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Case Report
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Atypical Presentation of Erythroid/Megakaryocytic Leukemic Transformation of a Myeloproliferative Neoplasm Associated with Mutation and Loss of TP53

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The BCR-ABL negative myeloproliferative neoplasms (MPNs) include essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). These MPNs are generally characterized by clonal proliferation of mature hematopoietic cells.[1] ET and PV may progress to MF, and all 3 disease entities may progress to acute myeloid leukemia (AML). Amongst the chronic-phase MPNs, ET is generally associated with the lowest rates of transformation to MF and AML.Transformation to AML has a poor prognosis, and the clinical risk factors for transformation as well as biology of this process remains to be understood.[2]

The hallmark of MPN pathogenesis is activating mutations in the JAK-STAT pathway (*JAK2*, *MPL*, *CALR*). Non JAK-STAT pathway mutations, such as *ASXL1*, *SRSF2*, *EZH2*, *IDH1/2*, and *RAS* pathway mutations are all associated with increased risk of transformation of MF to AML.[3,4] Of note, mutations in *TP53* are observed frequently at the time of leukemic transformation, and appear to play a role in the biology of disease transformation.[5]

A 57-year-old woman with beta-thalassemia minor presented in March 2014 with an incidental finding of thrombocytosis to 994K/mcl and white blood count (WBC) count of 12.4K/mcl. Molecular genetic analysis identified a *JAK2*V617F mutation and cytogenetics demonstrated a normal female karyotype. Bone marrow examination was consistent with ET. Given her low-risk IPSET score the patient was started on aspirin. She subsequently developed both a deep venous thrombosis and pulmonary emboli in August 2014 and was started on hydroxyurea and rivaroxaban, which she was maintained on for the next 3.5 years.

In March 2018, the patient's platelet count began to decrease, and shortly thereafter new leukoerythroblastosis was noted on peripheral blood smear. A bone marrow examination identified dysplastic megakaryocytes and reticulin fibrosis (MF-2) consistent with post-essential thrombocythemia myelofibrosis (pET-MF). No increase in blasts was noted. Cytogenetic analysis detected a complex karyotype in 19 of 20 metaphase cells with a dicentric chromosome, dic(5q;17p), in the stem line. Loss of chromosome 7, and a deletion of the long arm of chromosome 13 and an addition of the short arm of chromosome 15 in 2 subclones, was noted as well. The dic(5q;17p) results in loss of the long arm of chromosome 5 and the short arm of chromosome 17, including *TP53* (Fig. 1A), which was confirmed by FISH tests (Table 1). DNA sequencing studies from bone marrow, peripheral blood, and lytic bone lesion (using the MSK-IMPACT platform and Raindance and Thunderbolt platforms as previously described[4,6]) was performed. These studies demonstrated a *JAK2*V617F mutation as well as *TP53*Q167* and *TP53*R306* mutations (Table 1).

Three months later, the patient developed progressive diffuse pain in her shoulders, chest, lower back, and hips associated with generalized weakness, culminating in hospital admission. Physical exam revealed tenderness to palpation of the lumbosacral spine and hips; however, radiographs and a bone scan noted no fractures or focal osseous lesions. An MRI of the left femur noted periostitis for which she received methylprednisolone with a transient response. She was discharged with an opiate regimen and a trial of ruxolitinib for presumed myelofibrosis-related bone pain.

Several weeks later the patient was again admitted for intractable bone pain. Initial labs were notable for hypercalcemia. A CT scan of the abdomen and pelvis noted new lytic lesions of the axial and appendicular skeleton (Fig. 1B-C). Workup for a plasma cell dyscrasia was negative. A bone biopsy of a lytic lesion identified erythroid/megakaryocytic leukemic transformation of disease. Immunohistochemistry of neoplastic cells demonstrated staining for CD61, CD71, CD117, Spectrin, LMO2, and ERG

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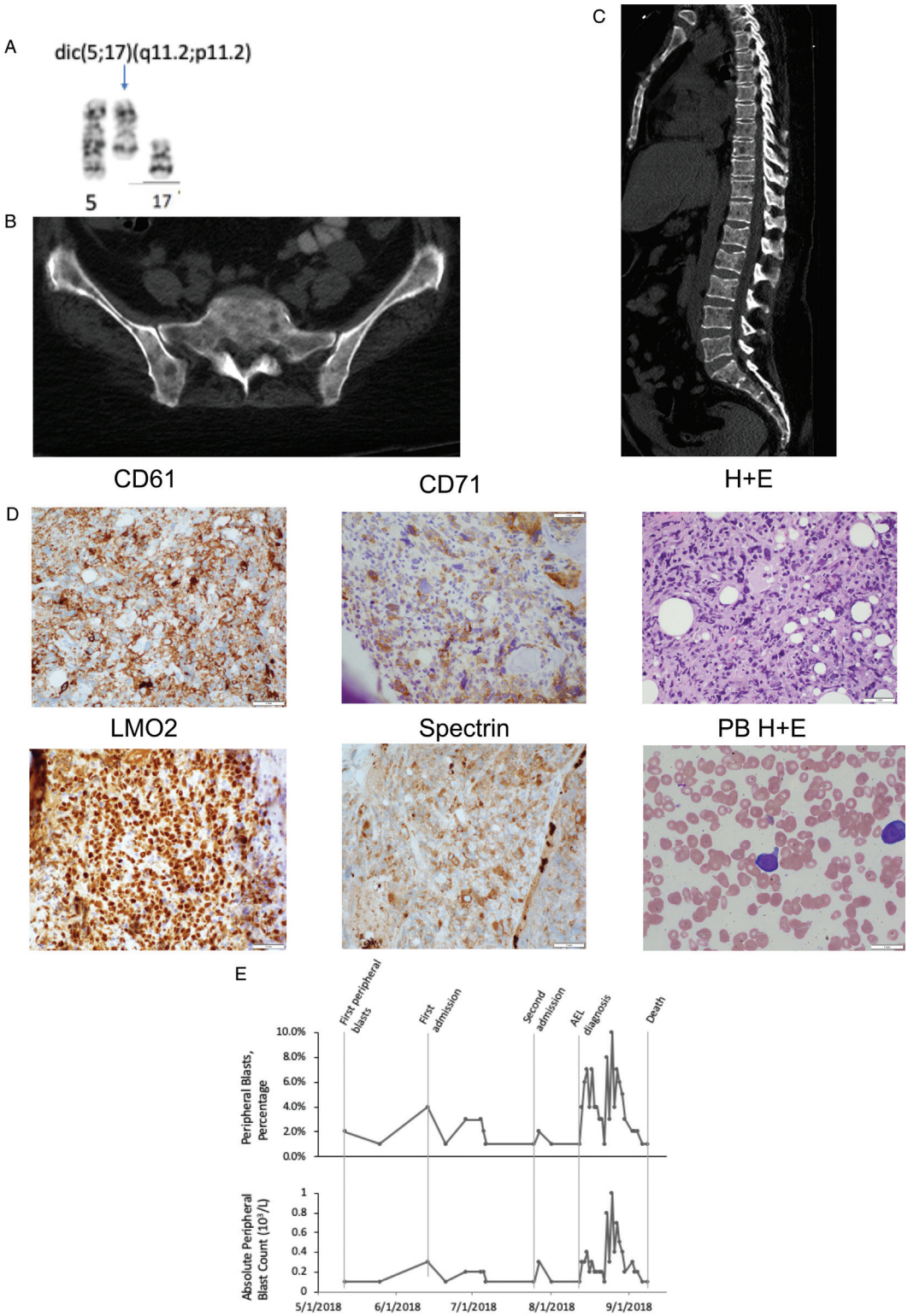

Figure 1. Radiologic, cytogenetic and hematologic changes associated with disease transformation. (A) A partial karyogram with dicentric chromosome dic(5q;17p) which was detected in 19 of 20 metaphase cells (B) Sacral and iliac necrosis secondary to leukemic transformation demonstrating appendicular skeletal involvement (C) Extensive lytic lesions of the axial skeleton (D) Staining of neoplastic cells identifying erythroblastic origin without evidence of significant peripheral blasts. Bone biopsy staining noted positivity for CD61, CD71, LMO2 and Spectrin; peripheral blood however noted few peripheral blasts on blood smear (E) Peripheral blast count trend (absolute count and percentage): over the course of 2018 the patient's peripheral blast count remained low and changed little during the patient's progression from ET to MF and finally transformation to acute erythroid leukemia (AEL). No blasts were noted in the peripheral blood until May 2018, after diagnosis of myelofibrosis.

Table 1

Molecular and cytogenetic evolution over disease course

	7/2014[a]	5/2018[#b] (bone marrow biopsy)	8/2018 (lytic bone lesion)[c]	
Molecular Genetics	JAK2 (V617F)	JAK2 (V617F)	JAK2 (V617F)	KMT2C (I811V)
		TP53 (Q167[a])	TP53 (Q167[a])	PRSS3 (X124_splice)
		TP53 (R306[a])	MGA (I2281K)	
Karyotype	46,XX[15]	45,XX,dic(5;17)(q11.2;p11.2)[12]/44,idem,-7[4]/45, idem,del(13)(q12q22),add(15)(p11.2)[3]/46,XX[1]	Not Assessed	
FISH	Negative for t(9;22)	Deletion of 5q31 (EGR1): 30% Deletion of 17p13.1(TP53): 33%	Not Assessed	

[a] Raindance Hematologic Malignancies panel (30 genes, inclusive of coverage TP53 region corresponding to amino acid 167).
[b] ThunderBolt MSK-Heme Panel (49 genes).
[c] MSK HemePACT (576 genes).
[#] Performed three months prior to diagnosis of lytic bone lesions.
Black font = oncogenic variants; Blue font = variants of uncertain significance.

(Fig. 1D). Staining was negative for CD34, MPO, E-Cadherin, CD138 and BCMA. Cytogenetics studies could not be performed. Mutational profiling from the bone lesion demonstrated the presence of a heterozygous *JAK2*V617F mutation, and *TP53*Q167*, as well as several other variants of unknown significance (Table 1).

The patient rapidly declined and developed multi-organ failure. She subsequently expired (within 4 weeks of diagnosis of leukemic transformation).

This case highlights several important and unusual features that are of significance to clinicians treating MPN patients. First, the patient had an unusually rapid progression from ET to post-ET MF to AML (4 years), whereas historical data demonstrates a 10-year incidence of progression from ET to post-ET MF and of leukemic transformation of 0.8% and 0.7%, respectively.[7] As well, application of prognostic modeling at the time of progression to MF, utilizing tools such as the MYSEC-PM model risk calculator[8] or MIPSS-70,[9] predicted for a far longer survival; the patient expired within 6 months of progression to MF as compared to a predicted median survival of 4.5 years.

Second, the presentation of leukemic transformation in this case appears to be extremely rare, as this patient presented only with severe diffuse skeletal pain. Initial imaging found no evidence of osteolytic disease; however, 1 month later her CT scan noted diffuse lytic lesions due to biopsy-proven erythroid/megakaryocytic leukemia. A key cautionary observation in this case was the lack of a markedly elevated or rising peripheral blood blast count. Indeed, the peripheral blood blast count was largely unchanged from the time of MF diagnosis to that of AML diagnosis (Fig. 1E). Our review of the literature identified only three similar cases of myeloproliferative neoplasms associated with osteolytic bone lesions.[10–12]

Finally, serial genomic and cytogenetic studies clearly indicate a complex clonal evolution. At the time of progression to MF the patient had developed two truncation mutations of *TP53* (only one of which was retained at the time of leukemic transformation) and a complex karyotype with dicentric chromosome dic(5q;17p), along with loss of chromosome 7 and deletion of 13q as clonal evolution. Dic(5;17) is a recurring chromosome abnormality in myeloid neoplasia, particularly in therapy-related and secondary leukemia, which result in loss of the *TP53* locus on 17p and deletion of 5q, and is frequently associated with *TP53* mutations.[13] This observation is consistent with prior human genomic and murine functional studies indicating cooperativity between *JAK2*V617F and *TP53* loss in post-MPN AML.[5] Notably, acute leukemia with megakaryocytic and erythroid differentiation was recently described in two previously healthy patients without a prior diagnosis of MPN, both of whom harbored *JAK2* and *TP53* mutations, one of which presented similarly with diffuse lytic lesions of the bone.[14] The TP53 pathway can also be altered by changes in MDM2 and MDM4 (which regulate TP53 levels) expression in post-MPN AML.[15] Thus, disregulation of the TP53 pathway appears to be a common event in leukemic transformation of MPNs.

Importantly, current prognostic scoring systems in MF do not adequately capture the impact of *TP53* mutations, particularly cases with both *TP53* mutations and concomitant loss of the *TP53* locus owing to chromosomal alterations. The bulk of the evidence from clinical and genomic studies, including this case, strongly suggest that MF/MPN patients with such a genotype should be considered high-risk for leukemic transformation.

This case serves to remind clinicians taking care of MPN patients that while many patients will have favorable outcomes, disease progression may be rapid, present atypically, and that the risk of progression may not always be adequately captured by current risk-scoring systems. Further understanding and refinement of genomic and other biomarkers of disease progression are needed in this patient population.

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