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Acute leukemia with predominantly myeloid differentiation and *TBL1XR1*::*CSF1R* fusion

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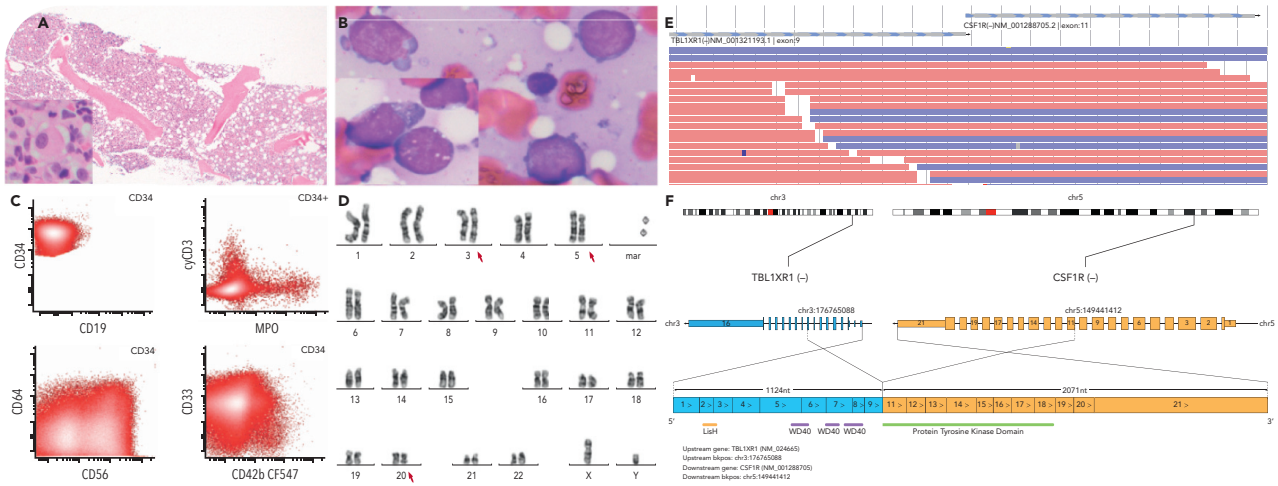

A 67-year-old man presented with anemia (10.4 g/dL), thrombocytopenia (49 000/μL), and circulating blasts. Bone marrow examination revealed hypercellularity, multilineage dysplasia (panel A: hematoxylin and eosin stain, original magnification ×4; inset: micromegakaryocyte, original magnification ×40), and 70% blasts (panel B: Wright-Giemsa stain, original magnification ×100; inset: cytoplasmic blebs and vacuoles in subset, original magnification ×100) with predominantly monocytic differentiation (panel C: flow cytometry, $CD34^+$ blasts coexpress CD56, CD64 [variable], myeloperoxidase (MPO) [partial], CD33), subset (3.6%) with megakaryoblastic differentiation (CD42b), and minimal blast component (<1%) showing T-cell lineage differentiation (cytoplastic-CD3). Karyotype detected t(3;5) and del(20q) (95% of metaphases) (panel D). Targeted next-generation sequencing (NGS) detected somatic variants at high allele frequencies: *NRAS* p.G12V(c.35G>T), *ETV6* p.Y344*(c.1032C>A), *PHF6* p.Y195*(c.585T>A), *RET* p.R297C(c.889C>T); copy number loss of *ETV6*, and *CDKN1B* on chr12p13. Given the possibility of mixed lineage leukemia, targeted RNA sequencing utilizing a commercially available NGS-based assay (Archer) was performed, identifying an in-frame *TBL1XR1*::*CSF1R* fusion (panel E: JBrowse supporting reads; panel F: rearrangement between *TBL1XR1* [exon9] and *CSF1R* [exon11]). This case was best classified as acute myeloid leukemia with a minimal component showing T-cell differentiation. Induction 7 + 3 (cytarabine + daunorubicin) was initiated, followed by intermediate-dose cytarabine reinduction.

TBL1XR1::*CSF1R* fusion has been reported once in B-lymphoblastic leukemia. This is the first report in a predominantly myeloid acute leukemia. *TBL1XR1* is a regulator of hematopoietic stem cell self-renewal and lineage differentiation. We hypothesize that this fusion may lead to overexpression and/or ligand-free activation of *CSF1R*. An intact tyrosine kinase domain in *CSF1R* potentially serves as a therapeutic target.

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