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CASE REPORT OPEN ACCESS

Clonal Progression and Leukemic Transformation of a *TP53* Mutated Post-Polycythaemia Vera Myelofibrosis

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ABSTRACT

Previous studies investigating the role of *TP53* mutations in chronic phase MPN have yielded inconsistent results. As such, the clinical relevance of these mutations remains to be elucidated. We report a case of a 67-year-old woman with a leukemic transformation of a post-polycythaemia vera myelofibrosis (post-PV MF) that culminated in the rare development of a myeloid sarcoma. During a 4-year follow-up, the patient had a stable *JAK2* Val617Phe and *NFE2* mutation (Variant Allele Frequencies (VAF's) 85%–87% and 43%–50%, respectively) and low-burden *TP53* mutation (VAF 2%–7%) in blood and bone marrow. Despite having a low-risk post-PV MF, the patient soon presented with an aggressive lytic lesion in the humerus, which proved to be a myeloid sarcoma. The sarcoma was positive for *JAK2* Val617Phe but, interestingly, was also highly enriched for the *TP53* mutation (VAF 81%), implicating a role of the *TP53* mutation in the leukemic progression. This case provides molecular evidence that a *TP53* mutation, even at a low burden, may contribute to leukemic progression of a chronic phase myeloproliferative neoplasm (MPN). These observations increase our understanding of the pathophysiologic behavior of *TP53* mutations and underscore the importance of further causal research towards the clinical implications of these mutations in chronic phase MPN.

A 67-year-old female with a history of post-polycythaemia vera myelofibrosis (post-PV MF) presented with severe pain in her right upper arm. She had initially been diagnosed with chronic phase PV 23 years before, based on the combination of polycythaemia, a mild leukocytosis, trilinear bone marrow hyperplasia, and a subnormal erythropoietin level. This diagnosis was later confirmed molecularly with the identification of the characteristic *JAK2* Val617Phe mutation, and regular phlebotomies were initiated. After a follow-up of 12 years, the patient presented with a slow but progressive abdominal swelling, which was found to be caused by splenomegaly measuring 12 cm. At this time, her blood smear showed leuko-erythroblastosis, and subsequent bone marrow examination revealed pronounced fibrosis, indicating progression towards post-PV MF and prompting hydroxyurea therapy. During follow-up, next generation sequencing (NGS) analyses (Illumina, San Diego, CA, USA), targeting all exons of 107 myeloid genes, were performed to monitor for potential disease progression. NGS analyses on blood and bone marrow were done in duplicate and reached a sequencing depth of at least 500X, allowing for a detection

André B. Mulder and Emanuele Ammatuna contributed equally to this work and share last authorship.

TABLE 1 | Clinical course and clonal progression of pathogenic mutations.

	February 2001	January 2013	January 2016	September 2020	October 2023	August/ September 2024	October 2024	November 2024
Clinical findings	Patient is diagnosed with a *JAK2* positive PV.	Patient develops a splenomegaly. Based on additional findings, progression towards a post-PV MF is established.	Persistently aberrant blood counts prompt re-evaluation of bone marrow.	Clinically stable, regular follow-up visit. Low-risk MYSEC-PM score.	Clinically stable, regular follow-up visit.	Lytic lesion in humerus midshaft.	Hospitalization for treatment of myeloid sarcoma.	Patient has deceased.
Bone marrow findings	< 5% blasts, fibrosis not assessed.	< 5% blasts, grade 3 fibrosis.	< 5% blasts, grade 3 fibrosis.	< 5% blasts, grade 3 fibrosis, *JAK2* mutation with VAF of 87%, *TP53* mutation with VAF of 2%, and normal karyotype (*NFE2* not assessed).	N/A	N/A	N/A.	N/A
Peripheral blood findings	Isolated polycythaemia, no blasts, *JAK2* mutation (VAF not assessed).	Leuko-erythroblastosis, teardrop cells, and < 1% blasts.	Leuko-erythroblastosis, teardrop cells, and < 1% blasts.	Leuko-erythroblastosis, teardrop cells, slightly hypersegmented and hypogranular neutrophils, and 1% blasts.	Leuko-erythroblastosis, teardrop cells, slightly hypersegmented, hypogranular, and enlarged neutrophils, 1% blasts, *JAK2* mutation with VAF of 85%, *NFE2* mutation with VAF of 43%, and *TP53* mutation with VAF of 4%.	Leuko-erythroblastosis, teardrop cells, slightly hypersegmented, hypogranular, and enlarged neutrophils, and 1% blasts.	Leuko-erythroblastosis, teardrop cells, slightly hypersegmented, hypogranular, and enlarged neutrophils, 1% blasts, *JAK2* mutation with VAF of 87%, *NFE2* mutation with VAF of 44%, and *TP53* mutation with VAF of 7%.	N/A

(Continues)

TABLE 1 | (Continued)

	February 2001	January 2013	January 2016	September 2020	October 2023	August/ September 2024	October 2024	November 2024
Myeloid Sarcoma findings	N/A	N/A	N/A	N/A	N/A	See Figure 1. Additionally, the *JAK2* mutation with VAF of 96%, *NFE2* mutation with VAF of 50%, and *TP53* mutation with VAF of 81%.	N/A	N/A
Therapy	Phlebotomies.	Phlebotomies and hydroxyurea.	Phlebotomies and hydroxyurea.	Phlebotomies and hydroxyurea.	Phlebotomies, hydroxyurea, and peginterferon a2a.	Hydroxyurea and peginterferon a2a.	Local irradiation of humerus.	N/A

Note: The reference identifiers for the *JAK2*, *NFE2*, and *TP53* variants were NM_004972.4:c.1849G>T, NP_004963.1: p.(Val617Phe), NM_001136023: c.782_785del, NP_001129495:p.(Glu261Alafs*3), and NM_000546.6:c.581T>G, NP_000537.3: p.(leu194Arg), respectively.
Abbreviations: MF, myelofibrosis; MYSEC-PM, myelofibrosis secondary to PV and ET-prognostic model; PV, polycythaemia vera.

threshold of 1% variant allele frequency (VAF). The NGS analyses revealed that the *JAK2* Val617Phe mutation had a high VAF of 85% in peripheral blood and 87% in bone marrow, which is typically seen in PV as a result of loss of heterozygosity (LOH). Additionally, an *NFE2* mutation with a VAF of 43%–50% and a small *TP53*-mutated subclone of 2%–4% were identified, Table 1. Karyotyping analysis, performed on the bone marrow sample in September 2020, did not show any chromosomal aberrations, and no copy number variations were found in the sequencing analyses. Based on the Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) [1], the patient was considered to have a low risk post-PV MF, which is associated with a median survival of over 14 years (median not reached in the cited study). Lastly, in October 2023, peginterferon a2a therapy had been initiated due to inadequate control of the patient's condition (hematocrit > 0.45%) during hydroxyurea treatment.

In August 2024, magnetic resonance imaging revealed a pending fracture due to a lytic lesion in the humerus midshaft, with cortical interruption and extraosseous growth, measuring 4.6 cm. The patient underwent a primary resection of the proximal humerus, which proved difficult due to unexpected extensive involvement of surrounding soft tissue, resulting in an R1 resection. Gross examination of the cut surface revealed a salmon-pink, homogeneous, partially necrotic mass involving the fractured bone, Figure 1B. The tumor measured up to 8 cm and extended into the resection margins, confirming rapid progression compared to preoperative imaging. A biopsy, taken from the tumor, showed solid sheets and nests of tumor cells with round, polymorphic, hyperchromatic nuclei and brisk mitotic activity. The tumor cells were positive for the haematopoietic and myeloid (precursor) markers CD45, CD33, CD34, partially positive for CD117, but negative for MPO and lysozyme, Figure 1. While a rare extramedullary leukemic transformation of post-PV MF was the principal differential diagnostic consideration, a diffuse positivity for the vascular markers ERG and CD31 made us secondarily consider a primary angiosarcoma of the bone. To more definitively rule out the latter malignancy, DNA extracted from the lytic humerus lesion was analyzed for the mutations that were previously found in the patient's bone marrow and blood. This analysis was performed using a pan-cancer NGS assay (TruSight Oncology 500, Illumina, San Diego, CA, USA) targeting 532 genes implicated in the pathogenesis of malignancies and covering virtually all myeloid genes analyzed in the blood and bone marrow assessments at a sequencing depth of at least 100X and with a detection threshold of 5% VAF. Indeed, the tumor was positive for the *JAK2* Val617Phe mutation, Table 1, thus implying a causal relationship with post-PV MF and confirming a diagnosis of myelofibrosis-associated myeloid sarcoma (chloroma). Interestingly, the *TP53* mutation was highly enriched in the tumor (81% VAF), which was explained by a copy number variation loss of TP53 (CNV ratio score of 1.3). Optical Genome Mapping (OGM, Bionano Genomics, San Diego, CA, USA), performed on the myeloid sarcoma, revealed a complex karyotype and excluded the presence of known AML-defining genetic aberrations [2]. In the weeks thereafter, PET-CT imaging unfortunately revealed rapid progression of disease with extensive bone involvement and lower neck localizations. With limited treatment options available, palliative treatment was initiated, and the patient died soon thereafter.

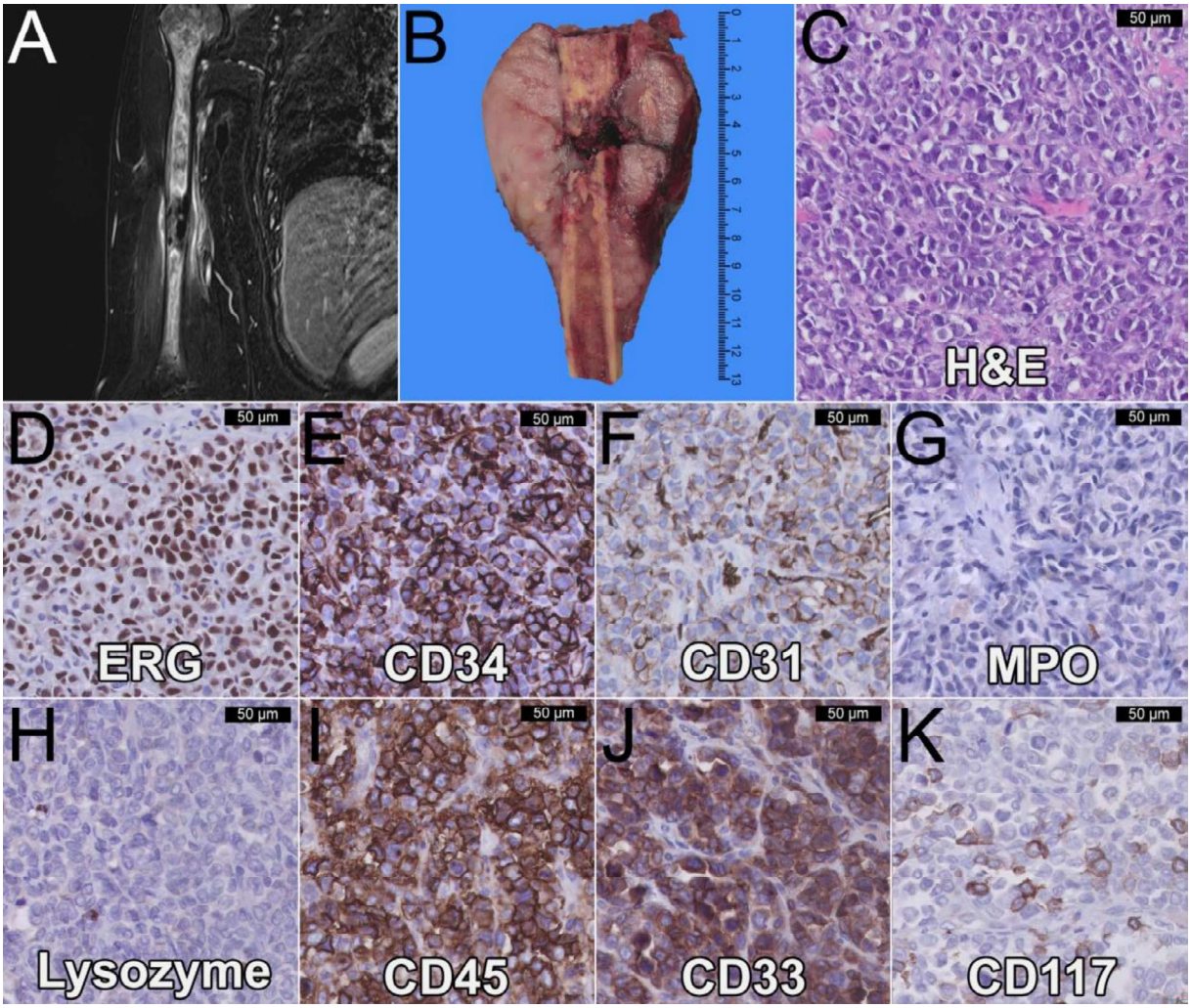

FIGURE 1 | Radiological, gross, and (immuno)histological findings. (A) magnetic resonance imaging of the right upper arm, showing a pathologic fracture due to a lytic lesion in the humerus midshaft, with cortical interruption and extraosseous growth, measuring 4.6 cm. (B) Gross appearance of the resected tumour. (C) Histological (H&E) image showing solid sheets and nests of tumour cells (> 80%) with round, polymorphic, hyperchromatic nuclei and brisk mitotic activity. (D–I) Immunohistochemical images, demonstrating positivity for ERG (D), CD34 (E), CD31 (F), CD45 (I), CD33 (J), and partial positivity for CD117 (K) but negativity for MPO (G) and lysozyme (H). H&E, hematoxylin and eosin; MPO, myeloperoxidase.

While the clonal architecture of myeloproliferative neoplasms (MPN) in chronic phase is relatively homogeneous, clonal progression and the factors predisposing leukemogenesis are quite heterogeneous [3]. Interestingly, albeit not part of MPN risk scoring models, somatic mutations in *NFE2*, including the particular variant found in the present case, have been shown to promote leukemic transformation, possibly by predisposing to the acquisition of secondary genetic aberrations, including mutations in *TP53* [4]. The role of *TP53* mutations in MPN has been the subject of discussion in recent studies, with some showing no risk of progression [5] and others implying that under certain circumstances *TP53* mutations may in fact confer a poor prognostic course [6]. This may be particularly the case for multihit *TP53* mutations, which are defined by the 5th edition of the World Health Organization classification system in the context of MDS as a single *TP53* mutation with VAF > 50%, two or more *TP53* mutations (VAF not assigned), or a single *TP53* mutation (VAF not assigned) associated with LOH [6]. The available data that fuel these discussions, however, are largely indirect and based on cohort studies that have inherent limitations as to the assessment of causal relationships. The present case report provides data suggesting that a *TP53* mutation with a low VAF may indeed contribute to a leukemic transformation of a chronic phase MF.

The long-term use of hydroxyurea raises the question of whether the drug may have had an impact on the selection and progression of the *TP53* mutated subclone. A study by Kubesova et al. [5] did not find convincing evidence that a median 5.4–6.3 year use of hydroxyurea had any impact on low *TP53* mutation VAFs in a cohort of chronic phase MPNs. However, a more recent preliminary study by Zhao et al. [7] in a larger MPN cohort appreciated an increased *TP53* mutation rate in patients receiving hydroxyurea as compared to those receiving other therapies like IFN, during a median follow-up period of 2.5 years, possibly also indicating some degree of progression of prior low-VAF TP53 subclones. Albeit it is important to recognize that these findings could be subject to bias due to the possibility that patients receiving hydroxyurea may have had more advanced disease, the disjunctive rates

between mutations in *TP53* and other myeloid genes among the hydroxyurea- and IFN-treated groups remain striking and warrant further confirmation in longer-term and more extensive follow-up studies.

Author Contributions

Isidor Minović: conceptualization, investigation, data curation, writing – original draft, visualization. **Bart Koopman:** visualization, writing – review and editing. **Joris J. W. Ploegmakers:** writing – review and editing. **Elise M. J. van der Logt:** resources, data curation, writing – review and editing. **Arjen H. G. Cleven:** resources, writing – review and editing. **Anouk van der Veen:** data curation. **Arjan Buijs:** resources, writing – review and editing. **André B. Mulder:** resources, conceptualization, supervision, writing – review and editing. **Emanuele Ammatuna:** conceptualization, writing – review and editing.

Ethics Statement

This case report was conducted in accordance with the applicable institutional guidelines and regulations of the UMCG.

Consent

The patient has provided written informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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