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Case Report

Megakaryocytic Sarcoma Transformed from a Long-Standing Essential Thrombocythemia: An Extremely Rare Clinical Scenario

Ahmed Arfa[1], Ling Zhang[2*]

[1]Department of Pathology, Augusta University, Augusta, GA, USA

2Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

[*]**Corresponding author:** Ling Zhang, Department of Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

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Abstract

Essential thrombocythemia is a myeloproliferative neoplasm. Leukemic transformation occurs among 1% to 4% of patients with a median follow-up of 7 to 10 years. Few patients manifest with acute megakaryocytic leukemia or, rarely, with megakaryocytic sarcoma. The clinical outcomes of megakaryocytic transformation are dismal, with a median overall survival of <2.2 months. Herein, we report on a 55-year-old patient with a *CALR*^{mut} ET who remained stable over 20 years while receiving hydroxyurea and anagrelide therapy, then rapidly progressed to megakaryocytic sarcoma after an acquired TP53 mutation. Laboratory studies at the time of transformation showed normal white blood cells, anemia (hemoglobin of 10 g/dL), and thrombocytopenia (platelet count of 77 × 10^9/L). A computed tomography/positron emission tomography scan revealed generalized lymphadenopathy, splenomegaly (6.5 × 17 × 19 cm), and a bone lesion with increased bone-marrow metabolic activity. Despite receiving immediate chemotherapy, the patient died 3.5 months after the leukemic transformation. To our knowledge, this is the first report of a *CALR*^{mut} and *TP53*^{mut} megakaryocytic sarcoma, derived from essential thrombocythemia. We believe that the acquired somatic *TP53*^{mut} played a critical role in disease transformation. Advanced molecular diagnosis during follow-ups would be beneficial not only for early diagnoses but also to enable targeted therapy, thereby improving overall survival.

Keywords: Megakaryocytic Sarcoma; Leukemia; *CALR*; *TP53*; Essential Thrombocythemia; Case Report

Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm (MPN) that primarily affects the megakaryocytic lineage and is commonly associated with JAK2, CALR, or MPL gene mutations. Unlike other MPNs, transformation of ET into acute myeloid leukemia (AML) or myeloid sarcoma rarely occurs except among approximately <1% to 6.5% of patients who have a median follow-up of 7 to 10 years [1]. The transformation from ET into AML is typically attributed to advanced age, disease duration, platelet levels, white blood cell (WBC) count, myelofibrotic transformation, or cytoreduction therapy (eg, melphalan). The relationship between hydroxyurea or busulfan and ET transformation is currently being debated [2]. ET transformation to acute megakaryocytic leukemia is rare, and transformation to megakaryocytic sarcoma is even rarer, presenting a diagnostic challenge. Clinically, megakaryocytic transformation has a dismal clinical outcome with a median overall survival (OS) of <2.2 months, which prompts an earlier diagnosis and immediate treatment. Additionally, molecular mechanism of this transformation is poorly understood.

Case Presentation

Herein, we present an extremely rare case of a 55-year-old man with a 20-year history of ET on hydroxyurea and anagrelide therapy who ultimately progressed to secondary myelofibrosis

and concurrent AML with megakaryocytic differentiation and extramedullary megakaryocytic sarcoma with retained *CALR*^{mut} and acquired *TP53*^{mut}.

Results

For the past 20 years, the patient had moderate thrombocytosis, and his platelet count ranged from 460 × 10^9/L to 899 × 10^9/L with accompanying with anemia leukocytosis, organomegaly, or thrombotic episodes. Since diagnosis, he received hydroxyurea, low-dose aspirin, and intermittent anagrelide. Within the last 12 months, he experienced a progressive decrease in platelets. Recent complete blood count data showed anemia (hemoglobin level of 10 g/dL) and thrombocytopenia (platelet count of 78 × 10^9/L). He complained of chronic fatigue, low back pain, and a palpable enlarged axillary lymph node. A bone marrow biopsy was performed at an outside hospital and reported increased CD34-positive blasts (80%) and diffuse severe reticulin fibrosis (marrow fibrosis [MF] 3/3) consistent with a blastic-phase MPN.

According to an outside report, karyotyping revealed a normal male karyotype of 46,XY[20], and next-generation sequencing (NGS) demonstrated a *CALR* p.L367fs mutation (VAF, 77%). The patient was prescribed decitabine and venetoclax for 2 cycles for management of his leukemia. He demonstrated a transient response after the first cycle but developed persistent severe pancytopenia that necessitated intermittent transfusions.

The patient was transferred to Moffitt Cancer Center for consideration of other therapeutic options. Upon admission, his labs showed a WBC count of 0.3 × 10^9/L, a hemoglobin level of 6.9 g/dL, and thrombocytopenia (11 × 10^9/L). His absolute neutrophil count was only 0.009 × 10^9/L (3% of WBCs). A computed tomography/positron emission tomography scan revealed numerous multilevel metabolically active left neck, supraclavicular, subclavian, and axillary lymph nodes with a maximum standardized uptake value (SUV_{max}) of 10.1; splenomegaly (6.5 × 16.9 × 19 cm); a left inferior scapula lytic lesion with an SUV_{max} of 10.8; and a heterogeneous increased metabolic activity throughout the bone marrow.

A bone marrow biopsy was conducted at Moffitt Cancer Center approximately 4 months after his initial leukemic transformation and after he received induction chemotherapy. The received aspirate appeared acellular and markedly hemodiluted. Touch imprint showed 7% myeloblasts. The core biopsy exhibited normocellularity (50%) with partial histomorphology of myeloid preponderance and atypical megakaryopoiesis as well as a focal collection of blasts (Figure 1A-D). The blasts showed overlapping CD34 and CD61 staining (Figure 1E, F). An additional biopsy from axillary masses revealed diffuse effacement of normal lymph-node architecture, with sheets of intermediate-to-large immature cells associated with active mitosis (Figure 2) and moderate-to-marked reticulin fibrosis (score of MF 2-3/3). These immature precursors were positive for CD34, megakaryocytic markers (CD61, CD31, factor VIIIa), and p53 protein, with a high proliferation index highlighted by its Ki67 score (70%-80%) (Figure 2); the immature precursors were negative for myeloperoxidase, spectrin, lysozyme, CD68, CD163, CD3, CD20, PAX-5, CD138, MUM1, and CD30.

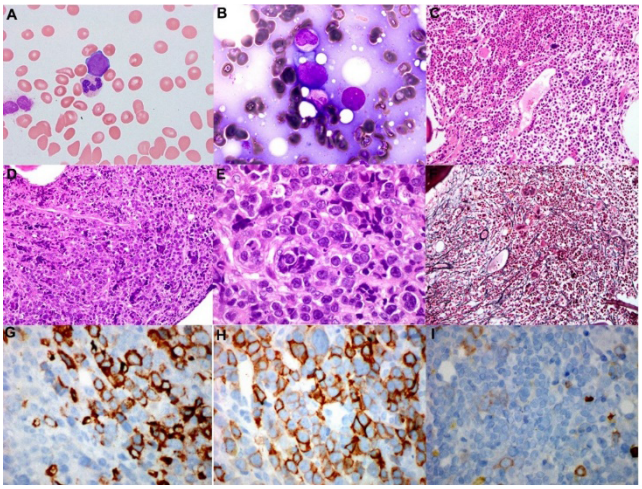

Figure 1: A. Peripheral circulating blasts (Wright, 1000×). B. Bone marrow aspirate/touch imprint shows megakaryoblasts (Wright-Giemsa, 1000×). C, D. Low-power view of H&E section of the bone marrow core biopsy shows atypical megakaryopoiesis associated with mild myeloid preponderance, dilated sinusoid space, and increased vasculatures (C) and focal increase in immature precursors/blasts in sheets (D) (H&E, 200×). E. Higher-power view reveals atypical megakaryocytes with hyperchromatic nuclei, and focally, sheets of immature precursors with dispersed-to-open chromatin, visible nucleoli, and scant cytoplasm associated with brisk mitosis associated with a couple of abnormal multilobate megakaryocytes (H&E, 600×). F. Reticulin stain highlights reticulin fibrosis (MF 2-3/3) (reticulin, 200×). G-I. The immature precursors/blasts are partially positive for CD34 (a stem cell marker) (G) and diffusely express megakaryocytic marker CD61 (H) consistent with megakaryoblasts, and they are negative for CD117 (I) (immunoperoxidase, 600×). Abbreviation: H&E, hematoxylin and eosin.

Karyotyping at this time still revealed a normal male karyotype 46,XY[20]. A fluorescence in situ hybridization study panel, including del(5q)/−5, del(7q)/−7, +8, del(17p), and del(20q) probe sets, did not reveal any abnormalities. NGS performed on the bone marrow specimen showed only a *CALR* frameshift mutation (VAF, 41.4%). The paraffin-embedded biopsy tissue from the axillary lymph node was submitted for Foundation One Heme genomic profiling (Beverly, MA, USA), which identified commutations of *TP53* p. Y163C and *CALR* L367fs46.

Diagnosis

The overall findings were consistent with AML with megakaryocytic differentiation and megakaryocytic sarcoma that had transformed from a long-standing ET.

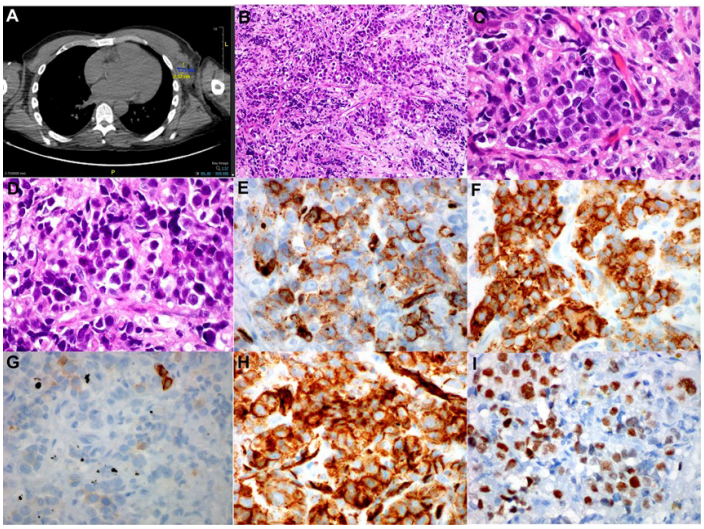

Figure 2: A. CT scan shows an enlarged left axillary lymph node measuring 2.32 cm**. B**. An H&E-stained section of the lymph-node biopsy demonstrates diffuse effacement of normal nodal architecture with a monotonous population of intermediate-to-large immature cells, some with big or hyperchromatic nuclei, associated with increased angiogenesis and fibrosis in the background (H&E, 200×). **C, D**. Higher-power view of these neoplastic cells display open-to-dispersed chromatin, irregular nuclear contours, and inconspicuous nucleoli (H&E, 600×). **E-I.** A panel of immunohistochemical stains was performed with appropriate controls which highlight these neoplastic/blasts to be megakaryocytic progenitors expressing CD34 (D), CD61 (F), CD31 (H), and p53 (I); The blasts are negative for CD117 (G), spectrum (image not shown) (immunoperoxidase, 600×, respectively). Abbreviation: H&E, hematoxylin, and eosin.

Treatment

Given the patient's acute leukemia and megakaryocytic sarcoma, he was prescribed salvage therapy with FLAG-IDA (a combination of fludarabine, high-dose cytarabine, idarubicin, and granulocyte-colony stimulating factor). However, the patient experienced a suboptimal treatment response complicated by neutropenic fever up to 103 ˚F. As such, he was discharged for palliative therapy.

Follow-up and outcomes

The patient died approximately 3.5 months after being diagnosed with megakaryocytic sarcoma and 7 months after being diagnosed with blastic transformation.

Discussion

The reported incidence of leukemic transformation in ETs is variable, ranging from <1% to 6.5% of patients with a median follow-up of 7 to 10 years [2] in different studies within the past decades upon years of follow-ups. Of these cases, most transform into acute myelomonocytic or acute monoblastic/monocytic leukemias. In rare cases, however, ETs can transform into megakaryocytic or lymphoblastic leukemia [3]. Transformation to myeloid sarcoma, in particular megakaryocytic sarcoma, is even rarer and may occur simultaneously with or after transformation to AML. To date, only 3 reported cases of megakaryocytic sarcoma transformed from ET (Table 1). Of a large series of myeloid sarcoma cases (92 adult patients), only 1 (1.1%) had megakaryocytic differentiation [4].

Table 1: Clinicopathologic Features of ET Transformation to Myeloid Sarcoma with Megakaryocytic Differentiation.

No.	Age/ gender	AML/ MS	Involved site	Duration* (years)	Genetic aberrations	Mutated genes	IHC (p53)	Treatment	Outcome cause (OS, mo.)	Reference
1	58/F	MS	Breast	10	del(5), del(7), gains of 9 & 17	N/A	N/A	None	DOD, 0.25	Obiorah IE et al, 2017[13]
2	68/M	MS	LN	5	Polysomy 9	N/A	N/A	ARA-C	DOD, 1	Famoso et al, 2006[14]
3	80/M	MS/AML	Bone	6	N/A	N/A	N/A	Pipobroman	DOD, 4	Desplechin et al, 2010[15]

4	55/M	MS/AML	LN	20	None	*CALR*, *TP53*	(+)	Palliative	DOD, 3.5	Current case report

*From diagnosis to death. **Abbreviations:** AML, Acute Myeloid Leukemia; ARA-C, Cytarabine; DOD, Died Of Disease; ET, Essential Thrombocythemia; IHC: Immunohistochemistry; LN, lymph Node; MS, Myeloid Sarcoma; N/A, not applicable; OS, Overall Survival.

Large datasets have shown that advanced age, thrombocytosis (>1000 × 10^9/L), anemia (using sex-adjusted values), and leukocytosis (15 × 10^9/L) are risk factors for the leukemic transformation of ET [1,2]. In the absence of both anemia and thrombocytosis, the incidence of leukemic transformation is approximately 0.4%; on the contrary, when anemia and/or thrombocytosis are present, the incidence increases to between 4.8% and 6.5% [1,2]. The patient in this report experienced only mild anemia and did not have overt thrombocytosis or leukocytosis during his clinical course.

The effect of cytoreductive drugs like hydroxyurea or busulfan on leukemic transformation is controversial, with some studies showing no increased risk and others reporting opposing results [2]. Administration of melphalan has been reported as a risk factor, but it was not prescribed to our patient. Anagrelide could induce myelofibrosis. However, our patient only received anagrelide intermittently. Marrow fibrosis was only documented at the time of his leukemic transformation, 20 years after his initial diagnosis, and could be part of his natural history, but the potential role of anagrelide herein remains unclear.

The *JAK2* and *CALR* mutations are mutually exclusive. The molecular role of *CALR* mutations in leukemic transformation is less important than that of *JAK2* mutation. The type 1 *CALR* mutation, a 52-base pair deletion (like our patient's CALR L367fs46), is more common than the type-2 *CALR* mutation, a 5-base pair TTGCC insertion [5]. In ET, type 1 is more often associated with a higher risk of myelofibrosis, which could explain the presence of myelofibrosis in our patient, whereas type 2 is associated with a higher platelet count but a lower risk of thrombotic events [6]. Overall, when compared to *JAK2* mutations, *CALR* alterations confer a lower risk of thrombosis and have no significant impact on OS or leukemic transformation [7].

Emerging data have shown *TP53* mutations are crucial for disease transformation in MPNs. *TP53* mutations have been reported in a subpopulation of patients (25%-45%) with post-MPN AML [8]. The presence of acquired somatic mutations, such as *TP53* and *EZH2* mutations, though infrequent, is associated with an increased risk of ET with leukemic transformation [2]. A recent case study reported that commutated *JAK2/TP53*-mutated megakaryocytic/erythroid progenitors can lead to leukemic transformation, which might be due to BMP2/SMAD pathway activation [9]. To our knowledge, our current report is the first to show commutated *CALR* and *TP53* in megakaryocytic leukemia from ET. A recent in vitro study showed that transcriptomic changes associated with *CALR* mutations induce an increase in hematopoietic stem cell proliferation and excess megakaryocytes [10]. Assumably, the synergy of commutations occurs at the pluripotential stem cell level, promoting megakaryocytic differentiation and resulting in megakaryoblastic transformation.

Studies have also shown that patients with $TP53^{mut}$ AML usually experience poorer responses to conventional chemotherapy in conjunction with venetoclax, a BCL-2 inhibitor, than patients with other gene mutations [11]. This was also seen in our patient. To date, there are no FDA-approved or NCCN Compendium–listed treatments specifically for patients with *CALR* mutations [7]. The outcome of acute megakaryocytic leukemia is dismal, and a previous case report has indicated that it could recur even after a haploidentical allogenic hematopoietic stem cell transplant [12].

Conclusion

ET transformation into megakaryocytic sarcoma is rare and requires a comprehensive investigation, including clinical and imaging findings, histology, immunophenotyping, and molecular profiling for earlier diagnosis. The acquired *TP53* mutation during the disease course played a key role in disease progression and transformation. Advanced molecular studies during disease follow-ups would be beneficial for providing guidance on treatment decisions.

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References

1. Gangat N, Wolanskyj AP, McClure RF, Li CY, Schwager S, et al. (2007) Risk stratification for survival and leukemic transformation in essential thrombocythemia: a single institutional study of 605 patients. Leukemia 21: 270-276.
2. Yogarajah M, Tefferi A (2017) Leukemic Transformation in Myeloproliferative Neoplasms: A Literature Review on Risk, Characteristics, and Outcome. Mayo Clin Proc 92: 1118-1128.
3. Radaelli F, Mazza R, Curioni E, Ciani A, Pomati M,et al. (2002) Acute megakaryocytic leukemia in essential thrombocythemia: an unusual evolution? Eur J Haematol 69: 108-111.

4. Pileri SA, Ascani S, Cox MC, Campidelli C, Bacci F, et al. (2007) Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia 21: 340-350.

5. Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, et al. (2013) Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 369: 2379-2390.

6. Tefferi A, Wassie EA, Guglielmelli P, Gangat N, Belachew AA, et al. (2014) Type 1 versus Type 2 calreticulin mutations in essential thrombocythemia: a collaborative study of 1027 patients. Am J Hematol 89: E121-124.

7. Nangalia J, Massie CE, Baxter EJ, Nice FL, Gundem G, et al. (2013) Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2. N Engl J Med 369: 2391-2405.

8. Harutyunyan A, Klampfl T, Cazzola M, Kralovics R. (2011) p53 lesions in leukemic transformation. N Engl J Med 364: 488-490.

9. Li B, An W, Wang H, Baslan T, Mowla S, et al. (2022) BMP2/SMAD pathway activation in JAK2/p53-mutant megakaryocyte/erythroid progenitors promotes leukemic transformation. Blood 139: 3630-3646.

10. Prins D, Park HJ, Watcham S, Li J, Vacca M, et al. (2020) The stem/progenitor landscape is reshaped in a mouse model of essential thrombocythemia and causes excess megakaryocyte production. Sci Adv 6.

11. Wei AH, Strickland SA, Jr., Hou JZ, Fiedler W, Lin TL, et al. (2019) Venetoclax Combined With Low-Dose Cytarabine for Previously Untreated Patients with Acute Myeloid Leukemia: Results from a Phase Ib/II Study. J Clin Oncol 37: 1277-1284.

12. Imamura T, Nitta Y, Miyachi M, Ishida H, Ito M, et al. (2014) Relapse of acute megakaryocytic leukemia as hepatic myeloid sarcoma after allogeneic haploidentical hematopoietic stem cell transplantation. Int J Hematol 100: 109-110.

13. Obiorah IE, Ozdemirli M (2018) Myeloid sarcoma with megakaryoblastic differentiation presenting as a breast mass. Hematol Oncol Stem Cell Ther 11: 178-182.

14. Famoso G, Ponzoni M, Freschi M, Lo Cunsolo F, Tresoldi M, et al. (2006) Megakaryoblastic differentiation of myeloid sarcoma in a patient with essential thrombocythemia. Leuk Lymphoma 47: 2414-2417.

15. Desplechin A, Mekinian A, Rossignol J, Denis G, Gosset P, et al. (2010) Isolated megakaryoblastic bone sarcoma revealing acute myeloproliferative syndrome. Joint Bone Spine 77: 277-278.