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SETBP1 in Myeloid Malignancies—Putting Breadcrumbs Together in Rare, Uncommon, and Common Pediatric Cases

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In resource-constraint settings, genetic testing is rarely available for patients. We report the association of SETBP1, a major oncogene of interest in myeloid malignancies, with juvenile myelomonocytic leukemia (JMML) and with GATA 1 mutation. The modulating role of SETBP1 in Rat sarcoma virus (RAS)-driven myeloid malignancies, especially JMML, is unknown. In vivo and in vitro studies point to the role of SETBP1 in aggressive leukemogenesis.[1] SETBP1 mutation is not considered the primary event.[2] The association of SETBP1 with RAS and PTPN11, protein tyrosine phosphatase nonreceptor type 11 (PTPN11) confers both self-renewal and oncogenic transformation. The outcome of SETBP1 with confounding mutations like PTPN11 and interlinked pathways of Mitogen-activated protein kinase (MAPK) may be difficult to predict.[3,4] PTPN11 in co-association with RAS in JMML is an independent poor prognostic factor[5] and confounds the effects of those associated with SETBP1. PTPN11 also has poor prognostic outcomes post-hematopoietic stem cell transplantation in JMML patients.[3]

We present three cases of rare associations of SETBP1 with GATA1 mutation, JMML, and one with concomitant PTPN11 mutation. Our first case was a novel association of SETBP1 in transient abnormal myelopoiesis (TAM) with a fatal outcome, the second case was JMML with a blastic transformation-like presentation with tumor lysis, and the third case was a case of JMML. These different outcomes could be attributed to the association of an underlying SETBP1 or one of the pathway mutations downstream of myeloid leukemogenesis. The presentation, however, in all cases was similar: severe anemia, massive organomegaly, presentation with high leucocyte count, and tumor lysis syndrome in one patient (another rare occurrence in JMML) (►**Table 1**). Two of the patients died within 4 days despite the best supportive treatment. One of the JMML cases with isolated SETBP1 mutation has an indolent course compared to the other two and is alive on follow-up awaiting transplantation (►**Table 1**). SETBP1 may not confer a dismal outcome and is just evidence of complex mutagenesis and could also mean heterogeneous clones with isolated mutations rather than co-existent mutations.

SETBP1 co-expression leads to increased phosphorylated-driven MAP kinases, with a possible role of trametinib in these disorders.[2] Co-occurrence with other known mutations highlights the interrelated roles of the downstream leukemoid pathogenesis in these strikingly different neoplasms. The case of TAM with SETBP1 could initiate new insight into myeloid leukemogenesis. Next-generation sequencing is essential in the diagnostic management of all pediatric myeloproliferative disorders and can improve outcomes with better risk stratification.

Ethical Statement

All ethical consideration and permissions were obtained for preparation of manuscript.

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Table 1 Clinicopathological characteristics of the novel, uncommon, and common case with *SETBP1* mutation

Case	1. TAM with *SETBP1* case	2. Uncommon *SETBP1* mutated JMML case	3. Common *SETBP1* in JMML
Brief history	A 2-day-old baby boy born out of nonconsanguineous marriage, 3rd in birth order presented with leucocytosis, thrombocytopenia and anemia with myeloid blasts	A 1-year-old child presented with a history of progressive paleness of the body, frequent infections, fever, and abdominal distension for 1 month. The child had monocytic leucocytosis, 20% blasts on peripheral smear with laboratory evidence of tumor lysis syndrome	A 1-year-old male child born out of nonconsanguineous marriage, presented with complaints of fever with abdominal distension for 3 months
Primary investigations	Flow cytometry: AML with MPO + CD34 + CD117 + CD33 +, CD56 +, and CD7dim+ (►**Fig. 1**)	Investigations suggested myeloid blast crisis in a known case of JMML with tumor lysis syndrome	Investigations showed leucocytosis with monocytosis, thrombocytopenia, and massive hepatosplenomegaly. The child met the criteria for JMML on the investigations (Splenomegaly, 8% blasts on Peripheral smear, leucocytosis, absolute monocytosis, myeloid precursors
Sequencing result	*GATA1, SETBP1*	*PTPN11, SETBP1*	*PTPN11, SETBP1*
Details of variants	1. Delins variant (chrX:g.48791258_48791271delinsTCAGGCAGT; c.149_162delinsTCAGGCAGT) in the GATA1 gene (561X, 8.4% MAF). 2. Frameshift deletion (chrX: g.48791243_48791246del; c.134_137del) 560X, 24.8% MAF in GATA1 gene (►**Fig. 1**) 3. *SETBP1* gene mutation at c.2843G > A (ENST00000649279.2) in Exon 4 was found (859X, MAF- 48.9%) (►**Fig. 1**)	*1. PTPN11* mutation [(chr12: g.112450406G > A; c.226G > A) not reported in ExAC and 1000 genomes databases[VCV000013336.5]] *2. SETBP1* mutation [(chr18: g.44951942G > A; c.2602G > A) gain-of-function mutation MAF-0.002%, not reported in 1000 genomes database] (►**Fig. 2A** and **B**)	*1. PTPN11* gene [c.179G > T (ENST00000635625.1) 51X, MAF- 49.3%]. *2. SETBP1*mutation [c.1102A > G (ENST00000649279.2) with heterozygous allele burden (50%) and 258X depth read (►**Fig. 3A** and **B**)
Treatment	Supportive	Supportive	On supportive transfusion care, awaiting BMT
Outcome	Mortality at day 2 of admission	Mortality at day 4 of admission	Alive and hemodynamically stable on transfusion
Remarks	Never reported in literature co-association of *SETBP1* with *GATA1*in a patient could highlight the inter-related myeloid pathway in Leukemia and MPNS	The child was detected to have concurrent. The rare presentation as tumor lysis syndrome could be attributable to co-existent *PTPN-11* and *SETBP1* mutation in the same clone by simultaneous or additional hit	*SETBP1* in JMML in our case three did not have a dismal outcome, suggesting the *SETBP1* and *PTPN11* could be heteroclonal or subclonal, rather than concomitant in single malignant clone

Abbreviations: AML, acute myeloid Leukemia; BMT, bone marrow transplant; GATA 1, GATA binding protein 1; JMML, juvenile myelomonocytic leukemia; PTPN11, protein tyrosine phosphatase nonreceptor type 11; SETBP1, SET binding protein 1.

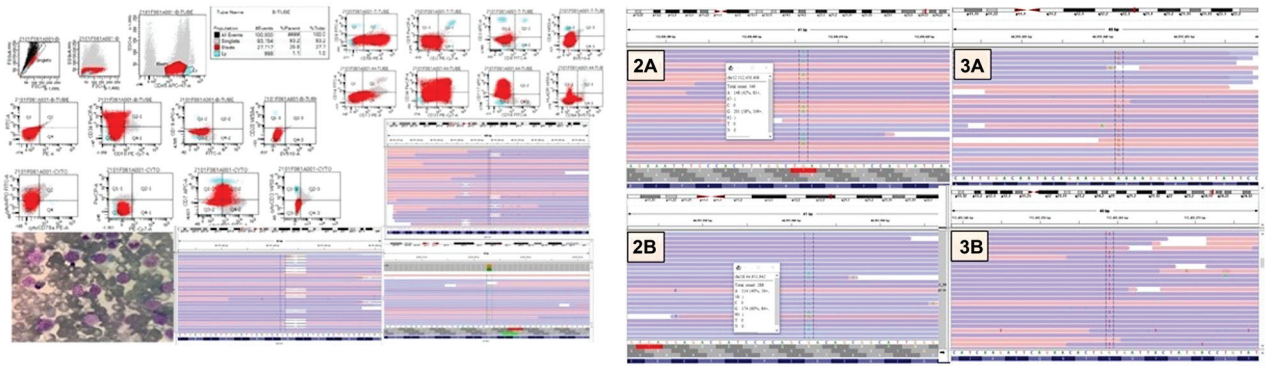

Fig. 1 The morphological features, flow-cytometry characters, and sequencing result of patient 1 in the left-side plane and the sequencing results for patients 2 (2**A** and **B**) and patient 3 (3**A** and **B**) on the right-side pane.

Conflict of Interest
None declared.

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