

# Co-existence of triple-negative essential thrombocythemia and double transcript chronic myeloid leukemia: A case report

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**Abstract.** Chronic myeloproliferative neoplasms (MPN) include polycythemia vera (PV), primary myelofibrosis, essential thrombocythemia (ET) and chronic myeloid leukemia (CML). Overlapping MPNs are rare; however, they can occur in the same individual. The present case report describes a patient with both triple-negative ET and CML. A 64-year-old woman was followed-up at our hematology clinic at Feist Weiller Cancer Center, Louisiana State University Health Shreveport (Shreveport, LA, USA) since 2000 after she was diagnosed with JAK2V617F-negative ET. The patient remained stable on hydroxyurea until 2012, when they underwent a bone marrow biopsy for progressively increasing white blood cell counts, and the pathology was consistent with CML; PCR for BCR-ABL was positive for both P210 and P190 transcripts. The patient was then initiated on dasatinib. After dasatinib, they were given a trial of imatinib, and were later transitioned to nilotinib and finally to bosutinib (2019) due to unchanged thrombocytosis. Next-generation sequencing from a bone marrow biopsy in 2019 demonstrated an EZH2 mutation that may be associated with triple-negative ET. CML was in major molecular response at that time. The patient was continued on bosutinib with hydroxyurea, after which hydroxyurea was changed to anagrelide due to worsening anemia and persistent thrombocytosis. However, bosutinib and anagrelide were discontinued due to worsening pulmonary hypertension. The patient was noted to have peripheral blasts of 14% by flow cytometry, after which they underwent a repeat bone marrow biopsy in 2022, which showed extensive myelofibrosis. BCR-ABL transcripts were undetectable. Given their accelerated myelofibrosis, the patient was started on a hypomethylating

agent, decitabine/cedazuridine, along with darbepoetin for anemia in June 2022. Given their persistent thrombocytosis, the patient was also started on peginterferon  $\alpha$ . Most studies reporting two clonal processes in the same patient have been for PV and CML. To the best of our knowledge, this is the first reported case of triple-negative ET with double transcript CML in the same individual.

## Introduction

Chronic myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), and chronic myeloid leukemia (CML) (1). The World Health Organization (WHO) in 2001 classified MPNs under a broader category now including chronic neutrophilic leukemia, chronic eosinophilic leukemia/hypereosinophilic syndrome, and unclassified (2). In 2016, WHO introduced the criteria for overlapping MPNs, in the form of four adult-onset etiologies, including chronic myelomonocytic leukemia (CMML), BCR-ABL1 negative atypical CML, MPN ring-sideroblasts and thrombocytosis and MPN unclassifiable, and a pediatric etiology, juvenile myelomonocytic leukemia (3).

The diagnosis of MPNs should be chased in increased blood cell count excluding secondary or reactive etiologies, with leukoerythroblastic smear. MPN characteristic clinic features include anemia, unusual thrombosis, splenomegaly, and signs of extramedullary hematopoiesis (4). Cytogenetic anomalies are demonstrated in about 70% of MPNs patients relying on conventional cytogenetic and single nucleotide polymorphism array karyotyping testing (5). The approach to clonal markers starts with JAK2-V617F first (96% sensitivity for PV and 60% for ET or PMF), then CALR (present in 20-25% patients with ET or PMF), followed by MPL (3-7% of patients with ET or PMF) (6). A bone marrow examination holds importance to morphologically distinguish clonal expansion and make accurate diagnosis of myeloid anomalies. Allogenic hematopoietic stem cell transplant (AHSCT) remains a curative option in high risk MPNs, with a long-term disease-free survival ranging between 18-47% (7).

ET has been associated with mutations in the JAK2V617F, CALR, or MPL driver genes; however, there are 5-10% of patients with ET without these mutations, presently called triple-negative ET (8). Limited studies are available on

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triple-negative ET, presently acknowledged as an indolent disease with constrained leukemic evolution (9).

Overlapping MPNs can rarely occur in the same patient, as in addition to morphological mimicry, each MPN has the genetic ability to evolve into another or a malignant form. The coexistence of BCR-ABL translocation and the JAK2-V617F mutation has been reported in the same individual previously (10). We report a unique case of long-standing triple-negative ET and CML with both P210 and P190 BCR/ABL transcripts in the same patient.

### Case report

A 64-year-old female was referred to our hematology-oncology clinic at Feist Weiller Cancer Center, Louisiana State University Health Shreveport (Shreveport, LA, USA) in May 1999 for persistent thrombocytosis of  $800-900 \times 10^3/\mu\text{l}$  during a pre-operative visit with ENT. After a diagnostic workup, she was diagnosed with triple-negative ET, started on Anagrelide for 4 years, and later switched to hydroxyurea. She remained stable on hydroxyurea for 12 years when she was noted to have a progressive increase in WBC counts ( $43.85 \text{ K}/\mu\text{l}$ ). She underwent a bone marrow biopsy, which was consistent with CML in the chronic phase, with BCR/ABL1 translocation in a total of 84.5 percent of nuclei. PCR for BCR-ABL was positive for both P210 and P190 transcripts (p190e1a2 0.016, p210b2a2 30.285 and p210b3a2 14.927). The patient was started on Dasatinib. She continued to have thrombocytosis, which was thought to be initiated due to uncontrolled CML. She was given a trial of Imatinib, later transitioned to Nilotinib, and finally to Bosutinib due to her unchanged thrombocytosis. She underwent a repeat bone marrow biopsy in 2019, which showed abundant megakaryocytes and the same M: E ratio (10:1) as in 2012. Next-generation sequencing (NGS) demonstrated an EZH2 mutation that can be associated with MPN. She was continued on hydroxyurea along with bosutinib, with overall poor control of thrombocytosis. In 2021, the patient was noted to have worsening anemia requiring blood transfusion, and hydroxyurea was stopped. A repeat bone marrow biopsy done in 2021 showed a markedly hypercellular marrow with erythroid hypoplasia and MPN or MDS/MPN unclassifiable, with no significant fibrosis (Fig. 1). With worsening anemia and persistent thrombocytosis, hydroxyurea was switched to low dose anagrelide to control thrombocytosis. Platelet counts improved on anagrelide. However, she developed acute hypoxic respiratory failure and was diagnosed with pulmonary hypertension. BCR/ABL transcripts that were repeated were negative. Anagrelide and bosutinib were discontinued as both drugs could worsen pulmonary hypertension. She was started on peginterferon  $\alpha$ -2a. Flow cytometry of peripheral blood showed 14% myeloblasts, and she underwent a repeat bone marrow biopsy, which showed myeloid-predominant bone marrow and extensive myelofibrosis (Fig. 2). Given accelerated myelofibrosis and negative BCR/ABL transcripts, she was started on a hypomethylating agent, decitabine/cedazuridine, along with darbepoetin for anemia and peginterferon  $\alpha$  (Table I). The patient is clinically stable and continues to follow with our outpatient clinic.

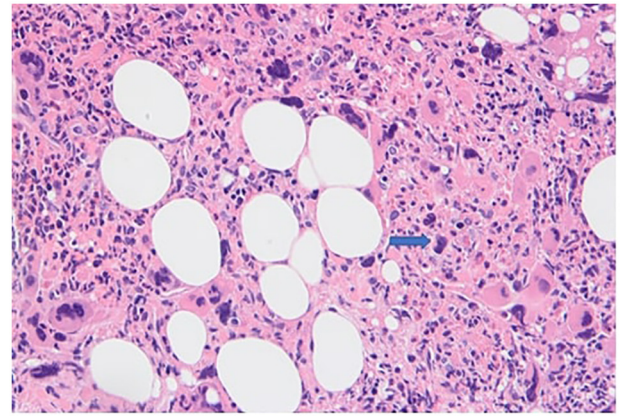


Figure 1. Histology of bone marrow (H&E) showing increased megakaryocytes (blue arrow).

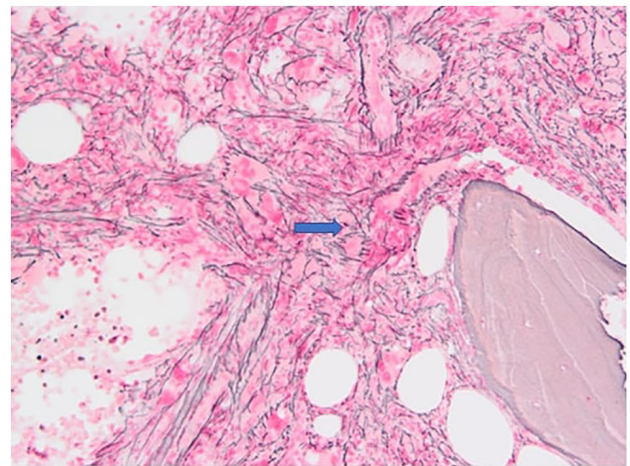


Figure 2. Histology of bone marrow (reticulin stain) showing increased reticulin staining representing bone marrow fibrosis (blue arrow).

### Discussion

This challenging and highly educative case has multiple unique milestones, including the coexistence of EZH2 positive, triple-negative ET, and CML with both P210 and P190 transcripts in the same individual. Three theories exist for the possible origin of concurrent MPNs. Firstly, two mutations can arise independently from a polyclonal stem cell, secondly, the initial mutation causes a subclone of the subsequent one, and finally both mutations follow another independent mutation (11).

ET follows a chronic, indolent course with a low incidence of leukemic evolution. A prospective study done on 40 triple-negative ET patients found only one case progressing to myelodysplastic syndrome over a follow-up period of 32 years (8). Acute transitions of ET have been specifically studied when accompanied by the Philadelphia chromosome. Stoll *et al* followed six women with ET who were noted to have leukocytosis and found to have the Philadelphia chromosome on karyotype analysis of their bone marrow. Five of these six women underwent clinical transformation to the accelerated phase of CM (12).

Table I. White blood cell and platelet counts associated with therapeutic intervention and disease progression of the patient.

Year	Therapeutic intervention	White blood cell count, K/ $\mu$ l	Platelet count, $\mu$ l	Disease progression
1999	Anagrelide for 4 years and switched to hydroxyurea	12.34	889	Diagnosed with triple-negative essential thrombocytosis
2012	Initiated on dasatinib	43.85	973	Diagnosed with chronic myeloid leukemia
2016	Trial of imatinib	9.2	828	Unchanged thrombocytosis
2017	Transitioned to nilotinib and finally bosutinib	14.26	1,462	Repeat bone marrow biopsy showed abundant megakaryocytes, and elevated myeloid cells to nucleated erythroid cells ratio (10:1), indicating myeloid hyperplasia significant for CML-like disorders
2021	Hydroxyurea switched back to anagrelide	5.59	1,060	Developed pulmonary hypertension; anagrelide and bosutinib were discontinued
2022	Peginterferon-2 $\alpha$ added	5.18	916	Flow cytometry of peripheral blood showed 14% myeloblasts, repeat bone marrow biopsy showed extensive myelofibrosis
2022	Hypomethylating agent, decitabine/cedazuridine, started	4.74	432	Stable platelet count

Mutations leading to platelet proliferation in ET have been identified in prospective studies. JAK2V617F mutations are found in 50 to 65% of the patients, CALR exon 9 mutations in 20 to 25%, and MPL exon 10 mutations in 5% (13). Another prospective study done on 40 patients with ET found the most frequent sequence variants were in the TET2 gene, followed by the KIT gene (14). Our patient had an EZH2 mutation, which is not extensively studied in patients with ET.

Most studies reporting two clonal processes in the same patient have been for PV and CML. As per our best knowledge, this is the first reported case of triple negative ET with CML with both P210 and P190 in the same individual. This case signifies the importance of cytogenetic and molecular testing in cases of chronic MPNs to look for leukemic transformation. Additional literature is needed to explore the co-existence of MPNs.

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#### Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

#### Authors' contributions

RL was responsible for drafting the entire manuscript, reviewing past literature, designing and conceptualizing the manuscript, critically reviewing it for intellectual content and gave the final approval of the version to be published. RL is also accountable for all aspects of the manuscript, including any concerns for accuracy or integrity. SJG was involved in writing the description of the images, reviewing the manuscript and was also responsible for critically revising the manuscript for intellectual content. SJG also substantially contributed to the conception and design of the manuscript and is accountable for all aspects of the manuscript, including any concerns for accuracy or integrity. PR identified the clinical significance of this case, supervised, reviewed and edited the final case report, and conceived the idea for the case report. RL and PR confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

#### Ethics approval and consent to participate

Not applicable.

#### Patient consent for publication

Full written informed consent was obtained from the patient. The patient is fully aware that her case has been submitted for publication.

## Competing interests

The authors declare that they have no competing interests.

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