


# Isolated ten-eleven translocation 2 positive in triple negative essential thrombocythemia: Case report and literature review

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Rehab Y AL-Ansari<sup>1</sup> , Dena Al Otaibi<sup>2</sup>,  
Nourah Al Hudaithi<sup>3</sup> and Leena Abdalla<sup>1</sup>

## Abstract

Essential thrombocythemia is one of the famous diseases under the category of myeloproliferative disorder. It is an end result of a genetic mutation of one or more of the most frequent oncogenes such as Janos kinase 2 (JAK2), MPL proto-oncogene, thrombopoietin receptor (MPL), and calreticulin (CALR). However, negative genetic markers, so-called (triple negative disease), can happen in the presence of other uncommon types of mutation. TET2 (ten-eleven translocation 2) positive as isolated genetic marker in triple negative essential thrombocythemia is uncommon genetic presentation. For that, we are reporting a 22-year-old lady who presented with a feature of dyspepsia and accidentally found to have persistently high platelet count, even after treating her mild iron deficiency anemia with no other secondary causes. Further investigations and bone marrow biopsy supported the diagnosis of isolated TET2 positive in triple negative essential thrombocythemia. We treated her conservatively with good hydration and low dose of aspirin. In conclusion, isolated TET2 positive in triple negative essential thrombocythemia at presentation is uncommon with no clear management or risk stratification guideline. However, it is hypothesized that *TET2* mutation precedes *JAK2*; therefore, the detection of isolated TET2 in a triple negative essential thrombocythemia case should be closely followed for clonal evolution in long term. Further study and guidelines required in this area.

## Keywords

Essential thrombocythemia, myeloproliferative disorder, TET2 positive, triple negative, gene

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## Learning points

- Isolated TET2 positivity in triple negative essential thrombocythemia at presentation is an uncommon presentation.
- There are no guidelines on treatment as well as no clear significance of TET2 in essential thrombocythemia, the area needs further study and research works.

## Introduction

Essential thrombocythemia (ET) is one of the hematological diseases under the classification of myeloproliferative disease.<sup>1</sup> It is predominantly acquired genetic disease that occurs due to somatic gene mutations of the stem cells. Janos kinase 2 (JAK2) (V617F), MPL, and calreticulin (CALR)

(that account for 60%, 8%, and 30%–35%, respectively) were incorporated by the World Health Organization (WHO) as major diagnostic criteria to diagnose ET. Up to 20% of ET cases have no mutations of those common oncogenes so-called triple negative disease.<sup>2,3</sup> Less commonly, ET can be

<sup>1</sup>Adult Hematology Unit, Internal Medicine Department, KFMMC, Dhahran, Kingdom of Saudi Arabia

<sup>2</sup>Internal Medicine Department, KFMMC, Dhahran, Kingdom of Saudi Arabia

<sup>3</sup>College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Kingdom of Saudi Arabia

### Corresponding Author:

Rehab Y AL-Ansari, Adult Hematology Unit, Internal Medicine Department, KFMMC, Dhahran 31932, Eastern Province, Kingdom of Saudi Arabia.

Emails: dr\_rehab10000@hotmail.com; rehab@kfmmc.med.sa



inherited as an autosomal dominant familial ET.<sup>4</sup> Damla Olcaydu et al.<sup>5</sup> in a study of the role of genetic mutation in familial type of myeloproliferative neoplasm stated that, the germline mutations of ten-eleven translocation 2 (TET2) do not explain familial type of myeloproliferative disorder.

## Case report

A 22-year-old female is not known to have chronic medical illnesses. Presented to the emergency department with epigastric pain and vomiting for a couple of days with no similar presentation before. Thoroughly investigated by gastroenterologist and labeled as dyspepsia after gastroscopy. Found to have persistently high platelet count ranging between 600 and 900 × 10<sup>9</sup>/L level for 4 years duration. Referral to hematology service was done for further investigation.

Patient had thrombocytosis since 2015, had no history of thrombosis or bleeding, and no history of significant weight loss. She has no risk factors for Coronary Vascular Disease. Has positive family history of myeloproliferative disease in her aunt who was diagnosed recently to have high-risk ET with positive *CALR* gene mutation.

On examination, the patient looks well, not pale, jaundiced, or cyanosed. Blood pressure was 113/53 mm Hg, temperature was 36.6°C, pulse was 85 beats per minute, respiratory rate was 19 per minute, and oxygen saturation was 100% on room air. There was no lymphadenopathy. Respiratory system and cardiovascular system examination was unremarkable. Abdominal examination was negative for any masses or organomegaly. Grossly intact neurological examination was carried out. In lower limbs, there is no edema or evidence of deep veins thrombosis clinically.

Initial investigations showed hemoglobin of 12.7 g/L, white blood cell (WBC) of 6.08 × 10<sup>9</sup>/L, platelets of 680 × 10<sup>9</sup>/L with normal mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH). Reticulocytes count was 1.39%. Liver panel and renal panel were within normal, lactate dehydrogenase (LDH) was 163 U/L, aspartate aminotransferase (AST) was 15.2 U/L, total bilirubin was 6 μmol/L, and direct bilirubin was 2 μmol/L. Partial thromboplastin time (PTT) was 31.9 and international normalized ratio (INR) was 1.13. Ferritin was 20.8, iron was 10 which is the borderline level, as per our reference range, and total iron binding capacity (TIBC) was 66. Peripheral Blood Film showed normochromic normocytic red blood cells picture with normal weight blood cells count and morphology, platelets were increased in distribution, and no blast or abnormal cell was seen. Ultrasound abdomen showed no organomegaly, spleen measures were 9.5 cm, and liver measures were 12.6 cm, otherwise unremarkable scan.

Bone marrow examination showed increased megakaryocytes with no increased in blast cells or dysmorphic cell and no fibrosis (Figure 1). Flow cytometry showed normal study

with no signaling that indicated the presence of any active hematological malignancy. Cytogenetic study for *BCR/ABL* gene mutation showed negative test for any mutation, and no mutation was detected in *JAK2* gene, Exon 12 and 14, as well as *CALR* and *MPL* genes. Extended cytogenetic and molecular study showed TET2 (c.3813C>T) mutational burden 45%. Other genes such as *ASXL1*, *CBL*, *DNMT3A*, *EZH2*, *IDH1*, *RUNX1*, *SF3B1*, *SRSF*, *TP53*, *UAF1*, and *ZRSR2* were not mutated.

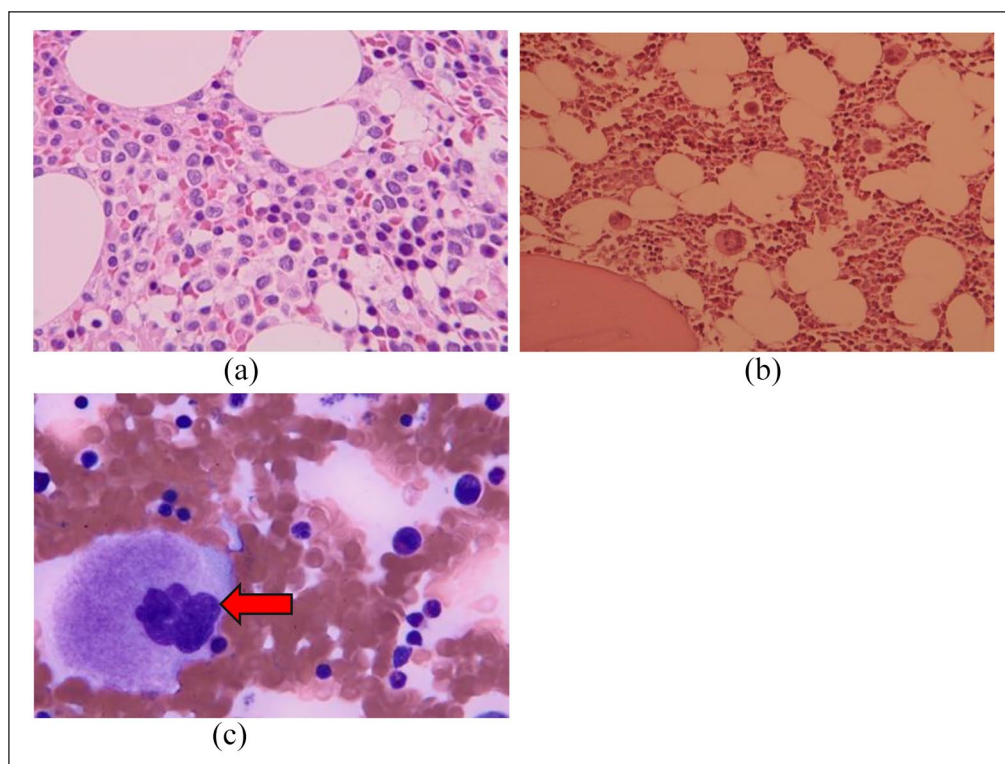
Hence, the patient was labeled as very low-risk triple negative—TET2 positive—ET and she was advised to increase fluid intake, her iron deficiency was treated, and to maintain on prophylaxis, aspirin 81 mg was given per oral once daily. Since then, she is on follow-up with hematologist for any progress in her condition. She had no further admissions for any reason since then.

## Discussion

In 2016, WHO updated the diagnostic criteria for ET. The diagnosis requires meeting either all four major criteria or first three major criteria and one minor criterion. The major criteria are as follows (1) platelet count ≥450 × 10<sup>9</sup>/L, (2) bone marrow (BM) biopsy showing proliferation mainly of the megakaryocyte lineage, (3) not meeting WHO criteria for chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), or other myeloproliferative or myeloid neoplasms, and (4) the presence of *JAK2*, *CALR*, or *MPL* mutation. The minor criteria were the presence of a clonal marker or the absence of evidence for reactive thrombocytosis.<sup>5</sup> Based on the above criteria, our case was matching first three major criteria and one minor criterion to diagnose ET. *TET2* mutation is not involved as criteria neither major nor minor to diagnose ET. As well, it is not considered as a marker for familial ET which was expected in our case scenario with positive family history of ET. The importance of the presence of *TET2* mutation and its prognostic impact in ET was of major concern in such a case, especially with the absence of major oncogenes that have prognostic and diagnostic value in ET. For that, we are reporting this case with further review of the literature to clarify how isolated TET2 will play a role in the management and outcome of patients with ET.

### What is TET2?

The *TET2* is a gene that encodes in epigenetic regulator which is important for myeloid cell function. It is one of the genetic variants which has diagnostic and prognostic impact in several hematological diseases such as myeloid malignancy.<sup>6</sup> Although it accounts for 5%–10% of genetic changes that occurs in normal population especially in above 65 years old group of age, *TET2* mutation is also detected in chronic myelomonocytic leukemia (CMML) by around 40%–50% of positive cases, 20%–30% in MDS, and 10%–15% of acute



**Figure 1.** Real bone marrow picture for the same patient showed (a) trephine biopsy with increase cellularity and no blast cell seen, (b) trephine biopsy with increase megakaryocyte distribution, and (c) morphology from aspiration with healthy appearing megakaryocyte (arrow).

myeloid leukemia (AML) cases.<sup>7,8</sup> *TET2* mutation plays an important role in myeloid cell function, DNA demethylation of hematopoietic cell which affects the myeloid malignancy such as MDS and tumor progression as well as the patient outcome and reduces the overall survival in AML of intermediate risk group of patients.<sup>9,10</sup> Moreover, *TET2* mutations have been found in lymphoid malignancies as in some T cell lymphomas, as well and to a less extent in B cell lymphoma as in mantle cell lymphomas and diffuse large B cell lymphoma.<sup>11</sup> Even more, *TET2* mutation was also reported in benign cases as in patients with bronchial asthma and chronic obstructive pulmonary disease (COPD) patients with no clear relationship.<sup>12</sup>

#### Frequency of *TET2* positive in ET?

The incidence of *TET2* mutations in myeloproliferative disorders in general ranges between 0% and 17%.<sup>13</sup> Luz Martinez-Aviles et al.<sup>14</sup> reviewed 62 cases with myeloproliferative disorder those are negative for *JAK2* and *MPL* gene mutations, 52 cases were diagnosed as ET, and three of them were isolated *TET2* gene mutation positive. Julia Asp et al.<sup>2</sup> studied the genetic mutation detected by TruSight Myeloid Sequencing Panel in 129 patients diagnosed with ET between 2008 and 2013, and they found that 6% were triple negative and extended genetic panel showed the expression of *TET2*, *SRSF2*, or *ASXL1*, around 2% of them were isolated *TET2*

positive. Recent genetic study revealed that around 50% of patients with ET have types of mutations other than *JAK2*, *MPL*, or *CALR* mutation such as *TET2*, *ASXL1*, *DNMT3A*, and *SF3B1* with frequency of 16%, 11%, 6%, and 5%, respectively.<sup>15</sup>

#### Significance and prognosis of *TET2* in ET

Patients with ET are at risk of both thrombosis and bleeding which account for the major cause of morbidity and mortality. However, less than 5% of cases with ET will end by transformation to myelofibrosis or acute leukemia especially in high-risk group stratification. The presence of *JAK2* or *MPL* mutations in ET patients has been associated with higher risk of arterial thrombosis. Moreover, the presence of at least one of the following mutations *SH2B3*, *SF3B1*, *U2AF1*, *TP53*, *IDH2*, and *EZH2* is associated with inferior overall survival in ET population. Julia Asp et al.<sup>2</sup> stated that *TET2* mutations have different types and cannot use it as diagnostic or prognostic marker with no effect in overall survival. This fact is not applicable to *SRSF2* and *ASXL1* as both were found to have worse overall survival.

In experimental mice, *TET2* mutation and deficiency were found to play a role in the pathogenesis of cardiovascular events and atherosclerosis as well it increases lung inflammation and increases pulmonary arterial pressure.<sup>16</sup> There is no study about cardiovascular events and atherosclerosis in

human being affected by TET2 positive ET. However, some studies showed that *TET2* mutations may be an independent risk factor for thrombosis in patients with polycythemia vera but not in ET. Recently, one publication by Ayalew Tefferi et al.<sup>15</sup> presented the analytic data of deep sequencing in ET, and it highlights the association between positive *TET2* mutations and thrombosis in ET independent to the presence of famous oncogenes or age.

TET2 has more prevalence in old age population affected by ET in comparison to younger age group. In the study by Tefferi et al.,<sup>17</sup> three out of fifty ET patients who had *TET2* mutations were senior age and followed up for several months showed no leukemic transformation, as well as, there was no correlation between the presence of mutant *TET2* and survival or leukemic transformation in other types of myeloproliferative disorder.

TET2 proteins play a significant role in epigenetic regulation which affects immune responses and regulation. Furthermore, TET2 mediated the oxidation of 5-methylcytosine (5mc) and regulated DNA methylation as well as demethylation which by itself affect differentiation and function of lymphoid and myeloid. In case of such gene mutation, function of TET2 will be impaired, oxidation to 5mc will be affected and DNA methylation will be altered. Alteration of DNA methylation plays an important role in pathogenesis of myeloproliferative disorder (MPD) and other hematological malignancy. Furthermore, the possibility exists that *TET2* mutations at the level of the stem cell might result in increase likelihood of hematopoietic transformation and aberrant myelopoietic due to alteration in DNA methylation.<sup>8,18</sup>

Up to date, there is no strong evidence to support poor prognosis, inferiority of overall survival, leukemic or fibrotic transformation in patient with isolated TET2 positive—triple negative ET. Although the possibility of increase thrombosis with TET2 is there, but it is still area of controversy which requires more study in large sample size.

### Treatment and follow-up of TET2 positive ET

The aim of treatment of patient with ET is to prevent mortality and morbidity that could be secondary to either thrombosis or bleeding.<sup>19</sup> Not all patients will be requiring treatment and it is highly depended on risk stratification (very low risk, low risk, intermediate risk, and high risk): very low risk (no history of thrombosis, no *JAK2* mutation and age  $\leq 60$  years), low risk (no history of thrombosis, *JAK2* mutation with age  $\leq 60$  years), intermediate risk (no history of thrombosis, no *JAK2* mutation and age  $> 60$  years), and high risk (history of thrombosis at any age or *JAK2* mutation with age  $> 60$  years). Based on NCCN guideline for 2020, very low and low-risk patients do not require cytoreduction and the cornerstone of management on those groups is to prevent and control cardiovascular risk factor, monitor for any thrombosis or acquired Von Willebrand deficiency, and adding low dose of aspirin in selective cases for vasomotor symptoms. In

intermediate-risk patient, the guideline recommends same recommendations for very low/low-risk group with using of aspirin and frequent follow-up for symptoms and complication which could be indicative tool to start cytoreduction therapy. High risk group patients are the candidates for cytoreduction preferably hydroxyurea, but other therapy such as peginterferon alfa-2a and anagrelide can be used, in addition to aspirin and controlling cardiovascular risk factor and monitoring for thrombosis or bleeding.<sup>20</sup> TET2 was not considered in any risk groups, as well as no specific site recommendation. Agathocleous and Meacham<sup>21</sup> in 2017 demonstrated that vitamin C regulates TET2 function in hematopoietic stem cells, but there are no data about the effect of vitamin C as a part of treatment for TET2 positive myeloproliferative disorder.

As *TET2* mutation plays a dynamic role in alteration of DNA methylation and development as well as progression of hematological malignancy, consideration of hypomethylating agent as a treatment option could carry significant value. Studies showed that clonal *TET2* mutations predicted response to hypomethylating agents such as azacitidine (AZA) in MDS and improved survival rate in promyelocytic leukemia (PML).<sup>22,23</sup> Although the alteration of DNA methylation plays an important role in pathogenesis of MPD, there is no report or study supports the rule of hypomethylating agent in MPD with *TET2* positive mutation.

Whether TET2 is positive or not, triple negative ET seems to have risk of complications almost similar to ET with *JAK/MPL* or *CALR* mutation. In case series of 22 triple negative ET, the rate of thrombosis and symptom burden is similar to other ET patient with positive famous genes mutation in low-risk group.<sup>24</sup> Although we risk stratify and manage our patient as very low-risk group based on NCCN guideline, yet quarterly a year is desired for follow-up and assessing for any complications or transformation.

Since there is no specific guideline for management of TET2 positive ET, the follow-up of the patient will be as other ET patient which is every 3–6 month and as per need to monitor for active symptoms, complications, Von Willebrand disease (VWD), and any transformation. In general, our case scenario is considered as series to what was reported previously rather than reporting for novelty and the aim of such report is to promote further research to help in more understanding of the importance of such finding.

### Conclusion

Isolated *TET2* positive mutation in ET is an uncommon genetic presentation of the disease. It could carry some significant prognosis and outcome that requires attention and life-long follow-up. There is no guideline to classify the patient with isolated TET2 positive ET to specific risk group stratification. Moreover, there are no guidelines in how to manage this group of patients and whether cytoreduction agent is indicated or not. However, it is hypothesized that *TET2* mutation



precedes *JAK2*; therefore, the detection of isolated TET2 in a triple negative ET case should be closely followed for clonal evolution in long term. Further studies and guidelines are required in this area.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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### Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

### ORCID iD

Rehab Y AL-Ansari  <https://orcid.org/0000-0003-4331-5769>

### References

- [https://rarediseases.info.nih.gov/diseases/6594/essential-thrombocythemia#ref\\_1257](https://rarediseases.info.nih.gov/diseases/6594/essential-thrombocythemia#ref_1257)
- Asp J, Andréasson B, Hansson U, et al. Mutation status of essential thrombocythemia and primary myelofibrosis defines clinical outcome. *Haematologica* 2016; 101(4): e129–132.
- Thiele TBJ, Gisslinger H and Kvasnicka HM. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J* 2018; 8: 15.
- TET2 gene. *Genetics Home Reference*, 2014, <https://ghr.nlm.nih.gov/gene/TET2>
- Olcaydu D, Rumi E, Harutyunyan A, et al. The role of the JAK2 GGCC haplotype and the TET2 gene in familial myeloproliferative neoplasms. *Haematologica* 2011; 96(3): 367–374.
- Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. *Blood* 2013; 122: 3616–3627.
- Ferrone CK, Blydt-Hansen M and Rauh MJ. Age-associated TET2 mutations: common drivers of myeloid dysfunction, cancer and cardiovascular disease. *Int J Mol Sci* 2020; 21: 626.
- Delhommeau F, Dupont S, DellaValle V, et al. Mutations in TET2 in cancer. *N Engl J Med* 2009; 360: 2289–2301.
- Zhang X, Fu R, Yu J, et al. DNA demethylation: where genetics meets epigenetics. *Curr Pharm Des* 2014; 20(11): 1625–1631.
- Patel J, Gönen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med* 2012; 366: 1079–1089.
- Ito K, Lee J, Chrysanthou S, et al. Non-catalytic roles of Tet2 are essential to regulate hematopoietic stem and progenitor cell homeostasis. *Cell Rep* 2019; 28(10): 2480–2490.e4.
- Buscarlet M, Provost S, Zada YF, et al. DNMT3A and TET2 dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. *Blood* 2017; 130: 753–762.
- Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. *Leukemia* 2010; 24(6): 1128–1138.
- Martínez-Avilés L, Besses C, Álvarez-Larrán A, et al. TET2, ASXL1, IDH1, IDH2, and c-CBL genes in JAK2- and MPL-negative myeloproliferative neoplasms. *Ann Hematol* 2012; 91(4): 533–541.
- Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. *Blood Adv* 2016; 1: 21–30.
- Fuster J, MacLauchlan S, Zuriaga M, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science* 2017; 355: 842–847.
- Tefferi A, Pardanani A, Lim KH, et al. TET2 mutations and their clinical correlates in polycythemia vera, essential thrombocythemia and myelofibrosis. *Leukemia* 2009; 23: 905–911.
- Cong B, Zhang Q and Cao X. The function and regulation of TET2 in innate immunity and inflammation. *Protein Cell* 2021; 12(3): 165–173.
- Ashorobi D and Gohari P. *Essential thrombocytosis*. Treasure Island, FL: StatPearls Publishing, 2020.
- NCCN clinical practice guideline in oncology—Myeloproliferative Neoplasm-Version 1, 2020, [https://www.nccn.org/professionals/physician\\_gls/pdf/mpn.pdf](https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf)
- Agathocleous M and Meacham C. Ascorbate regulates hematopoietic stem cell function and leukemogenesis. *Nature* 2017; 549: 476–481.
- Bejar R, Lord A, Stevenson K, et al. TET2 mutations predict response to hypomethylating agents in myelodysplastic syndrome patients. *Blood* 2014; 124: 2705–2712.
- Song C, Wang L, Wu X, et al. PML recruits TET2 to regulate DNA modification and cell proliferation in response to chemotherapeutic agent. *Cancer Res* 2018; 78(10): 2475–2489.
- Sadjadian P, Wille K, Becker T, et al. Triple-negative essential thrombocythemia: not per se low risk: a case series of 22 patients. *EHA Library*. Sadjadian P. 06/12/20; 298039; PB2125, <https://library.ehaweb.org/eha/2020/eha25th/298039/parvis.sadjadian.triple-negative.essential.thrombocythemia.not.per.se.low.risk.html?f=listing%3D0%2Abrowseby%3D8%2Asortby%3D1%2Asearch%3Dpb2125>