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Brief Communication

Essential thrombocytosis transformed AML with TP53 mutations and its clinical implications

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Abstract
Essential thrombocytosis (ET) is a chronic myeloproliferative neoplasm. There is a rare possibility of its transformation from ET into acute myeloid leukemia (AML). While the TP53 mutation is a well-known risk factor for AML, limited research exists regarding ET patients who develop AML with TP53 mutations. Among three ET transformed AML patients, two exhibited TP53 mutations, with an increased number of AML cells. Conversely, the third ET patient who transformed to AML without TP53 mutations had a lower burden of AML cells. The patients with TP53 mutations had shorter survival times compared to that without mutations, in response to decitabine treatment. In contrast, the patient with ET transformed AML without TP53 mutations showed a better response to decitabine. The ET transformed AML without TP53 mutations patient exhibited a survival period exceeding 20 months. ET patients who develop AML with a high allelic burden of TP53 mutations may experience a more aggressive disease progression and severe complications compared to AML patient without TP53 mutations. Our report sheds light on the distinct clinical presentations of ET patients who develop AML, characterized by different TP53 mutations and varying therapeutic outcomes when treated with decitabine. However, further studies that include a larger quantity of samples are needed to elucidate the precise underlying molecular mechanisms involved in this process.

Highlights
What is the new aspect of your work? The new aspect of our current study is that AML transformed ET with TP53 mutation appears to have a worse prognosis than without TP53 mutations, partly due to a higher tumor load of white blood cells.
What is the central finding of your work? There is a poor outcome for ET transformed AML with TP53 mutations despite the addition of demethylation therapy or other traditional chemotherapy.
What is (or could be) the specific clinical relevance of your work? We hypothesise that TP53 mutations lead to a poor prognosis in ET transformed AML, although a clinical trial of arsenic trioxide may demonstrate an improvement in the response of the patients.

Keywords Essential thrombocytosis · Acute myeloid leukemia · Transformation · Prognosis

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1 Introduction

Essential thrombocytosis (ET) is a chronic myeloproliferative neoplasm (MPN) characterized by an overproduction of platelets. It is typically associated with specific genetic mutations, including Janus kinase 2 (JAK2) V617F, calreticulin (CALR), or thrombopoietin receptor (MPL) mutations [1]. Common complications of ET include transient ischemic attacks, ocular migraines, erythromelalgia, and acquired von Willebrand's disease. ET is considered the least aggressive form of MPN, but there is a rare possibility of transformation into acute myeloid leukemia (AML) [1]. The incidence of leukemic transformation among ET patients is low, ranging from 0.5 to 1% per year within the first ten years following diagnosis [2–4]. Unfortunately, the prognosis for patients who undergo AML transformation is generally extremely unfavorable, with most individuals succumbing to the disease within a few months [2–4].

As the MPN progresses, genes relevant to the transformation into AML undergo further mutations, leading to clonal evolution. This process is considered a key factor in the pathogenesis of AML, yet the precise mechanisms underlying these mutations and their association with the transformation of ET to AML require further investigation [5]. It has been established that TP53 mutation is a significant risk factor for AML [6–9] and has been inversely correlated with AML prognosis. The progression from ET to AML involves hematopoietic stem cell disorders that acquire clonal evolution [6, 10–12] and is accompanied by gene mutations such as TP53, ASXL1, and IDH [6, 10–14]. However, the specific genes that regulate this transformation remain unclear [11, 15]. Despite extensive clinical and basic research conducted over several decades to identify potential therapeutic targets for novel drugs, the management of AML resulting from ET transformation remains a subject of debate [4, 11, 12, 16].

This report presents the clinical and laboratory findings of three patients with ET who underwent transformation into AML. Notably, two of the patients had TP53 mutations with a high variant allele frequency (VAF), and exhibited a particularly poor prognosis, while the third patient did not have any TP53 mutations and exhibited a better prognosis. These data lead us to hypothesize that the presence of TP53 mutations with a high VAF may lead to a poorer prognosis during AML transformation from ET.

2 Patients

From January 2012 to May 2023, three individuals undergoing their annual health checkup were identified to have abnormal peripheral blood profiles, exhibiting significantly elevated platelet counts. Following this discovery, these patients were subsequently referred to the Department of Haematology at The Ninth People's Hospital, Shanghai Jiaotong University School of Medicine. Upon evaluation, these individuals presented with severe thrombocytosis, characterized by markedly elevated platelet counts ranging from 926 to 1031 $\times 10^9$/L. Additionally, bone marrow biopsies revealed the presence of megakaryocytes with hyperlobulated nuclei, further supporting the diagnosis. This study has received approval from the Ethics Committee at The Ninth People's Hospital, Shanghai, China and is in accordance with The Declaration of Helsinki guidelines and regulations. Consent to Participate and Consent to Publish were obtained from all participants. In addition, all methods were carried out in accordance with relevant guidelines and regulations.

3 Results

The diagnosis and management of these patients followed *The Management Recommendations from The European LeukemiaNet* [17].

Case 1: A 64-year-old male patient presented with an abnormal full blood count during a routine annual checkup, prompting referral to the Hematology Department. Upon further evaluation, the patient was diagnosed with ET based on bone marrow biopsy findings, and the presence of a CALR gene mutation along with a high platelet count (926 $\times 10^9$/L). WBC in case 1 was 53.34?×?10^9/L. No TP53 mutations were identified at this time, using the NGS method, as described [18] (Supl Table S3). The patient underwent treatment with interferon (IFN) without experiencing any adverse events, including thrombotic events, resulting in one year of remission following treatment. However, during regular monthly consultations with the Hematology Department, an abnormal full blood count (leucocytosis 53.34 $\times 10^9$/L) was detected one year after the initial ET diagnosis. Subsequently, a second bone marrow biopsy was performed, confirming the development of AML.

The biopsy indicated the presence of a TP53 p.V172A mutation (with a VAF of 51.3%), in addition to the previously identified CALR mutation, which had not changed since the diagnosis of ET. The TP53 mutation (p.V172A) is a missense mutation that has been observed in several solid tumors [19] (Genomic Mutation ID: COSV52683521), but has not previously been seen in AML, based on extensive online searches, including COSMIC. Consequently, we cannot confirm that it is pathogenic or that it was the cause of the AML.

Notably, no abnormal chromosomal karyotype was observed prior to or after the development of AML. The patient received immediate treatment with D-HA chemotherapy regimens (including decitabine, homoharringtonine, and cytarabine) upon AML diagnosis. Unfortunately, despite the treatment, the patient passed away within seven days. Consequently, this patient's response is not evaluable due to early mortality.

Case 2: A 61 year-old male patient was referred to the Department of Hematology after an abnormal full blood count was detected. Following a bone marrow biopsy, the patient was diagnosed with ET without any gene mutations. The bone marrow morphology showed megakaryocytic hyperplasia, but no dysplasia/ringed sideroblasts. A MPN/MDS diagnostic panel, that including testing for TP53 mutations, was used for genetic testing in China [20]. Treatment with hydroxyurea led to remission, and the patient underwent regular monthly consultations for routine checkups. However, seven years after achieving remission, the patient visited the Department of Hematology complaining of fatigue. A routine evaluation revealed an extreme abnormality in the full blood count, characterized by markedly elevated white blood cell counts (96.28×10^9/L) with 94% blast cells, as well as severe anemia with a hemoglobin level of 54 g/L. Immediate bone marrow biopsy confirmed a diagnosis of AML. The biopsy revealed the presence of TP53 p.Y220C (with a VAF of 43.3%) and TP53 p.H179R mutations (with a VAF of 48.5%). The two TP53 mutations (p.H179R and Y220C) are missense mutations that have been observed in AML, based on extensive online searches, including COSMIC [19] (Genomic Mutation ID: COSV52661282; Genomic Mutation ID COSV52661712). Unfortunately, re-testing of the initial ET sample was not performed. Additionally, chromosomal karyotyping demonstrated a 45,XY,−3,del(4)(q21),?add(5)(q13),−7,+mar [4] mutation. The addition of fluorescent in situ hybridization (FISH) would provide more solid evidence in the current diagnosis, however, it was not routinely performed. We will investigate in more depth in future. D-HA chemotherapy, consisting of decitabine, homoharringtonine, and cytarabine, was initiated as the treatment approach. Unfortunately, despite receiving this therapy, the patient did not respond, and succumbed to the heavy burden of leukemic cells within three days. Consequently, this patient's response is not evaluable due to early mortality.

Case 3: A 74-year-old female patient was referred to the Department of Hematology following an abnormal full blood count. Subsequent bone marrow biopsy confirmed the diagnosis of ET with a JAK2 V617F positive gene mutation. The VAF was not determined at this time. Megakaryocyte system hyperplasia was active, while hyperplasia within the erythrocyte system was absent. The patient achieved remission after receiving treatment with hydroxyurea. She underwent routine follow-up for nearly seven years until leukocytopenia (white blood cell count of 1.2×10^9/L) was observed, leading to a second bone marrow biopsy. The biopsy confirmed the diagnosis of AML, with the presence of both a JAK2 V617F mutation (VAF 3.4%) and an IDH2 mutation (VAF 2.3%). Notably, no abnormal chromosomal karyotype was observed prior to or after the development of AML. Considering the unique transformation and the patient's overall health condition, a different chemotherapy regimen consisting of decitabine, aclarubicin, homoharringtonine, and cytarabine was administered. This treatment resulted in remission for 14 months. However, the patient subsequently became unable to tolerate further therapy. As a result, palliative care was provided, but unfortunately, she passed away 20 months after the transformation to AML due to uncontrollable septicemia.

The detailed characteristics are presented in Supl Table S1. In addition, the laboratory tests at the diagnosis of ET (Supl Table S1) or AML (Supl Table S2, Supl Table S3) are presented.

4 Discussion

In our study, two patients with AML following ET transformation showed a correlation between a high allelic frequency (VAF) of TP53 mutations [21, 22]and poor prognosis, with a significant AML cell load indicated by log scale upregulation. In contrast, a third ET-transformed AML patient lacked TP53 mutations and displayed a low AML cell burden. The lack of any response in patients 1 and 2 with high allelic frequency TP53 mutations looks like intrinsic resistance may be due to a lack of apoptotic signaling rather than an indirect effect of TP53 mutations on, say, aneuploidy, with an increased chance of the selection for genetic drug resistance. We hypothesize that ET-transformed AML patients with high TP53 mutation allelic frequency may experience more aggressive disease progression and severe complications compared to those without TP53 mutations.

A correlation between TP53 mutation allelic frequency [6–9] and poorer prognosis in AML has been reported, though TP53's role in AML development due to ET transformation is unclear [9]. TP53 mutations aren't generally considered driver mutations for MPN or ET but are found in around 2% of MPN patients [23] and are often treatment-related in MPN-to-AML transformation [24]. Epigenetic changes can also affect TP53 function [23].

All three ET-transformed AML patients initially received decitabine, the first-line treatment for older AML patients with TP53 mutations [5, 8, 15, 25]. However, those with TP53 mutations showed poor responses and died within days, while the patient without TP53 mutations responded well, achieving 14 months of remission. Additional drugs (aclarubicin and homoharringtonine) were used to counter resistance, as decitabine lacks rapid tumor-killing effects. Leukapheresis wasn't available, and hydroxyurea was given as supportive care.

Arsenic trioxide can restore function in mutated p53 *via* a hidden allosteric site [26], suggesting that patients with TP53 mutations (such as p.V172A, p.Y220C, and p.H179R in our cases) might benefit from this treatment, potentially to be explored in clinical trials. Unfortunately, the two ET-transformed AML patients in our study did not survive long enough to complete a decitabine course. This raises questions about the optimal first-line treatment for ET-transformed AML patients with high-allelic frequency TP53 mutations, especially elderly ones. Should decitabine remain the preferred option, or should arsenic trioxide be considered as an alternative?

The 2017 NCCN guidelines [27] for AML recommended decitabine as the preferred first-line treatment but did not endorse combining it with aclarubicin, homoharringtonine, or cytarabine, as was done in these cases. By 2022, the guidelines updated to suggest combining a hypomethylating agent like decitabine with venetoclax. Thus, findings from these cases should be interpreted with caution, as the treatment regimens used were not part of standard recommendations.

While venetoclax is now standard for older AML patients [28, 29], TP53 mutations may confer resistance to it [30, 31], and studies show no significant benefit of combining venetoclax with decitabine in TP53-mutated AML patients. In our study, early mortality in two cases with TP53-mutated secondary AML raises questions about whether chemotherapy or venetoclax-based therapies should be used, and suggests that alternative treatments may be more appropriate for future trials.

At the time of admission, venetoclax wasn't yet authorized by the national health board in China, and rapid disease progression limited treatment options. In one case, venetoclax could have been added due to an IDH2 mutation, but financial constraints made it inaccessible.

The third ET-transformed AML patient, without TP53 mutations, responded well to decitabine, suggesting that TP53 mutations may impact AML patients' response to this drug. However, prior studies show that decitabine effectively reduces blast cells in primary AML patients, regardless of TP53 mutation status [32]. Additionally, research by Papaemmanuil et al. associates TP53 mutations with poor AML prognosis [6], emphasizing TP53's role in AML progression. Differences between our findings and theirs may stem from distinct mechanisms in primary versus ET-transformed AML with TP53 mutations, highlighting the need for further research on TP53-related pathways in ET-transformed AML.

In our cases, patients with high TP53 mutation allelic frequency showed no response to decitabine, possibly due to intrinsic resistance linked to impaired apoptotic signaling rather than indirect effects like aneuploidy-driven drug resistance. Among these patients, two had a normal karyotype, while one exhibited a complex chromosomal profile, aligning with previous studies linking chromosome del 7q to transformation [33]. These findings underscore the limitations of chromosomal analysis alone in managing ET-transformed AML and suggest a need for additional molecular and genetic testing.

A VAF near 50% implies the TP53 mutation is clonal in nearly all AML cells, possibly reflecting a strong selection for TP53 subclones within the ET clone. Thus, the timing of TP53 mutation emergence and its allelic frequency may be crucial in understanding transformation to AML.

This study has several limitations. Due to the rarity of ET-transformed AML, the analysis included only three patients, making it primarily hypothesis-generating and underscoring the need for further research. A prospective study could allow for additional analyses, including in vitro or animal models, to deepen molecular insights. For example, sensitive TP53 mutation analysis in initial samples could clarify if these mutations arise de novo in the AML phase. Examining other co-occurring mutations in both ET and AML stages may also reveal their role in disease progression.

From these three cases, we hypothesize that ET-transformed AML with high TP53 mutation allelic frequency may be more aggressive and involve more severe complications than AML without TP53 mutations. Our findings highlight the unique clinical profile of ET-transformed AML, involving distinct TP53 mutations and varied responses to decitabine. Further studies in larger cohorts are needed to explore the molecular mechanisms behind these observations and validate these preliminary findings.

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Author contributions Yang Si: made substantial contributions to the conception, wrote paper; Jiyuan Wang: collected data and wrote the paper; Brett Hambly: revised the paper; Yuli Wang: revised the paper; Yanfang Zhang: revised the paper; Shisan Bao: conception and revised the paper.

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Data availability These data are available statement: The information for this study was collected from three patients using the electronic database of the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. The datasets generated during and/or analysed during the current study are not publicly available due to security and privacy issue for both the patients and the hospital, but are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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