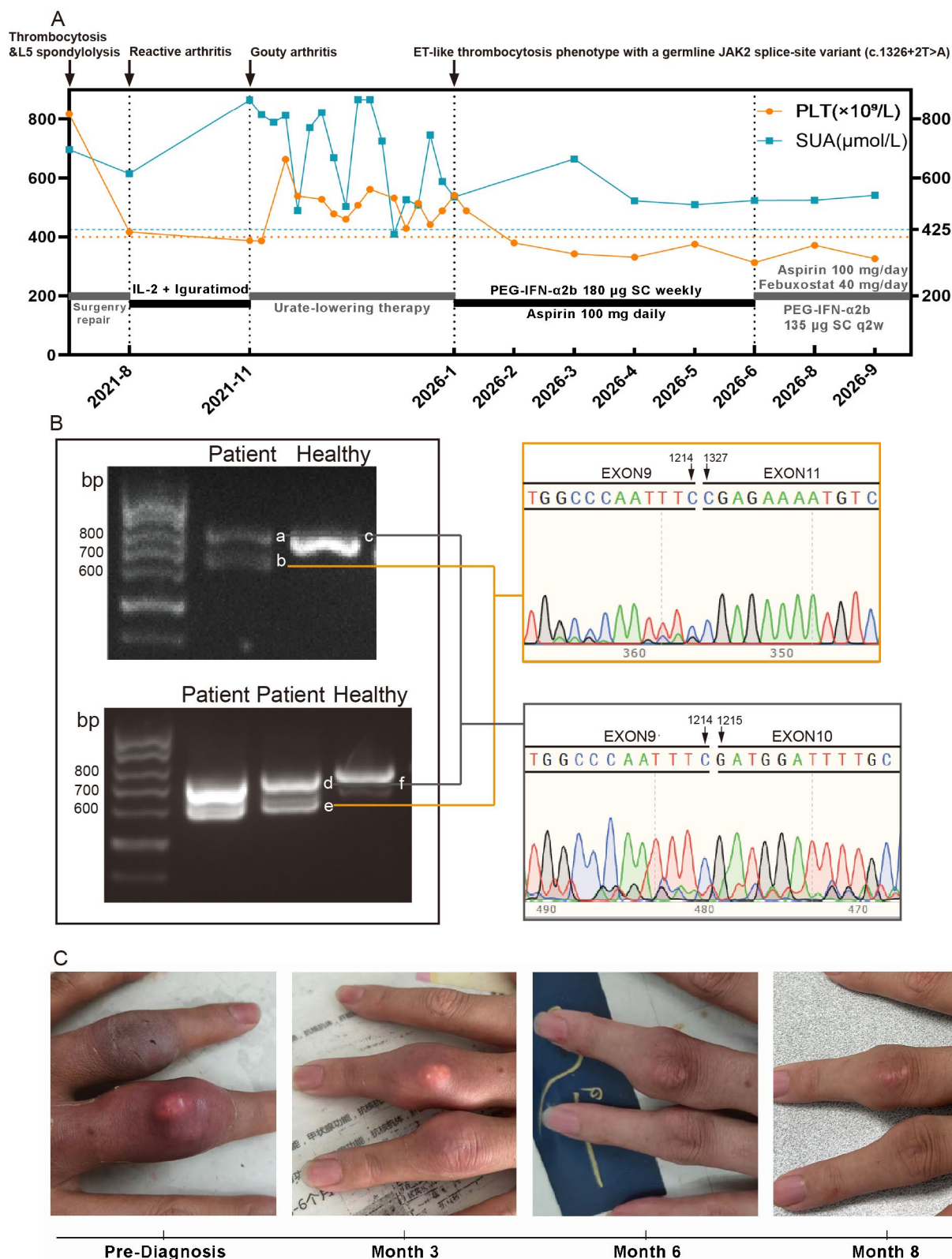


**Figure 1.** Treatment timeline, dynamic hematological parameters, and serial appearance of the tophi of the case.

Essential Thrombocythemia (rIPSET-T) because of his prior venous thrombotic event.

Accordingly, cytoreductive therapy with PEG-IFN- $\alpha 2b$  was initiated together with low-dose aspirin (100 mg daily) as antithrombotic prophylaxis. PEG-IFN- $\alpha 2b$  was given subcutaneously at 180  $\mu\text{g}$  once weekly, then

extended to 180  $\mu\text{g}$  every 2 weeks, and reduced to 135  $\mu\text{g}$  every 2 weeks from June 2026 after platelet normalization. The platelet count fell from  $588 \times 10^9/L$  at the start of treatment to  $332 \times 10^9/L$  at month 3 and subsequently remained within the reference range ( $314\text{--}376 \times 10^9/L$ ). The aberrant JAK2 transcript remained

detectable in peripheral blood during treatment (**Figure 1**). No colchicine, glucocorticoid, or anti-inflammatory dose of a nonsteroidal anti-inflammatory drug was administered at any time during PEG-IFN- $\alpha$ 2b therapy. No urate-lowering therapy was used between initiation of PEG-IFN- $\alpha$ 2b and 9 June 2026, when febuxostat 40 mg daily was prescribed; dispensing was intermittent thereafter, and adherence was not formally assessed. Joint symptoms and tophaceous swelling improved by month 3, before febuxostat was prescribed, and SUA remained elevated throughout treatment, including after febuxostat was prescribed, never reaching the treat-to-target range recommended for tophaceous gout. The treatment timeline, dynamic hematological parameters, and serial appearance of the tophi are summarized in **Figure 1**.

**Discussion.** This case is notable for several reasons. First, tophaceous gout in the setting of an MPN is extremely rare.<sup>2</sup> To our knowledge, only one case of JAK2 V617F-positive ET with gout has been reported, in a 66-year-old patient.<sup>3</sup> In contrast, our patient developed severe tophaceous gout at only 21 years of age, representing an unusually early presentation. The young age raises the possibility that mechanisms beyond age-related metabolic dysregulation contributed.<sup>4</sup>

Second, while the canonical JAK2 V617F mutation involves exon 14, our patient harbored a novel intronic variant causing complete skipping of exon 10. Notably, exon 10-skipping JAK2 transcripts have previously been described as physiologically occurring isoforms in healthy individuals and patients with hematologic disorders.<sup>5</sup> Their generation was not dependent on DNA mutations, and their physiological significance remains unclear. Unlike these low-abundance physiological transcripts, the c.1326+2T>A variant directly disrupts the canonical splice donor site and produces a prominent exon 10-skipped transcript in this patient. Nevertheless, because the frameshift introduces a premature termination codon, the exon 10-skipped transcript would be expected to be susceptible to nonsense-mediated mRNA decay, although it remained detectable by RT-PCR. Interestingly, Liu et al. recently reported that the germline JAK2 truncating variant E305Vfs\*4 (retaining only the FERM domain) acts as a potent autonomous driver in familial ET with constitutive STAT5 activation.<sup>6</sup> If the transcript in the present case partially escapes nonsense-mediated mRNA decay, a truncated FERM-containing product might in principle act similarly; however, this comparison does not establish functional equivalence. The evidence should be read at three levels: exon 10 skipping is demonstrated; a contribution to thrombocytosis is a reasonable hypothesis; and an autonomous driver role for a truncated FERM-containing protein remains unproven.

Third, the germline origin of the variant broadens the

biological interpretation of this ET-like thrombocytosis phenotype. Germline JAK2 alterations are an increasingly recognized cause of hereditary thrombocytosis, although the reported spectrum remains confined to a few missense and truncating variants.<sup>6,7,8</sup> To our knowledge, no germline splice-donor variant generating an exon 10-skipped transcript has been reported in this setting, and the present case may therefore extend that spectrum. We cannot determine whether this patient is best classified biologically as having acquired ET or germline JAK2-associated thrombocytosis without an acquired clonal marker and family segregation data. The negative family history does not establish the mode of inheritance.<sup>9</sup> Nevertheless, persistent thrombocytosis, a prior venous thrombotic event, and a clinically significant disease burden led to management based on the thrombocytosis phenotype, regardless of the eventual molecular classification.<sup>10</sup>

Fourth, the case raises important mechanistic questions about the relationship between MPN-associated inflammation and gout. Neutrophil extracellular traps (NETs) contribute to thrombosis and hyperinflammation in MPN<sup>11</sup> and have been implicated in monosodium urate-driven inflammation and tophus biology,<sup>12</sup> suggesting a mechanistic link between MPN-associated inflammation and gout.<sup>13</sup> PEG-IFN- $\alpha$  therapy has also been reported to reduce circulating NET levels in ET.<sup>14</sup> NET levels, inflammasome activity, and cytokines were not measured in this patient; the pathway outlined above therefore remains a speculative hypothesis.

In this patient, PEG-IFN- $\alpha$ 2b treatment normalized the platelet count, reduced the tophaceous swelling, and no further gout flares were documented; SUA remained elevated above the EULAR-recommended target of below 360  $\mu$ mol/L (below 300  $\mu$ mol/L in severe or tophaceous gout).<sup>15</sup> This raises the possibility that PEG-IFN- $\alpha$ 2b may improve gout by reducing crystal-driven inflammation rather than crystal burden, and that this improvement parallels the reported efficacy of canakinumab in reducing gout flares without lowering SUA.<sup>16</sup> However, spontaneous fluctuation cannot be excluded in a single patient. Notably, this observation should not be read as showing that control of inflammation can substitute for adequate urate-lowering therapy, since sustained lowering of SUA below target is required to dissolve monosodium urate crystals and prevent further deposition; attaining these thresholds has been associated with better outcomes.<sup>17</sup> In this patient, SUA remained above 500  $\mu$ mol/L at every assessment and urate-lowering therapy was delayed and intermittent, so biochemical control of gout was not achieved. Whether the observed reduction in tophi size reflects a true decrease in crystal burden therefore remains uncertain; longer follow-up with sustained attainment of the treat-to-target range would be required.

**Conclusions.** We describe a young man with an ET-like thrombocytosis phenotype and early-onset tophaceous gout in whom a novel germline *JAK2* splice-donor variant was shown to cause exon 10 skipping. The variant remains of uncertain significance, but its germline origin raises the possibility that this phenotype belongs to the emerging spectrum of germline *JAK2*-associated thrombocytosis. The experimentally demonstrated splice abnormality identifies this variant as a candidate for further functional study. In a young patient with unexplained thrombocytosis and negative canonical driver testing, extended molecular evaluation with germline confirmation may be informative.

**Statement of Ethics.** This study was approved by the Institutional Ethics Committee of Jinan University (Approval No. JNUECKY-20260720-133). All procedures involving human participants were conducted in accordance with local laws, institutional guidelines, and the Declaration of Helsinki. Written informed consent was obtained from all participants for both study participation and the potential publication of the data included in this article.

**Conflict of Interest Statement.** All authors declare that

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**Author Contributions.** Xun Zhu and Yaomei Long contributed to the collection of clinical information and manuscript preparation. Xun Zhu also performed the PCR experiments. Liye Zhong and Xiuli Wu contributed to revising the manuscript. Ling Xu contributed to the experimental design and manuscript revision. Jie Wu was responsible for patient diagnosis, treatment, and follow-up, and conceived the study concept. Xun Zhu and Yaomei Long contributed equally to this work. All authors read and approved the final manuscript.

**Data Availability Statement.** All data generated or analyzed during this study are included in this article and its supplementary material. Further inquiries can be directed to the corresponding author.