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CASE REPORT

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Rapid progression of myelofibrosis in polycythemia vera patient carrying *SRSF2* c.284C>A p.(Pro95His) and unique *ASXL1* splice site c.1720-2A>G variant

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Abstract

Background: The prognosis in polycythemia vera (PV) is comparatively favorable, but individual myelofibrosis/leukemic progression risk is heterogeneous. About a quarter of patients progress to the fibrotic phase after 20 years.

Methods: Multiplex PCR, allele-specific qPCR, high-resolution melt analysis, and Sanger sequencing were used to detect *BCR-ABL*, *JAK2*, *ASXL1*, *SRSF2*, *U2AF1*, and *IDH1/2* variants.

Results: Herein, we present a PV patient with rapid progression to secondary myelofibrosis probably due to the coexistence of homozygous *JAK2* V617F mutation, *SRSF2* c.284C>A p.(Pro95His) and splice site variant of *ASXL1* c.1720-2A>G. The detected *ASXL1* variant was first described in Bohring–Opitz syndrome and has not been reported in hematological malignancies so far. In the presented case, the *ASXL1* VAF was stable (50%) during the 4-year follow-up, despite an evident increase in the *JAK2* V617F VAF. Family history revealed cerebral palsy in the patient's grandson; however, germline character of the *ASXL1* variant was excluded.

Conclusion: The biological consequences of the variant acquisition by hematopoietic stem cells (HSC) seem to be similar to other mutations of *ASXL1* responsible for the truncation of ASXL1 protein, formation of hyperactive ASXL1–BAP1 (BRCA1-associated protein-1) complexes, and finally, the promotion of aberrant myeloid differentiation of HSC. Our report supports the hypothesis that ASXL1 alteration cooperates with JAK2 V617F leading to biased lineage skewing, favoring erythroid and megakaryocytic differentiation, accelerating the progression of PV to the fibrotic phase.

KEYWORDS
ASXL1, *JAK2*V617F, polycythemia vera, post-polycythemia myelofibrosis, *SRSF2*

1 | INTRODUCTION

The prognosis in polycythemia vera (PV) patients is comparatively favorable. The main factors influencing the overall survival of PV patients (pts) include individual risk of life-threatening thrombosis and disease progression to the blastic phase or myelofibrosis with myeloid metaplasia.[1–3] According to the available data, the risk of progression of PV to fibrotic phase is 4.9% and 9.4% at 10 and 15 years from the moment of diagnosis, respectively.[4] A population-based study of 327 pts with a confirmed diagnosis of PV revealed that after a median duration of 116 months from the diagnosis time, 11.5% of pts had developed secondary myelofibrosis, with a cumulative incidence of 6%, 14%, and 26% after 10, 15, and 20 years, respectively.[5] Initial reports documented that 95% of PV pts carry the *V617F* mutation (exon 14) of the *JAK2* gene, resulting in a diminished JH2 inhibitory effect on the adjacent JH1 kinase domain, thus keeping JAK2 in constitutively active conformation.[6] In another 3% of pts, exon 12 mutations of the *JAK2* gene are present (different in nature—synonymous substitutions, deletion variants, duplications).[7] Recently, a significant number of coexisting somatic gene mutations that affect epigenetic regulation, messenger RNA splicing, signaling, transcriptional regulation, and DNA repair in PV pts were identified. In Tefferi et al.'s study, the most frequently identified mutations were *TET2*, *ASXL1*, and *SH2B3* with the frequency of 22%, 12%, and 9%, respectively. In Song et al.'s study, the mutations of *ASXL1*, *KMT2A*, and *TP53* coexisted with the driver mutation with the frequency of 6.25%, 13.64%, and 6.25%, respectively. Rarely, the mutations of splicing machinery genes such as *SRSF2*, *U2AF1*, *SF3B1*, or *ZRSR2* are present.[8,9] *ASXL1*, *SRSF2*, and *IDH2* were identified as unfavorable risk factors in PV,[8] and in 2020, *SRSF2* has been incorporated in the prognostic scoring systems—MIPSS-PV, as an independent genetic risk factor in PV.[10]

Still, an unanswered question is the problem of the interplay between JAK2V617F-STAT-induced inflammation and disease progression to the post-PV myelofibrosis. It has been postulated that bone marrow fibrosis is a consequence of progressive replacement of blood-forming cells by reticulin fibers, caused not only by JAK-STAT-induced chronic inflammatory state but also by the acquisition of somatic mutations in hematopoietic stem cells (HSC).[11,12] According to initial reports, the coexistence of *SF3B1* and *IDH1/2* mutation in PV pts was associated with a high risk of disease transformation into post-PV myelofibrosis.[13] The lastly published study results confirmed the association between the coexistence of *ASXL1* mutation and disease transformation to the fibrotic phase.[14]

2 | CASE PRESENTATION

A 66-year-old woman with no previous medical history was admitted to the Hematology Outpatient Department in February 2016 due to abnormal results of a complete blood count. She did not report any abnormalities in previous complete blood count tests. Physical examination confirmed the presence of splenomegaly (abdominal ultrasonography spleen size 206 × 104 × 158 mm). The blood tests showed leukocytosis (20.3 G/L), red blood cells count 6.28 T/L, hemoglobin concentration 10.4 mmol/L, hematocrit value 0.51, and a decreased EPO level (<1.0 mIU/ml). The peripheral blood smear analysis showed normal red cells and platelets morphology. White cells differential showed 90% of segments, 2% of lymphocytes, 4% of monocytes, and 4% eosinophils. The bone marrow aspiration biopsy evaluation revealed the hypo/normocellular bone marrow with erythroid/granulocytic cell ratio 34:59 and normal megakaryopoiesis. The histopathological bone marrow evaluation performed in December 2016 revealed hypercellular bone marrow with locally increased number (mean 100 cells/mm^2) of dysplastic megakaryocytes. The repeated trephine biopsy performed in February 2020 showed hypercellular bone marrow (cellularity 90%–100%) and increased erythroid cell content (CD71[+], e-cadherin[+] – 50%), with shift to the left in the maturation pathway with no coexpression of CD34 and CD117. The granulocytic cells line (CD15[+], MPO[+]) evaluation confirmed its normal morphology and maturation pattern. Moreover, an increased number (mean 65 cells/mm^2) of atypic, hyperlobular, and hyperchromatic megakaryocytes (factor VIII+, CD61+) was found. Myelofibrosis (MF) grade determination according to the European consensus showed grade 2. The changes in the complete blood count results and in the spleen size are presented in Figure 1. A detailed genetic evaluation confirmed the *JAK2*V617F, *SRSF2* c.284C>A p.(Pro95His), and *ASXL1* c.1720-2A>G (intron 12, splice site) variant positivity (Table 1). The screening for the presence of *BCR-ABL* transcript, *U2AF1* (exon 2 and 6), *IDH1* (exon 4), *IDH2* (exon 4) mutations did not confirm their presence. The *JAK2*V617F variant allele frequency (VAF) was determined to amount to 59% at the time of diagnosis and 93% after 4-year follow-up. The analysis of *ASXL1* VAF revealed a stable level around 50% during the whole observation time. The karyotype analysis (GTG) performed at the initial evaluation revealed abnormal karyotype—46,XX, del(12)(p12)[6]/46,XX[5]. Initially, despite the treatment with phlebotomy, the hemoglobin level and hematocrit value remained above the recommended range. Therefore, hydroxycarbamide treatment in the dose of 1.5–3.0 g daily was started since May 2019 (Figure 1). A detailed analysis of resources data showed that the *ASXL1* variant detected in our patient had been reported only once in Clinvar (accession number VCV001075418).[15] It is considered pathogenic and not typical for hematological malignancies. The Functional Analysis Through Hidden Markov Models (FATHMM) categorizes this change as damaging with a 0.9981 score.[16] It is worth mentioning that the NM_015338.6(ASXL1):c.1720-2A>G variant was firstly described by Leon et al. in a patient with mild Bohring–Opitz syndrome (BOS).[17] BOS is a rare, autosomal dominant, multiple anomaly syndrome, characterized by organ malformations (including facial anomalies), and severe intellectual disabilities. Until now, there have been fewer than 300 cases reported worldwide.[18] According to the available data, approximately 80% of BOS occurs as the result of *de novo* germline heterozygous variant in *ASXL1*.[19] In the presented case, the *ASXL1* VAF was stable (50%) during the 4-year follow-up, despite

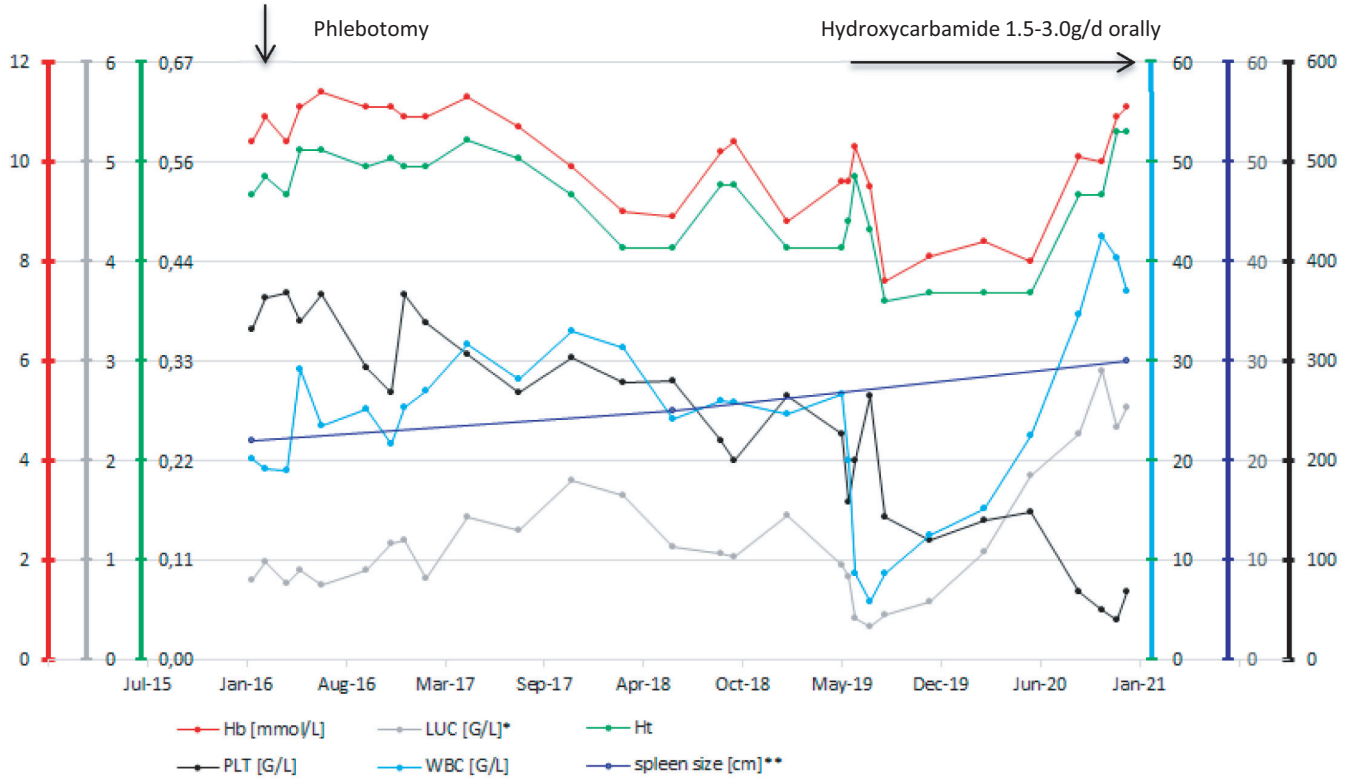

FIGURE 1 The changes in the complete blood count and spleen size during 4-year follow-up. (*LUC—large unstained cells, **spleen size in ultrasonography examination)

TABLE 1 Variant allele frequency of the studied genes detected at diagnosis and at follow-up in a patient with polycythemia vera progressing to the fibrotic phase

Gene	Variant	VAF at diagnosis	VAF at follow-up
JAK2	LRG_612t1:c.1849G>T LRG_612p1:p.(Val617Phe)	59%	93%
ASXL1	LRG_630t1:c.1720-2A>G LRG_630p1:p.(Ile574Valfs*22)	~50%	~50%
SRSF2	LRG_640t1:c.284C>A LRG_640p1:p.(Pro95His)	~43%	~48%

Abbreviation: VAF, variant allele frequency.

an evident increase in *JAK2*V617F VAF (59% vs. 93%, Table 1 and Figure 2). The family history revealed that the patient's grandson had been diagnosed with cerebral palsy, probably as a result of labor complications. Therefore, we also considered the family character of the detected variant. However, the analysis of the patient's buccal swab cell-derived DNA excluded the germline character of the *ASXL1* variant. It may confirm the hypothesis that *ASXL1* mutation is representative for the PV initiating hematopoietic progenitor cells not undergoing clonal expansion during disease evolution. Another explanation may be the loss of heterozygosity rescue, as *ASXL1* is indispensable for normal differentiation of blood cells and the maintenance of HSC function.[20–22] The observed increase in *JAK2*V617F VAF may be the result of mitotic recombination of the short arm of chromosome 9, as was previously postulated by Kralovics et al.[23]

3 | METHODS

The assessment for the presence of the *JAK2*V617F mutation and *BCR-ABL* transcript was conducted by quantitative allele-specific RQ-PCR according to Larsen et al.[24] and multiplex RT-PCR, respectively. HRMA was used to detect mutations in *SRSF2*, *U2AF1*, *IDH1/2* genes, as previously described by Lin et al.,[25] Qian et al.,[26] and Hatae et al.,[27] respectively. For identification of mutation's type screened by HRMA, the Sanger sequencing was applied using the BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Thermo Fisher Scientific). The sequence of exon 13 (range Ile574 to Ala735) of *ASXL1* gene (a region covering at least 83% of all known *ASXL1* mutations) was analyzed by Sanger sequencing.[28,29]

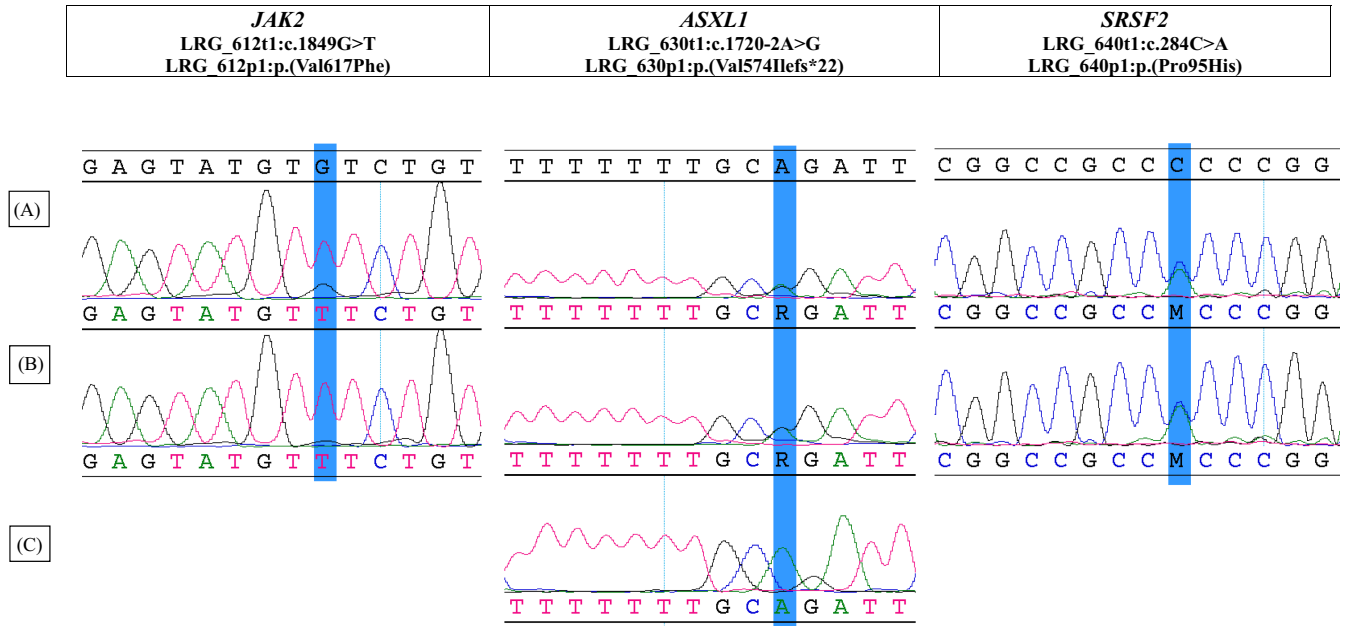

FIGURE 2 Results of Sanger sequencing of *JAK2* exon 14, *ASXL1* intron 12/exon13, and *SRSF2* exon 1 in patient with polycythemia vera and progression to fibrotic phase (the studied time points: A - at the diagnosis time, B - at the 4th year of the follow-up, C - at the 4th year of follow-up [the buccal swab])

4 | DISCUSSION

It was documented that the acquisition of somatic mutations in *ASXL1* by HSC increased the risk of hematologic neoplasms in healthy individuals.[30] However, there are no reports in the literature about the coexistence of BOS and hematological malignancies. It was confirmed that the cancer risk in BOS pts seemed to be increased in both *ASXL1* mutation negative and positive pts. In the first case, the nephroblastomatosis (diagnosed post-mortem)[31] and fatal medulloblastoma were reported in two separate individuals.[32] In the second case, the bilateral Willms` tumor developed at 2 and 6 years of age in two other BOS *ASXL1* mutation positive pts.[33]

ASXL1 is one of the most frequently mutated gene presented in healthy individuals with clonal hematopoiesis indeterminate potential (CHIP). Moreover, the *ASXL1* mutations' presence is associated with poor prognosis in pts with myeloid malignancies.[29,34] The majority of *ASXL1* gene structure aberrations (66%; 47.2% frameshift and 18.8% nonsense mutations) detected in human cancers are predicted to encode premature stop codons. They are almost universally located at the C-terminal and give rise to prematurely truncated variants of ASXL1 that retain the N-terminal region, which suggests that the amino terminal domain of ASXL1 retains a functional activity important for tumorigenesis.[35,36] Also, the *ASXL1* variant detected in our patient has similar functional properties, as was documented by Leon et al. Briefly, the novel aberrant transcript is not mediated by nonsense-mediated decay (NMD) process; therefore, the transcript is not spliced correctly. Affecting the canonical acceptor splice site at intron 12, the variant results in full retention of intron 12 and truncated protein lacking C-terminus.[17] On the basis of the literature data, the ASXL1 truncations might act as gain-of-function mutations, changing the function of the ASXL1–BAP1 (BRCA1-associated protein-1; ubiquitin carboxy-terminal hydrolase) complex. It was documented that a stable expression of truncated, hyperactive ASXL1–BAP1 complexes in a hematopoietic precursor cell line resulted in a global erasure of histone H2A ubiquitinylated at lysine 119 (H2AK119Ub), striking depletion of trimethylation of histone H3 at lysine 27 (H3K27me3), selective upregulation of a subset of genes whose promoters were marked by both H2AK119Ub and histone H3 trimethylated (H3K4me3), and the promotion of aberrant myeloid differentiation of hematopoietic progenitor cells.[36,37]

It has been postulated, according to the results of an *in vivo* study, that ASXL1 alteration cooperates with *JAK2*V617F mutation, leading to biased lineage skewing, favoring erythroid and megakaryocytic differentiation, which may accelerate myelofibrosis.[38] It is in agreement with the data obtained from our patient evaluation, confirming an increased number of erythroid and megakryocytic cells in the bone marrow specimens. Among the 70 PV pts recorded in our database, the presence of post-PV MF on the basis of IWG-MRT criteria was diagnosed in nine other *JAK2*V617F-positive pts with no *ASXL1*, *SRSF2*, *U2AF1*, and *IDH1/2* variants. The median myelofibrosis-free survival (MFS) in patients carrying *JAK2*V617F variant only was significantly longer than in the presented case - 168 [21–252] months vs. 57 months, respectively. It should be also mentioned that, in our database, there are other four *JAK2*V617F-positive PV patients with coexisting *ASXL1* mutations who have not progressed to the fibrotic phase so far. All of them have been carefully monitored in terms of clinical and laboratory symptoms of progression to the fibrotic phase (current median time of follow-up is 42 [36–180] months). Unexpectedly, contrary to the initial reports data, the *JAK2*V617F VAF seems not to affect myelofibrosis-free survival.[10,13]

The accelerated progression to the fibrotic phase in the presented patient may also be the result of *ASXL1* c.1720-2A>G variant specific alternation in the function of bone marrow stromal cells (BMSCs) or the coexistence of the *SRSF2* c.284C>A p.(Pro95His) variant. In the first case, it was documented that *Asxl1* loss or conditional deletion in osteoblasts and their progenitors led to a markedly decreased number of BMSCs, compared to wild-type littermates.[39] The latter phenomenon induced by the *ASXL1* mutation may perturb the BMSCs cooperation, influencing the fibroblast function, as well. Of course, it cannot be excluded that the coexistence of other mutations, including the *SRSF2* mutation, additionally accelerated the process of fibrotic transformation in the presented case.[40]

5 | CONCLUSION

According to our knowledge, it is a first case report of the occurrence of *ASXL1* splice site c.1720-2A>G variant in hematological malignancies. The biological consequences of the above-mentioned variant acquisition by HSC seem to be similar to other mutations of *ASXL1* leading to the truncation of the ASXL1 protein. In our opinion, the presented case well documented the necessity of individual molecular fingerprint determination in pts with PV. It allowed to introduce molecularly targeted therapy, especially in pts with high molecular risk and a progressive disease. It is especially evident in the light of the recently published data concerning a possible targeted therapeutic approach for *ASXL1*-mutated leukemia through the inhibition of ASXL1-BAP1 catalytic activity.[35] The above-mentioned strategy may delay the disease evolution to fibrotic phase, which itself is now considered an independent risk factor for a rapid blast progression of MPN.[41,42]

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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