TPM3::PDGFRB-rearranged MLN-TK with associated hematologic neoplasm: a three-phase clinical course supporting upfront NGS profiling

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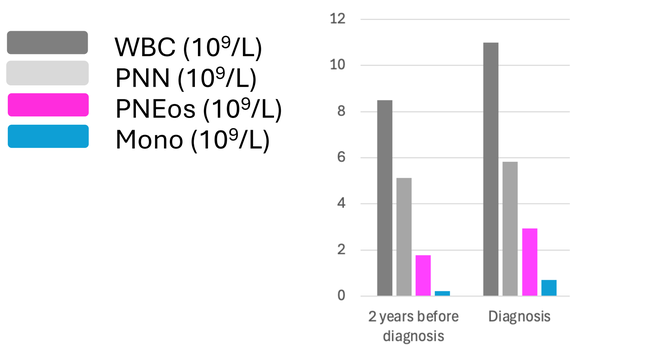
TPM3::PDGFRB-rearranged MLN-TK may evolve as a composite three-phase disease; fusion detection alone may miss clinically relevant clonal complexity.

TPM3::PDGFRB-rearranged MLN TK (*Diagnostic*)

Table 1a. Key clinical and hematologic features.

Parameter	Diagnosis
Age/sex	77/M
Clinical phase	MLN-TK with eosinophilia
Treatment	Imatinib 100 mg/day + short-course steroids
Hemoglobin (g/dL)	14.2
WBC (×10⁹/L)	11.1
ANC (×10⁹/L)	5.83
AEC (×10⁹/L)	2.94
Platelets (×10⁹/L)	205

Fig. 1a Longitudinal CBC profile.

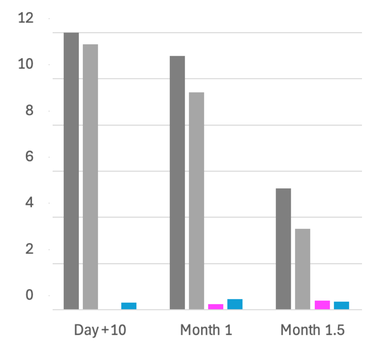


Complete Hematologic (CHR) and Cytogenetic (CCyr) Remission (*Treatment*)

Table 1b. Key clinical and hematologic features.

Early post-imatinib follow-up*
CHR under imatinib
Imatinib 100 mg/day
15.1
12.4
11.5
0.01
272

Fig. 1b Longitudinal CBC profile.

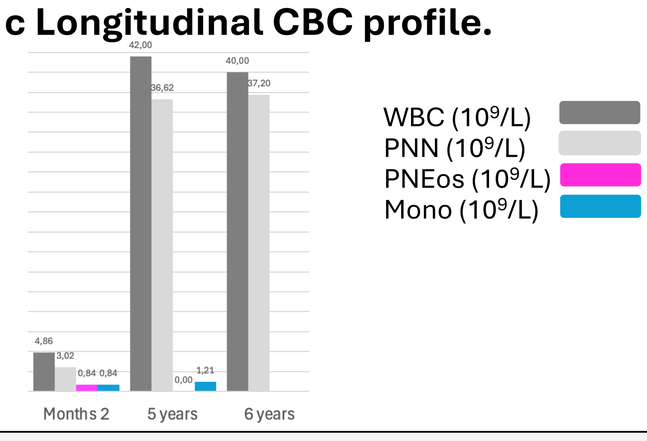


MLN-TK + Associated Hematologic Neoplasm (AHN) (*Neutrophilic phenotype evolution*)

Table 1c. Key clinical and hematologic features.

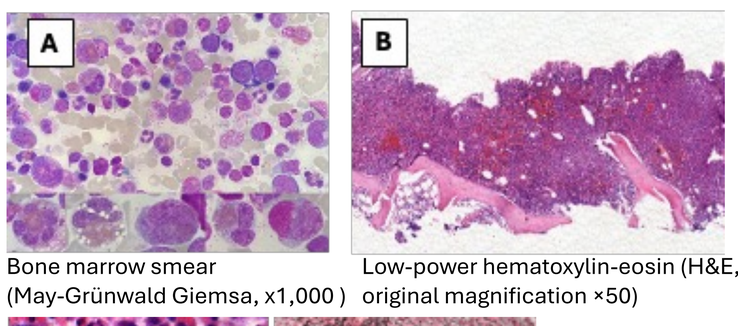
MLN-TK + AHN
Neutrophilic progression / MLN-TK + AHN
Imatinib stopped; hydroxyurea
13.0
42.1
36.62
0.84
116

Fig. 1c Longitudinal CBC profile.



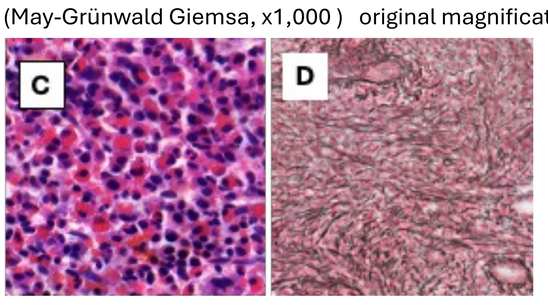
Differential leukocyte counts illustrate lineage-specific dynamics relevant for the differential diagnosis between MLN-TK, MLN-TK with associated myeloid neoplasm, MDS/MPN overlap syndromes, and chronic neutrophilic leukemia.

Fig. 2a Bone marrow morphology.



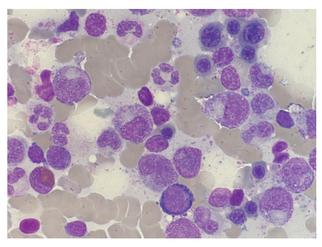
Bone marrow smear (May-Grünwald Giemsa, x1,000)

Low-power hematoxylin-eosin (H&E, original magnification ×50)



C. High-power hematoxylin-eosin (H&E, original magnification ×400)
D. Reticulin stain (×400)

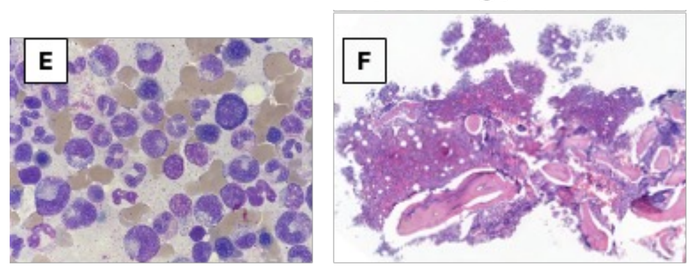
Fig. 2b Bone marrow smear.



Bone marrow smear (May-Grünwald Giemsa, x1,000)

Shift from eosinophil-rich marrow at presentation to a neutrophil-predominant marrow later in the disease course.

Fig. 2c Bone marrow morphology.



Bone marrow smear (May-Grünwald Giemsa, x1,000)

Low-power hematoxylin-eosin (H&E, original magnification ×50)

G. High-power hematoxylin-eosin (H&E, original magnification ×400)
H. Reticulin stain (×400)

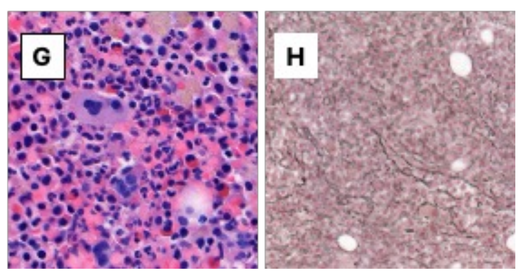
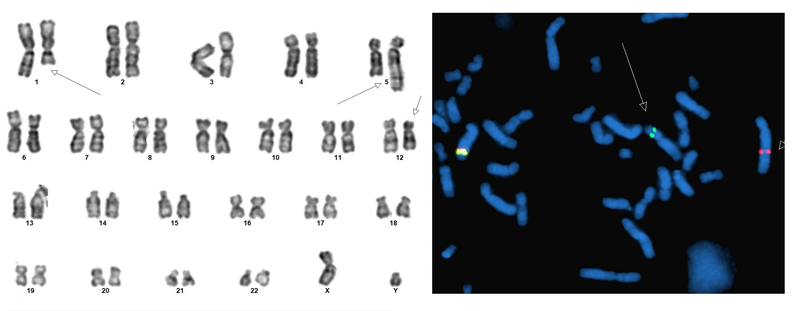


Fig. 3a Cytogenetics & molecular genetics.



Standard karyotype

Metaphase FISH analysis (PDGFRB break-appart probe (MetaSystems)

Fig. 3b RT-qPCR _TPM3::PDGFRB_ follow-up.

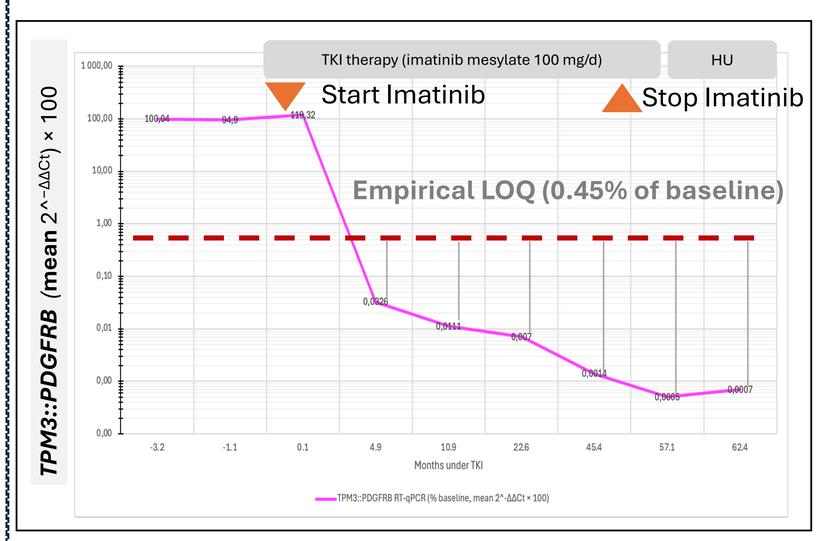
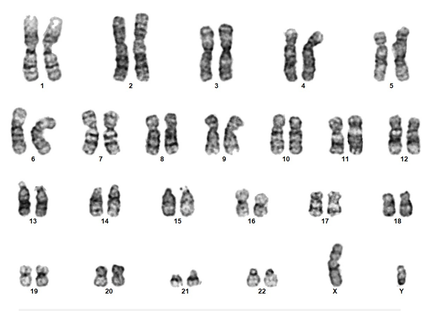
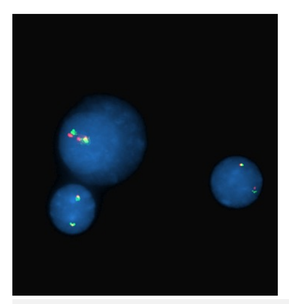


Fig. 3c Cytogenetics & molecular genetics.

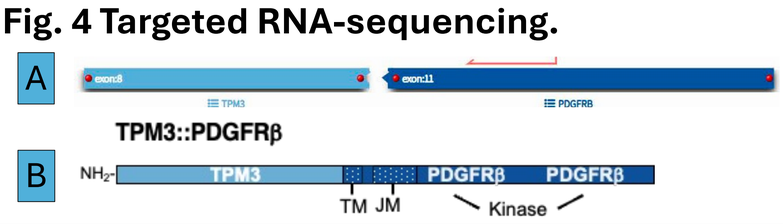


Standard karyotype



Interphase FISH analysis (PDGFRB break-appart probe (MetaSystems)

Fig. 4 Targeted RNA-sequencing.



In-frame _TPM3_ exon 8::_PDGFRB_ exon 11 fusion (A) and TPM3::PDFGRB protein (B).

TPM3::PDGFRB highlights suppression of the fusion-driven component.

Bibliography:

- Zhipeng Li et al., Molecular diagnosis and targeted therapy of a pediatric chronic eosinophilic leukemia patient carrying *TPM3::PDGFRB* Fusion. Pediatr Blood Cancer. 2011:463-6.
- Rosati R et al., *TPM3::PDGFRB* fusion transcript and its reciprocal in chronic eosinophilic leukemia. Leukemia. sept 2006;20(9):1623-4.

Table 2a. Molecular findings.

	T0 - Diagnostic
Karyotype	46, XY, t(1;5)(q21;q33)(20) 46, XY (1);
FISH	FISH PDGFRB-r (70%)
RNA-Seq	*TPM3::PDGFRB*+
Bulk DNA NGS	ASXL1; p.(Gln512*)(45%)
	EZH2; c.2195+1G>A(36%)
	SRSF2; p.(Pro95His)(5%)

Table 2b. Molecular findings.

	T1 - On imatinib
Karyotype	46 (X,Y))(11+9c)
FISH	FISH PDGFRB-r (0%)
RNA-Seq	TPM3::PDGFRB-
Bulk DNA NGS	ASXL1; p.(Gln512*)(47%)
	EZH2; c.2195+1G>A(10%)
	SRSF2; p.(Pro95His)(31%)
	SRSF2; p.(Pro95Leu)(1%)

Table 2c. Molecular findings.

	T2 - Late follow-up	T2 - Late follow-up
Karyotype	46 (X,Y))(10/10c)	
FISH	FISH PDGFRB-r (0%)	
RNA-Seq	TPM3::PDGFRB-	
Bulk DNA NGS	ASXL1; p.(Gln512*)(47%)	SRSF2; p.(Pro95Leu)(40%)
	EZH2; c.2195+1G>A(48%)	SETBP1; p.(Asp868Asn)(47%)
	TET2; p.(Cys1298Tyr)(42%)	CSF3R; p.(Thr618Ile)(26%)
		ETNK1; p.(Asn244Ser)(8%)

<u>Conclusion</u>: _TPM3::PDGFRB_ is a rare but recurrent fusion in MLN-TK and that these neoplasms may evolve as composite clonal diseases with associated hematologic neoplasm. It also supports upfront NGS-based profiling at diagnosis to capture complex clonal architecture, refine risk assessment, and guide therapeutic strategy beyond TKI therapy alone.