

REVIEW

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes: A workshop report with focus on novel entities and a literature review including paediatric cases

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Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes: A workshop report with focus on novel entities and a literature review including paediatric cases

Myeloid/lymphoid neoplasms with eosinophilia (M/LN-eo) and tyrosine kinase (TK) gene fusions are a rare group of haematopoietic neoplasms with a broad range of clinical and morphological presentations. Paediatric cases have increasingly been recognised. Importantly, not all appear as a chronic myeloid neoplasm and eosinophilia is not always present. In addition, standard cytogenetic and molecular methods may not be sufficient to diagnose M/LN-eo due to cytogenetically cryptic aberrations. Therefore, additional evaluation with fluorescence *in-situ* hybridisation and other molecular genetic techniques (array-based comparative genomic hybridisation, RNA sequencing) are recommended for the identification of specific TK gene fusions. M/LN-eo with JAK2 and

FLT3-rearrangements and ETV6::ABL1 fusion were recently added as a formal member to this category in the International Consensus Classification (ICC) and the 5th edition of the WHO classification (WHO-HAEM5). In addition, other less common defined genetic alterations involving TK genes have been described. This study is an update on M/LN-eo with TK gene fusions with focus on novel entities, as illustrated by cases submitted to the Bone Marrow Workshop, organised by the European Bone Marrow Working Group (EBMWG) within the frame of the 21st European Association for Haematopathology congress (EAHP-SH) in Florence 2022. A literature review was performed including paediatric cases of M/LN-eo with TK gene fusions.

Keywords: bone marrow biopsy, European Bone Marrow Working Group (EBMWG), myeloid/lymphoid neoplasms with eosinophilia, paediatric, tyrosine kinase gene fusion

Key message

This is an update on myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions, as

illustrated by cases submitted to the EAHP 2022 Bone Marrow Workshop with an extensive literature review including paediatric cases. These rare haematopoietic neoplasms have a broad range of

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clinicopathological presentations and are challenging to diagnose; therefore, recommendations for laboratory work-up are included.

Introduction

The myeloid and/or lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (M/LN-eo-TK) are a rare group of haematological malignancies driven by rearrangements involving genes encoding specific tyrosine kinases.¹ The common features shared among these neoplasms include: (1) constitutive tyrosine kinase (TK) signalling as a result of a gene fusion; (2) origin from mutated pluripotent bone marrow (BM) stem cells that can differentiate into myeloid and/or lymphoid progenitors, leading to clinically complex and heterogeneous manifestations; (3) frequent association with peripheral blood (PB) and/or BM eosinophilia; and (4) excellent responses to specific TK inhibitors.² The M/LN-eo-TK manifest with a very broad range of histological types, most frequently as a chronic myeloid neoplasm, such as myelodysplastic (MDS) and/or myeloproliferative (MPN) neoplasms and mixed MDS/MPN entities, but also as acute myeloid leukaemia (AML), mixed acute leukaemias (MPAL) and B-acute lymphoblastic leukaemia (B-ALL) or T lymphoblastic leukaemia/lymphoma (T-ALL/LBL). Extramedullary disease manifestation is common. The estimated incidence of M/LN-eo-TK is < 1/100 000 people,³ and is even more rare in children, with only few reported cases.^{4–9} The category of M/LN-eo-TK contains several specific disease groups (*PDGFRA*, *PDGFRB* and *FGFR1*) and was recently expanded with *JAK2*-rearrangement (formerly a provisional entity), *FLT3*-rearrangements and *ETV6::ABL1* in the 5th edition of the WHO classification (WHO-HAEM5)¹⁰ and the International Consensus Classification (ICC).¹¹ Other less common genetic alterations involving TK genes have been described in the literature and may be considered in the group of M/LN-eo with other tyrosine kinase gene fusions (WHO-HAEM5).^{12,13}

In a recent BM workshop (SH-EAHP congress, Florence 2022), 13 adult cases with M/LN-eo-TK were received, seven of which were newly included entities with *JAK2* (three cases) and *FLT3* rearrangements (two cases), and two cases with *ETV6::ABL1* fusion (Table 1). These cases are discussed in the context of a literature review (using PubMed) with focus upon novel entities, including both single case reports and previous reviews (Table 2). In addition, the literature was studied with respect to paediatric cases of M/LN-eo-TK (Table 3).

PDGFRA GENE REARRANGEMENT

The *PDGFRA*-rearrangement is the most common in the category of M/LN-eo with TK gene fusions, with a striking male predominance. The usual age at onset is in the late 40s, but paediatric patients may be affected. *PDGFRA* rearranged M/LN-eo present most frequently as chronic eosinophilic leukaemia (CEL) in the PB and BM, less commonly as other MPN, systemic mastocytosis (SM), AML or T-ALL/LBL, and are often associated with peripheral eosinophilia. Extramedullary tumours are present in 50%; extramedullary disease manifestation without concomitant BM involvement has been described, but is extremely uncommon.

FIP1L1 is the most frequent fusion partner in this group (85% of cases), typically resulting from a cryptic interstitial deletion at 4q12. The fusion is best detected by fluorescence *in-situ* hybridisation (FISH) or reverse transcriptase–polymerase chain reaction (RT-PCR), specifically designed for *FIP1L1::PDGFRA*, while RNA-based next generation sequencing (NGS) techniques are increasingly used for the detection of alternate fusions. Several variants with other fusion genes have been reported in the literature.^{14–16} *PDGFRA*-rearranged M/LN are otherwise genomically quiet, with few somatic mutations.¹⁷ The presence of significant tissue eosinophilia or subsequent development of a myeloid neoplasm should prompt FISH analysis to rule out *PDGFRA*. If molecular diagnosis is not possible, the diagnosis should be suspected in a Philadelphia chromosome-negative MPN with morphological features of CEL, increased number of mast cells, elevated mast cell tryptase, high level of serum vitamin B12 and splenomegaly.

PDGFRB GENE REARRANGEMENT

M/LN-eo with *PDGFRB* rearrangement are the second most common in this category. There is a male predominance (male:female ratio 2:1), with the usual age of onset also being in the late 40s. It can present as a myeloid or lymphoid neoplasm, often with prominent eosinophilia and sometimes neutrophilia or monocytosis. BM morphology shows a wide variety of presentations, including chronic myelomonocytic leukaemia (CMML), atypical chronic myeloid leukaemia (aCML; termed 'MDS/MPN with neutrophilia' in the WHO-HAEM5), CEL, AML, *de-novo* B-ALL or T-ALL/LBL. The disease is usually suspected in the presence of a rearrangement involving chromosome 5q31≈33 by conventional karyotyping. However, cases with cryptic fusions have increasingly been recognised.^{18,19} Therefore, it has been suggested that

Table 1. Clinical and morphological characteristics of cases with M/LN and TK gene fusions submitted to the bone marrow workshop (EAHP-SH congress, Florence 2022)

BMWS case no., author	Clinical presentation, laboratory data	Morphological presentation	Cytogenetics, molecular studies	Interesting features; follow-up
1223; Dr Chen <i>et al.</i> , University of Washington, Seattle	25-year-old man; splenomegaly, lymphadenopathy, WBC $75 \times 10^9/l$ (9% eosinophils); anaemia, thrombocytopenia	MDS/MPN-eo (CMML-like)	46,XY,inv(5)(q32q35)[20] FISH: <i>PDGFRB</i> rearr (5q32) NGS: normal RNA sequencing: <i>RUFY1::PDGFRB</i>	Novel fusion partner; treated with imatinib; complete haematological response; FISH undetectable after 5 months
1420; Dr Flood <i>et al.</i> , Department of Pathology, University of Chicago	65-year-old woman; anaemia, monocytosis, WBC $15 \times 10^9/l$	MDS/MPN-eo (CMML-like); increased mast cells (no aggregates)	Normal karyotype FISH: abnormal signal for <i>PDGFRB</i> RNA sequencing: <i>TNIP1::PDGFRB</i> NGS: <i>NRAS</i> gene, pathogenic variant (VAF: 44%)	Initial dx as CMML, revised after additional studies; no data on treatment/follow-up
1351; Dr Leguit; Pathology, UMC Utrecht	43-year-old man; back pain (thoracic mass), WBC $17 \times 10^9/l$ (monocytosis); anaemia; elevated serum-tryptase	MPN (CEL-like); extramedullary myeloid tumour	NGS: no <i>ASXL-1</i> , <i>CALR</i> , <i>FLT3</i> , <i>JAK2</i> , <i>MPL</i> , <i>RUNX1</i> , <i>SF3B1</i> , <i>TP53</i> <i>mut</i> Cytogenetics: trisomy chr.8 & 16 FISH: split signal of 5q32 <i>CSF1R/PDGFRB</i> locus; no <i>ETV6</i> rearrangement; fusion partner not identified	Concomitant chronic myeloid neoplasm and extramedullary tumour (thoracic mass); response to imatinib treatment
1452; Dr Almuhaissen <i>et al.</i> , Pathology & Laboratory Medicine, Indiana University School, Indianapolis	59-year-old female; WBC $1.9 \times 10^9/l$; anaemia, thrombocytopenia, PMH: indolent T lymphoblastic proliferation (LN)	<i>De-novo</i> B-ALL, mild eosinophilia	46,XX,t(1;13)(q12;q34); add(5)(q31), del(6)(q21-?23), del(8)(q21.2q22), add(9)(p13), del(9)(p21), add(17)(q21) [17]/46,XX NGS: <i>TPR::FGFR1</i> ; <i>PTCH1V1131M</i> , <i>RUNX1N146fd*16</i>	Died before treatment start; no evidence of chronic myeloid neoplasm prior to ALL diagnosis
1130; Dr Tzankov <i>et al.</i> , Pathology, University Hospital Basel	60-year-old male; WBC $26 \times 10^9/l$ (AEC 1.4), anaemia	MDS/MPN-eo, MF 1-2	46,XY, t(8;17)(p11.2; q12.1); NGS failed to detect fusion partner <i>FGFR1</i>	<i>FGFR1</i> -rearrangement with variant translocation. No follow-up data
1354; Dr Chan <i>et al.</i> , Pathology & Laboratory Medicine, Memorial Sloan Kettering Cancer Center, NY	68-year-old male; splenomegaly; WBC $3 \times 10^9/l$; anaemia	MPN-eo, MF 2, expanded left-shifted erythropoiesis, blast increase with aberrant immunophenotype (FCM)	FISH: <i>JAK2</i> (9p24.1) rearrangement (26%) Archer FusionPlex: <i>PCM1::JAK2</i> fusion No karyotype reported	No treatment/follow-up data
1240; Dr Garcia <i>et al.</i> , Pathology, MD Anderson Cancer Center, Madrid	55-year-old male; WBC $> 20 \times 10^9/l$; 62% eosinophils	MPN-eo (CEL-like); no blast increase (IHC, FCM)	46,XY, del(12)(p?p?),-13,-14,+2mar NGS: <i>BCR::JAK2</i> fusion	Follow-up (1.5/2.5 years): myeloid sarcoma (LN) and LBL (T/myeloid). <i>BCR::JAK2</i> fusion confirmed in both samples

Table 1. (Continued)

BMWS case no., author	Clinical presentation, laboratory data	Morphological presentation	Cytogenetics, molecular studies	Interesting features; follow-up
1319; Dr Montane <i>et al.</i> , Haematology, Institut Catala d'Oncologia, Barcelona	58-year-old male; splenomegaly CML-like WBC $102 \times 10^9/l$ (AEC 3), anaemia, thrombocytopenia	Myeloid neoplasm with significant marrow fibrosis	Complex karyotype with t(9;22)(p24;q11) FISH: <i>JAK2</i> (9p24) break-apart in 88% NGS: <i>BCR::JAK2</i> ; no <i>BCR::ABL1</i>	Hydroxyurea; HSCT, alive
1114; Dr Kelemen <i>et al.</i> , Pathology & Laboratory Medicine Mayo Clinic, Phoenix	33-year-old male; chronic eosinophilia, normal total WBC; elevated serum tryptase	Normocellular BM with eosinophilia, mast cell infiltrates (atypical immunophenotype by FCM), sheets of erythroid precursors	46,XY,t(13;14)(q12;q32) [6]/46,XY[14] <i>FLT3::TRIP11</i> fusion	Sheet-like proliferation of pro-erythroblasts (as described in MLN-TK with <i>PCM1::JAK2</i>); unusual mild clinical course
1214; Dr Willis <i>et al.</i> , Pathology, Duke University Hospital, North Carolina	58-year-old male; hepatosplenomegaly PB: 21% eosinophils 21% monocytes	B-ALL, mast cell infiltrates	46,XY; FISH: negative (10 probes) Single gene testing: negative (<i>JAK2</i> , <i>MPL</i> , <i>CARL</i> , <i>KIT</i> , <i>FLT3</i> , <i>BCR::ABL1</i>) NGS: <i>DNM3A</i> splice mut, <i>RUNX1</i> mut RNA seq: <i>FLT3::ZMYM2</i>	Myeloid neoplasm (MPN-like) 7 months after ALL-treatment; ALL-relapse at 17 months; post-mortem detection of a <i>FLT3::ZMYM2</i> fusion (RNA sequencing; cytogenetically cryptic)
1387; Dr Yao <i>et al.</i> , Pathology & Laboratory Medicine, Memorial Sloan Kettering Cancer Center, NY	50-year-old female; cerebral infarcts Platelets $880 \times 10^9/l$	MPN-eo (mimicking ET)	46,XX; negative for <i>BCR::ABL1</i> , <i>PDGFRA/PDGFRB</i> ; no MPN-related mutations (<i>JAK2</i> , <i>MPL</i> , <i>CARL</i>) Follow-up: <i>ETV6::ABL1</i> fusion identified by RNA-seq and FISH	Initial dx of ET (triple-negative); within 3 months progression to high-grade myeloid neoplasm with MF and blast increase (aberrant immunophenotype by FCM)
1373; Dr Maia <i>et al.</i> , Anatomia Patologica, Instituto Portugues de Oncologia, Lisboa	40-year-old man; lymphadenopathy, splenomegaly, anaemia, thrombocytopenia, WBC $182 \times 10^9/l$ (AEC $10 \times 10^9/l$)	MDS/MPN-eo and atypical mast cells; concomitant T-LBL (cervical LN)	46,XY, t(12;22)(p13;q12) [suggesting <i>ETV6::MNF1</i>] FISH: <i>ETV6</i> break-apart (BM & LN); no <i>JAK2/CARL/MPL</i> NGS (54 gene panel): no mutations	Clinical and molecular remission 4 months after allo-HSCT (4 months)
1388; Dr Hergott <i>et al.</i> , Pathology, Brigham and Women's Hospital, Boston	70-year-old female; pathological humerus fracture, lymphadenopathy, WBC $25 \times 10^9/l$ (4.9% eosinophils, up to 5% blasts), anaemia	MDS/MPN, increased mast cells; LN: myeloid sarcoma	45, XX, -7; confirmed by FISH NGS: <i>SEC31A::KIT</i> fusion (confirmed by RT-qPCR)	Novel KIT fusion; partial response to TKI

AEC, Absolute eosinophil count; B-ALL, B lymphoblastic leukaemia; CEL, Chronic eosinophilic leukaemia; CMML, Chronic myelomonocytic leukaemia; ET, Essential thrombocytemia; FCM, Flow cytometry; IHC, Immunohistochemistry; LN, Lymph node; MDS/MPN-eo, Myelodysplastic/myeloproliferative neoplasm with eosinophilia; MF, Marrow fibrosis; MPN-eo, Myeloproliferative neoplasm with eosinophilia; NGS, Next-generation sequencing; PMH, Past medical history; TKI, Tyrosine kinase inhibitors; T-LBL, T lymphoblastic lymphoma; WBC, Total white blood count.

PDGFRB rearrangement studies should be selectively performed in cases with PB and/or BM eosinophilia, particularly if morphological findings are suggestive of

a myeloid neoplasm that otherwise lack disease-defining molecular genetic alterations, such as inv(16). In addition, the presence of morphological and/or

Table 2. Myeloid/lymphoid neoplasms with *JAK2* and *FLT3* rearrangement and *ETV6::ABL* fusion: literature reviews, single case reports (not covered by previous reviews), single- and multicentre studies and bone marrow workshop reports

Author; reference	No. patients	Gender (M:F ratio) age/age range	Morphological presentation	Karyotype	Fusion partner; other molecular data
JAK2					
Poitras <i>et al.</i> , 2008 ⁴³	1	M, 39	B-ALL	t(5;9)(q14;p24.1)	<i>SSBP2::JAK2</i>
Tirado <i>et al.</i> , 2010 ⁴⁴ ; literature review (1997–2009)	1	M, 14	B-ALL	46,XY,t(9;22)(p24;q11.2)	?:: <i>JAK2</i>
Bain & Ahmad, 2014 ⁴⁸ ; literature review 1990–2013	33	M:F ratio 27:5; 12–75 years	MPN (17×), MDS-MPN (7×), AML (6×), T-ALL (1×), B-ALL (1×)	t(8;9)(p22;p24)	<i>PCM::JAK2</i>
	8	M:F 5:2; < 1–80 years	B-ALL (3×), T-ALL (2×) MDS (2×), aCML (1×)	t(9;12)(p24;p13)	<i>ETV6::JAK2</i>
	11	M:F 8:3; 2–84 years	aCML (4×), B-ALL (3×) MDS/MPN 1×, MPN 2×, AML 1×	t(9;22)(p24;q11.2)	<i>BCR::JAK2</i>
Baer <i>et al.</i> , 2018 ¹⁷	7	M:F, 6:1; 49–78 years	AML (2×) MPN (4×) NA (1×)	NA	<i>PCM1::JAK2</i> ; <i>TET2</i> mutation (1 of 7 tested patients)
Tang <i>et al.</i> , 2019 ⁴⁹ ; multicentre study	10	M:F 7:3; 37–86 years	MPN (5×), MPN BP (1×), MDS (1×), CMML (1×), B-ALL (2×)	t(8;9)(p22p24)	<i>PCM::JAK</i> (10×), other (3×); other mutation in 3/7 tested patients (NGS)
	3	NA	CEL (1×), B-ALL (2×)	Der(9)t(9;22)(p24.1;q11.2) t(5;9)(q14;p24.1) t(5;9)(q11.2;p24.1)	<i>BCR::JAK2</i> (1×), <i>JAK</i> variants (2×)
Schwaab <i>et al.</i> , 2020 ⁵⁰ ; multicentre study (registry-based)	9	M:F 8:1; 29–76 years	MDS/MPN (5×), CML (2×), AML (1×), B-ALL (1×)	t(8;9)(p22;p24) (6×); t(8;9;9)(p22;p24;p13); t(9;18)(p24;q12), t(14;18)(q21;q23); +6+8,t(8;9)(p22;p24),+22	<i>PCM1::JAK2</i> (8×) <i>BCR::JAK2</i> (1×)
Luedke <i>et al.</i> , 2020 ⁴⁵	1	M, 32	MPN; myeloid sarcoma	NA	<i>PCM::JAK2</i>
Snider <i>et al.</i> , 2020 ⁴⁶	1	M, 59	MPN, progression to MPAL (B/myeloid)	46,XY,t(3;21)(q21;22)	<i>BCR::JAK2</i>

Table 2. (Continued)

Author; reference	No. patients	Gender (M:F ratio) age/age range	Morphological presentation	Karyotype	Fusion partner; other molecular data
Pozdnyakova <i>et al.</i> , 2021 ⁵⁹ ; EAFP-SH workshop 2019	13	M:F 10:1; 1–86 years	CEL (7×), MPN (2×), B-ALL (1×), T-ALL (1×), AML (1×), MDS (1×) with T-LBL/ALL during follow-up	t(8;9)(p22;p24) (9×); other (3×); NA (1×)	PCM1::JAK2 (9×), BCR::JAK2 (1×), ETV6::JAK2 (1×); ?::JAK2 (2×); NGS: no mutations in 5 tested patients (37–54 gene panel)
Chen JA <i>et al.</i> , 2021 ⁴⁷	1	M, 41	CML; lymphoblastic transformation	46,XY, t(9;22)(p24;q11.2)	BCR::JAK2
FLT3 : multicentre study and case report with literature review					
Tang <i>et al.</i> , 2021 ⁵⁴ ; multicentre study (2005–2020) & literature review (2006–2020)	12	M:F 7:5; 2–80 years	MPN (1×), extramedullary M/LN with normal BM (2×), CMML (2×), CEL (3×), T-ALL (2×), MDS-EB (2×)	t(12;13)(ETV6::FLT3 (6×) ins (13;22)(BCR::FLT3 (1×) unconfirmed partner gene (5×)	ETV6::FLT3 (6×), BCR::FLT3 1×, unconfirmed partner gene (5×); NGS: mutations in 4/8 tested patients
	16	M:F 10:6; 3.5–71 years	CEL (10×), CMML (1×), aCML (2), SM (1×), JMML (1×); T-LBL (1×)	t(13q,12;q); t(12;13)(p13;q12) (6×) t(13;14)(q12;q32) (2×); other (5×) NA in three with ZMYM2 fusion	ETV::FLT3 (6×), ZMYM2 (3×), TRIP11 (2×), other (8×); no mutation in 3 tested patients
Venable <i>et al.</i> , 2023 ⁵⁵ ; case report (BMWS 1114); literature review (updated, <i>n</i> = 34)	1	M, 33	MPN with aberrant mast cell infiltrates	t(13;14)(q12;q32)	TRIP11::FLT3 FISH negative for PDGFR α , PDGFR β , FGFR1, JAK rearrangements; NGS: normal
ETV6-ABL1 : single and multicentre studies with literature review					
Yao <i>et al.</i> , 2021 ⁶⁰ ; case report & single-centre study (2014–2019)	1 (BMWS 1387)	F, 55	MPN-eo (mimicking ET); AML progression (5 years)	46,XX	ETV::ABL1
	5	M:F 4:1; 23–88 years	CML (3×), aCML (1×), MPN (1×); all with eosinophilia	46, XY, t(9;12)(q34;p13) (<i>n</i> = 2); 46,XY,-7 (<i>n</i> = 1); 53,XX,+X, 8+10+11+14+18+19 (<i>n</i> = 1); 46,XY (<i>n</i> = 1)	ETV::ABL1

Table 2. (Continued)

Author; reference	No. patients	Gender (M:F ratio) age/age range	Morphological presentation	Karyotype	Fusion partner; other molecular data
Schwaab <i>et al.</i> , 2020 ⁵⁰ ; multicentre study (registry-based)	9	M:F 7:2; 20–68 years	aCML (3×), CMML (1×), MPN (3×); secondary AML (1×), <i>de-novo</i> AML (1×); MPN with concomitant T-LBL (LN); all with eosinophilia	46,XX, t(9;12)(q34;p13) (<i>n</i> = 3); other with various aberrations (<i>n</i> = 5); normal karyotype (<i>n</i> = 1)	<i>ETV6::ABL1</i> ; all treated with TKI
Cessna <i>et al.</i> , 2019 ⁶⁴	1	M, 55	CMML-eo	46,XY, add(9)(q34)	<i>ETV6::ABL1</i>
Xie <i>et al.</i> , 2018 ⁶¹ ; case report & literature review (2001–2017)	1	M, 47	CML-eo	46,XY [20], cryptic ins (12;9)(p13;q34)	<i>ETV6::ABL1</i>
Zaliova <i>et al.</i> , 2016 ⁶⁵ ; literature review (1995–2015)	9	M:F 6:3	B-ALL (<i>n</i> = 5); T-ALL (1×); B-LBL (1×), MPN (1×), MPN with B-lymphoid blast crisis (1×)	Normal karyotype (4×); NA (2×); 46,XY, t(2;9), t(2;8), ins (12;9); 46, XY, t(5;12), 45, XY, t(9;12)	<i>ETV6::ABL1</i>
Yamamoto <i>et al.</i> , 2014 ⁶² ; literature review (2002–2011)	1	M, 31	MPN; T-LBL (LN)	46, XY, t(7;14)(p13;q11.2), der(9), t(9;12)(q34;p13), del(12)(p13)	<i>ETV6::ABL1</i>
Gancheva <i>et al.</i> , 2013 ⁶³ ; case report with literature review (1995–2013)	1	F, 46	CML-eo	46,XX, t(9;12)(q34;p13)	<i>ETV6::ABL1</i>

aCML, Atypical chronic myeloid leukaemia; ALL, Acute lymphoblastic leukaemia; AML, Acute myeloid leukaemia; BM, Bone marrow; CEL, Chronic eosinophilic leukaemia; CML, Chronic myeloid leukaemia; CMML, Chronic myelomonocytic leukaemia; Eo, Eosinophilia; ET, Essential thrombocytemia; MDS, Myelodysplastic syndrome; MDS/MPN-U, Myelodysplastic syndromes/myeloproliferative neoplasm–unclassified; MDS-EB, Myelodysplastic syndrome with excess blasts; MPN, Myeloproliferative neoplasm; NA, Not available; T-LBL, T lymphoblastic lymphoma; WBC, White blood count.

Table 3. Paediatric cases of M/LN-eo with TK gene rearrangements (literature review)

Author; reference	Clinical presentation	Diagnosis	Age/ gender	Karyotype; TK-gene fusion	Treatment	Follow-up
<i>PDGFRB</i>						
Darbyshire <i>et al.</i> , 1987 ⁷¹	Leucocytosis, eosinophilia; thrombocytopenia; hepatosplenomegaly;	MPN (CEL-like)	7 months/ M	46,XY, t(1;5)(q23;33) <i>PDGFRB</i>	Chemotherapy	Partial response (14 months)
	leucocytosis, eosinophilia, anaemia; thrombocytopenia; elevated VitB12; hepatosplenomegaly	MPN (CEL-like)	5 months/F	46,XX, t(1;5)(q23;33)	Chemotherapy	Died of infection, 9 months after dx
Wilkinson <i>et al.</i> , 2003 ⁷²	Anaemia, leucocytosis, eosinophilia, thrombocytopenia hepatosplenomegaly	MDS/MPN-eo	11 months/ F	t(1;5)(q23;33); <i>PDGFRB</i> :: <i>PDE4DIP</i> (RT-PCR)	Chemotherapy (refractory); CR after imatinib tx	5 months
Li <i>et al.</i> , 2011 ⁷⁴	Anaemia, leucocytosis, eosinophilia, skin ulcers, hepatosplenomegaly	MPN (CEL-like)	8 years/M	t(1;5)(q21;33); <i>TPM3</i> :: <i>PDGFRB</i> (RT-PCR)	Hydroxyurea, interferon; imatinib	> 7 years; CCyR (imatinib-treated)
Abraham <i>et al.</i> , 2012 ⁹	Nodular skin lesions; leucocytosis, eosinophilia; anaemia; hepatosplenomegaly	Skin and BM: myeloid proliferation with eosinophilia	Newborn/ M	46,XY, t(1;5)(q21;33); <i>TPM3</i> :: <i>PDGFRB</i>	Imatinib (340 mg/ m ² /day)	CR 1 month; FISH at 9 months negative for 5q33; OS > 2 years
	Respiratory symptoms; mediastinal lymphadenopathy; hepatosplenomegaly; leucocytosis, eosinophilia	Liver biopsy: portal inflammation, eosinophilia; BM with eosinophilia	7 months/ M	<i>PDGFRB</i>	Imatinib (340 mg/ m ² /day)	CR after 2 months; OS > 4 years (on imatinib tx)
Berking <i>et al.</i> , 2021 ⁷	Skin rash; leucocytosis, eosinophilia; splenomegaly	Skin biopsy: eosinophilic infiltrate; hypercellular BM with eosinophilia	6 months/F	46,XX; FISH: <i>PDGFRB</i> (5q32); <i>TNIP1</i> :: <i>PDGFRB</i> (RNA-seq)	Imatinib; normalisation of PB values within 2 weeks	CCyR > 4 weeks
Wang <i>et al.</i> , 2021 ⁸	Leucocytosis; eosinophilia; anaemia, hepatosplenomegaly;	M/LN with <i>PDGFRB</i> (MPN-eo)	1 year/F	<i>PDGFRB</i> (FISH); normal karyotype (46,XX)	Imatinib (200 mg/ m ²)	CR after 1 month; OS > 1 year
	leucocytosis; anaemia; thrombocytopenia; hepatosplenomegaly; skin rashes	M/LN with <i>PDGFRB</i> (MPN-eo)	2 years/F	<i>PDGFRB</i> (FISH); 46,XX, t(1;5) (q21;q33)	Imatinib (200 mg/ m ²)	CR after 1 month; OS > 2 years

Table 3. (Continued)

Author; reference	Clinical presentation	Diagnosis	Age/ gender	Karyotype; TK-gene fusion	Treatment	Follow-up
FGFR1						
Macdonald <i>et al.</i> , 1995 ⁷⁵ (<i>n</i> = 13) & Macdonald <i>et al.</i> , 2002 ²⁷ (<i>n</i> = 27); initially 2 paediatric cases	Original ref.: Lewis JP <i>et al.</i> , Am J Pediatr Hematol Oncol 1983; 5: 265–269	MPN-eo	3 years/F	46,XX; t(8;9)(p11;q12)	NA	NA
	Original ref.: Vannier JP <i>et al.</i> , Leukaemia Res 1984; 8: 647–657	MPN-eo with concomitant T-cell neoplasm (LN)	13/F	46,XX; t(6;8)(q27;p12)	NA	NA
Nakayama <i>et al.</i> , 1996 ⁷³	NA	NA	Child	8p abnormality	NA	NA
van den Berg <i>et al.</i> , 1996 ⁷⁸	NA	NA	Child	t(8;9)(p11;q34)	NA	NA
Wong <i>et al.</i> , 2007 ⁷⁶	Hepatosplenomegaly; lymphadenopathy; leucocytosis; eosinophilia; thrombocytopenia	MPN-eo; T-LBL	14/M	46,XY, t(8;13)(p11;q13) (both BM & LN) ZNF198::FGFR1 (RT-PCR)	Chemotherapy; partial response but molecular MRD	12 weeks CCyR; planned for HSCT
Zhang <i>et al.</i> , 2009 ⁴	Cervical lymphadenopathy; anaemia; normal total WBC, eosinophilia	T-LBL (cervical LN); BM hypercellular, eosinophilia; MF 1–2; FCM normal	5 months/F	47,XX, +8, t(8;13)(p12;q12); ZNF198::FGFR1 Cytogenetic abnormality present in BM & LN	Chemotherapy (CR); RT-PCR showed molecular MRD in the BM (8 months)	CR 18 months
Berking <i>et al.</i> , 2023 ⁷	Hepatosplenomegaly; lymphadenopathy; respiratory failure, cardiac involvement; leucocytosis, eosinophilia	MPN-eo; AML progression (8 weeks)	13 years/F	46,XX; FGFR1 (FISH); PCM1::FGFR1 fusion (RNA seq)	Prednisone, chemotherapy; ponatinib (TKI)	OS < 1 year
FLT3						
Spitzer <i>et al.</i> , 2021 ⁵	Hepatosplenomegaly, lymphadenopathy, skin rash; massive leucocytosis, eosinophilia	Initial dx JMML (blasts 14%); FCM immature T-cells, abnormal myeloid blasts	8 months/ M	46,XY, t(12;13)(p13;q12); ETV6::FLT3 fusion (RT-PCR)	Initial hydroxyurea; intensive chemotherapy; sorafenib (FLT3 inhibitor)	After 3 cycles persistent molecular MRD; CCy after 2 months; HSCT; post-tx with TKI

Table 3. (Continued)

Author; reference	Clinical presentation	Diagnosis	Age/ gender	Karyotype; TK-gene fusion	Treatment	Follow-up
Munthe-Kaas <i>et al.</i> , 2021 ⁶	Cervical & mediastinal lymphadenopathy; eosinophilia	T-LBL; BM involvement of T- LBL (3% by FCM)	3.5 years/ M	FISH normal; copy number analysis showed deletions on chrom 13q12.11 & 13q12.2- q12.3; ZMYM2::FLT3 fusion	Chemotherapy; imatinib (no response), sorafenib (dramatic response)	CR for 17 months; molecular MRD (PCR)

BM, Bone marrow; CCy, Clinical and cytogenetic remission; CEL, Chronic eosinophilic leukaemia; CR, Clinical remission, FCM, Flow cytometry; JMML, Juvenile myelomonocytic leukaemia; LN, Lymph node; TKI, Tyrosine kinase inhibitor; MPN-eo, Myeloproliferative neoplasm with eosinophilia; MRD, Measurable residual disease; T-LBL, T lymphoblastic lymphoma.

immunophenotypical abnormal mast cells in association with eosinophilia without *KIT* mutations, should trigger *PDGFRB* FISH studies. More than 40 fusion partners of *PDGFRB* have been reported, with t(5;12)(q33;p13)/*ETV6::PDGFRB* being the most common.^{18,20–24} *PDGFRB* gene rearrangements with alternate partners, such as *EBF1*, *SSBP2*, *TNIP1*, *ZEB2* and *ATF7IP*, often present as *de-novo* B-ALL, and it was suggested that these are best classified as Ph-like B-ALL.^{25,26} However, cases in which TK fusion genes involve the myeloid lineage in addition to lymphoblasts may be better classified as M/LN-eo-TK.² Often, patients have a chronic myeloid neoplasm that manifests prior to, concomitantly or in the post-treatment BM of ALL patients.

Three cases of *PDGFRB* rearranged M/LN-eo were submitted to the BM workshop, all three presenting as a chronic myeloid neoplasm with eosinophilia (cases 1223, 1420 and 1351). Importantly, two cases were cytogenetically cryptic without 5q31~33 karyotypic abnormalities, but FISH detected a split signal at the 5q32 locus and the fusion partner was identified by RNA sequencing in two cases. NGS studies (various gene panels) were performed in all three and reported normal in two cases, while one patient had a *NRAS* mutation. Two patients received imatinib with excellent response; treatment and follow-up data were lacking for one patient.

Case 1223 described a 25-year-old man presenting with splenomegaly, lymphadenopathy, skin rash, PB leucocytosis with eosinophilia, anaemia and thrombocytopenia. BM histology showed a CMML-like picture. Cytogenetic abnormality at the 5q32 break-point prompted FISH-analysis which confirmed a *PDGFRB* rearrangement, and FusionPlex RNA sequencing detected a novel *RUFY1* fusion. Complete haematological and molecular response was achieved upon imatinib treatment.

Case 1420 described a 65-year-old woman presenting with mild leucocytosis, monocytosis and anaemia. BM morphology was that of a myeloid neoplasm, initially diagnosed as CMML, associated with an increase (no aggregates) of mast cells. Cytogenetics were normal, but FISH showed an abnormal signal for *PDGFRB* and a *TNIP1::PDGFRB* fusion was confirmed by RNA sequencing. Treatment or follow-up data were not available for this case.

The third case (1351) was that of a 43-year-old man initially presenting with back pain. The PB showed eosinophilia, monocytosis and an elevated serum-tryptase. Clinical investigation revealed a thoracic mass, morphologically corresponding to a chronic myeloid neoplasm, and the BM showed features of CEL with atypical mast cell infiltrates. FISH

analysis demonstrated a split signal at the 5q32 locus (*CSF1R/PDGFRB*). Thus, the clinical and morphological findings combined were suggestive of M/LN-eo with *PDGFRB* rearrangement, but the fusion partner was not identified. A limited NGS panel was negative for myeloid and MPN-related mutations. The patient was treated with imatinib with good clinical and haematological response.

Of note, the t(5;12) translocation and other *PDGFRB* fusions can also be seen in *BCR::ABL1*-like B-ALL. Therefore, cases of B-ALL without any myeloproliferative component should be categorised as such. Similarly to *PDGFRA*, M/LN-eo with *PDGFRB* rearrangement tend to be cytogenetically silent with few other mutations.¹⁷

FGFR1 GENE REARRANGEMENT

The M/LN-eo with *FGFR1* rearrangement are clinically heterogeneous with a wide range of morphological presentations, and are cytogenetically defined by the presence of t(8;13)(p11.2;q12) or a variant translocation with formation of a variety of fusion genes, depending on the partner chromosome.^{20,27} The 14 *FGFR1* translocation partner genes thus far include *ZNF198/ZMYM2* at 13q12, *CEP110/CNTRL* at 9q33, *FGFR1OP1* at 6q27, *BCR* at 22q11, *FGFR1OP2* at 12p11, *TIF1* at 7q34, *MYO 18A* at 17q23, *CPSF6* at 12q15, *LRRFIP1* at 2q37, *RANBP2/NUP358* at 2q12, *TPR* at 1q25, *NUP98* at 11p15, *HERVK* at 19q13.3 and *CUX1* at 7q11. Rearrangements involving the *FGFR1* locus on 8p11 (formerly known as 8p11 myeloproliferative neoplasm) are typically not cryptic by karyotype and are mutationally complex with frequent *RUNX1* mutations.

In spite of being a rare entity,²⁸ a fairly large number of cases have been reported in the literature; 65 cases (1983–2009) with available cytogenetic data were reviewed by Jackson *et al.*,²⁹ followed by additional literature reviews with or without focus on distinct fusion genes,^{30–33} single²⁸ or multicentre studies,³⁴ registry-based studies³⁵ and a number of more recent single case reports, including identification of novel fusion genes.^{36–38}

According to the literature, the male-to female ratio is 1.5:1 and the usual age of onset is in the 30s.^{2,27} Constitutional symptoms are frequent (30–60%), as well as lymphadenopathy (40–60%); eosinophilia is present in 60–70% of cases.^{29,34} The most frequent presentation is that of a MPN with concomitant T-LBL (some of which relapse as B-ALL), followed by MPN with concomitant B-ALL, but other presentations such as MPN, MDS/MPN, AML, CEL, acute bi- or trilineage

leukaemia, *de-novo* T-ALL/LBL or B-ALL have also been described.^{29,30,34} Unlike M/LN-eo with *PDGFRA* and *PDGFRB* fusions, *FGFR1*-rearranged neoplasms are usually not responsive to imatinib.

Cytogenetically, the most frequent translocation is t(8;13)(p11;q12) or *ZNF198::FGFR1* (41–48%), followed by t(8;22)(p11.2;q11.2)/*BCR::FGFR1* (18–29%), t(8;9)(p12;q33)/*CEP110::FGFR1* (12–17%) and t(6;8)(q27;p11.2)/*FGFR1OP::FGFR1* (9–12%); other variant translocations or insertions are uncommon.^{29,30,34} Interestingly, the clinicopathological presentation varies depending on the translocation type, indicating that the clinical phenotype may be driven by the partner gene involved with *FGFR1*.^{1,39} For example, patients with t(8;22)(p11.2;q11.2)/*BCR::FGFR1* usually manifest with monocytosis and B-ALL, while approximately half the cases with t(8;9)(p12;q33)/*CEP110::FGFR1* display monocytosis and tonsillar hypertrophy.² Mutations in *FGFR1* rearranged cases are detected in 70–80% cases and typically involve *RUNX1* (80%),^{4,34} and have been associated with leukaemic presentation or progression.

In addition to the aforementioned published cases, five cases of MLN-eo and *FGFR1* rearrangement were submitted to the SH-EAHP workshop in 2019, reviewed and discussed in Pozdnyakova *et al.*,³⁹ and we received two cases with *FGFR1* rearrangement (1452, 1130) to the more recent EAHP 2022 BM workshop. Case 1452 describes a 59-year-old female presenting as *de-novo* B-ALL with focal eosinophilia in the biopsy but without peripheral eosinophilia. The patient had a history of indolent T lymphoblastic proliferation in an axillary lymph node 2 years prior to presentation. Cytogenetic and molecular studies revealed complex karyotypic abnormalities, including t(1;13)(q12;q34), a *RUNX1* mutation, homozygous loss of 9p (*CDKN2A*) by FISH and a *TPR::FGFR1* fusion. The patient had a poor response to induction chemotherapy and died within 3 months from diagnosis. Case 1130 describes a 60-year-old male patient with leucocytosis, eosinophilia and anaemia, morphologically presenting as a chronic myeloid (MDS/MPN-like) neoplasm. Cytogenetic analysis showed t(8;17)(p11.2;?), which prompted FISH analysis with detection of the *FGFR1* rearrangement. NGS failed to detect the fusion partner in this case. Clinical follow-up and treatment data were not available for this patient.

In summary, *FGFR1* rearranged M/LN-eo are rare, with a wide range of clinical and morphological presentations. The value of conventional cytogenetics and FISH for establishing the diagnosis cannot be overemphasised. Although there have been reports

on treatment response to investigational *FGFR1* inhibitors⁴⁰ prognosis is poor, which may be due, in part, to the lack of an approved targeted inhibitor and/or the frequent co-occurrence of *RUNX1* mutations in these cases. Previous studies have demonstrated that allogeneic haematopoietic cell transplantation (allo-HCT) can provide long-term disease control in a significant proportion of patients with *FGFR1*-rearranged MLN; however further registry-based studies will be essential for evaluating the results of post-transplant therapies.^{33,35}

JAK2 GENE REARRANGEMENT

M/LN-eo with t(8;9)(p22;p24)/PCM::JAK2 and its genetic variants (involving 9p24/JAK2), previously a provisional entity, is now a formal member of this category. These are rare neoplasms (estimated frequency < 0.1% of all myeloid neoplasms) with a wide spectrum of disease manifestations and variable molecular genetic features, usually with few co-mutations. The t(8;9)(p22;p24.1) was first reported in 1990 in patients with Philadelphia chromosome (Ph)-negative neutrophilic myelofibrosis,⁴¹ and the PCM1::JAK2 fusion resulting from this cytogenetic abnormality was described in 2005.⁴²

To date, approximately 100 cases of MLN associated with t(8;9)(p22;p24.1)/PCM1::JAK2 or variants have been reported as single case reports, multicentre or registry-based studies^{17,43–50} or BM workshop reports³⁹ (Table 2). Patients are predominantly male (M:F ratio 3:4) with a wide age range (12–82 years) and a median in the later 40s.^{48,49} The majority have features of a chronic MPN or MDS/MPN, commonly associated with eosinophilia, marrow fibrosis (MF) and an expansion of immature erythroid precursors. Other less common presentations include MDS, AML and *de novo* B-/T-ALL or B lymphoblastic crisis of a previous MPN. Importantly, cases presenting as '*de novo*' B-ALL often lack significant PB or BM eosinophilia.^{42,44,48,51} Extramedullary involvement is common and lymphadenopathy has also been reported.^{39,49} As JAK2 rearrangement in B-ALL is one of the genetic alterations in Ph-like B-ALL, it was suggested that cases with *SSBP2*, *PAX5*, *RFX3*, *USP25* and *ZNF274* fusion partners should be considered as Ph-like B-ALL, rather than M/LN.⁴⁹ However, B-ALL with a prior history of a chronic myeloid neoplasm, evidence of MPN in a post-treatment remission marrow and/or demonstration of the JAK2 rearrangement in myeloid/erythroid lineage (s) suggested the possibility of a B lymphoblastic transformation.⁴⁹ The PCM1::JAK2 fusion was demonstrated in the majority of previously reported cases

with t(8;9)(p22;p24),^{42,49,52,53} therefore it may be assumed that the presence of this translocation by conventional karyotyping *per se* is associated with JAK2 rearrangement. However, the JAK2 rearrangement should be confirmed by FISH, RT-PCR or RNA sequencing, as the t(9p24.1;v) involves only a small fragment of chromosome 9p.^{49,52}

Three cases with JAK2 rearrangement were submitted to our workshop, one with a t(8;9)(p22;p24)/PCM1::JAK2 (case 1354) and two cases with a t(9;22)(p24.1;11.2)/BCR::JAK2 (cases 1240, 1319). All three patients were male and two presented with splenomegaly, leucocytosis and anaemia; all three had features of a myeloid neoplasm (Figure 1).

Case 1354 was a 68-year-old patient with splenomegaly, anaemia and PB eosinophilia. BM histology was consistent with a myeloid neoplasm with an increase of immunophenotypically aberrant myeloid precursors by flow cytometry (FCM) and, for this type of rearrangement, frequently described, left-shifted, expanded erythropoiesis. FISH analysis demonstrated a JAK2 (9p24.1) rearrangement in 26% of cells and a PCM1::JAK2 fusion was identified by Archer Fusion-Plex Heme assay. Case 1240 describes a 55-year-old patient with leucocytosis and marked eosinophilia. BM morphology was that of a chronic MPN-eo. FISH and PCR studies were negative for *PDGFRA/B* and *FGFR1* rearrangement and tested mutations. Cytogenetic analysis demonstrated an abnormal karyotype involving del(12)(p?p?); a BCR::JAK2 fusion was detected by NGS. During follow-up (1.5 and 2.5 years after initial presentation), the patient had extramedullary (nodal) manifestation of a myeloid sarcoma and a T-LBL with confirmation of the BCR::JAK2 fusion in the surgical specimen. Case 1319 had a CML-like clinical presentation. BM examination showed marked MF with atypical megakaryocytes and presence of mast cell infiltrates. Cytogenetic/molecular work-up demonstrated a complex karyotype with JAK2 rearrangement (FISH) and a BCR::JAK2 fusion (NGS). The patient was treated with hydroxyurea and achieved complete haematological remission after autologous stem cell transplantation.

Mutation data are scarce in earlier reported cases of JAK2 rearranged M/LN-eo, largely due the unavailability of NGS. From the few reports available, approximately 40% (11 of 25) cases had mutations (including *ASXL1*, *TET2*, *RUNX1*, *TP53*, *BCORL*, *PTPN11* and *EP300*).^{17,39,49} Additional mutations were not reported in the three workshop cases.

The survival of patients with M/LN-eo and JAK2 rearrangement is highly variable; patients with MPN in chronic phase have a more indolent course, while

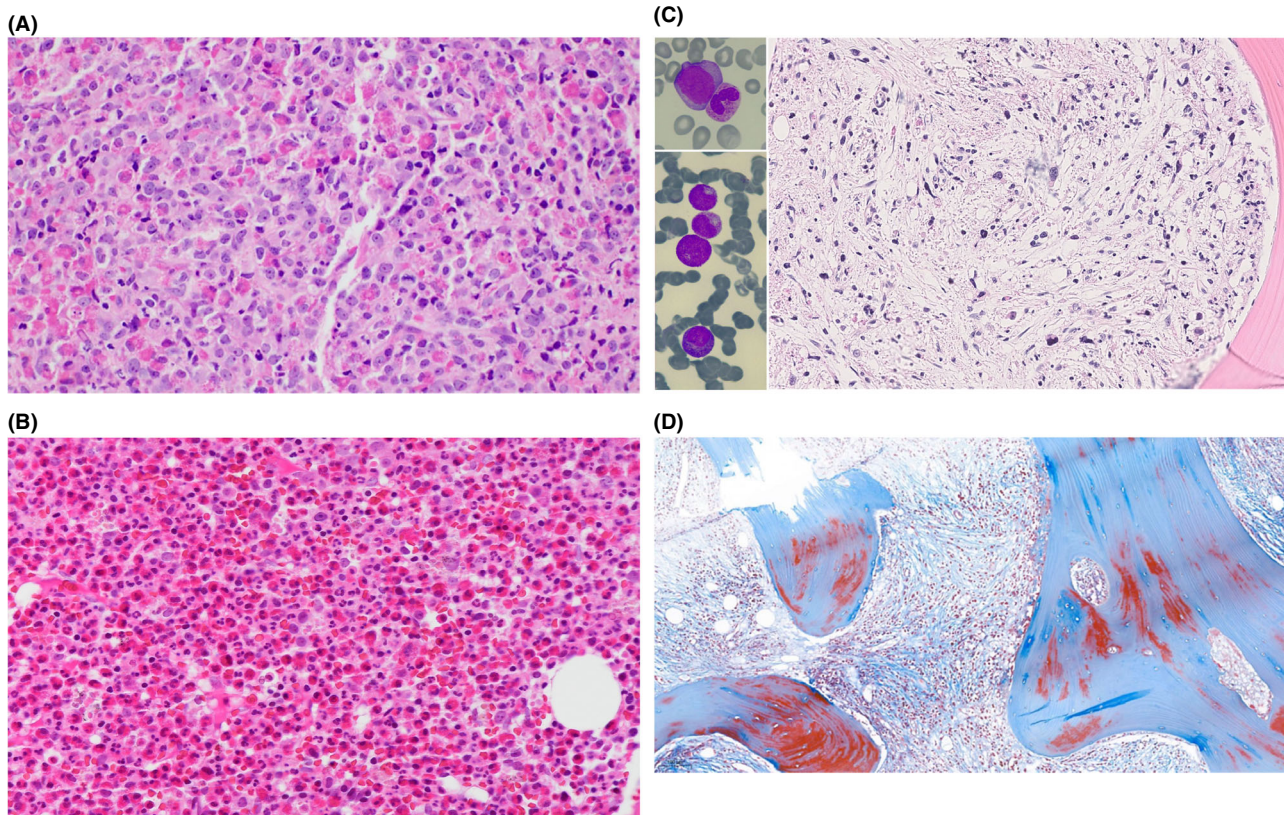


Figure 1. M/LN-eo with *JAK2* rearrangement. Spectrum of bone marrow (BM) morphology in patients with *JAK2*-rearranged MLN with high cellularity, significant eosinophilia and expansion of immature erythroid precursors (BMWS cases 1354 and 1240, A,B, H&E). Case 1319 presented with PB leucocytosis, absolute eosinophilia, dysplastic granulocytes and myeloid precursors (Giemsa stain); the corresponding BM biopsy showed significant myelofibrosis with atypical megakaryocytes and mast cells infiltrates (H&E stain, Masson trichrome stain, C,D).

patients presenting in either blast phase of MPN or as *de-novo* ALL behave more aggressively. However, long-term follow-up is not always available. Treatment options are much influenced by the underlying disease. Targeted therapy with *JAK2* inhibitors, such as ruxolitinib, may offer potential benefit,⁵³ and some patients may achieve CR after allogeneic stem cell transplant (case 1319).

FLT3 GENE REARRANGEMENT

Haematological malignancies with gene fusions involving *FLT3* have also recently been included among M/LN-eo-TK in the WHO-HAEM5 and ICC.^{10,11} These are particularly rare, and result from rearrangements involving chromosome 13q12.2. *FLT3*-rearranged cases often present as MPN-eo or as MDS/MPN, resembling CMML, atypical CML, JMML or systemic mastocytosis associated with haematological malignancy.² Extramedullary involvement is frequent, including T-LBL, MPAL, myeloid sarcoma and, rarely, B-ALL/LBL.

A total of 35 cases have been identified (Table 2), mainly single case reports and one multicentre study, including a literature review,⁵⁴ and a more recently published case report (also presented at the EAHP 2022 BM workshop) with an update on published cases.⁵⁵ The increased recognition of this entity probably stems from the recent inclusion in the WHO-HAEM5/ICC classifications, rigorous laboratory testing and the awareness of extramedullary disease manifestation.

Tang *et al.*⁵⁴ reported 12 patients with *FLT3* rearrangement as part of a multicentre study, based on the retrospective assessment of patients with haematopoietic neoplasms with chromosome 13q12 rearrangement, including a literature review. The study identified *BCR* as a novel partner gene of *FLT3*, in addition to known partner genes (*ETV6*, *ZMYM2*, *TRIP11*, *SPTBN1*, *GOLGB1*, *CCDC88C* and *MYO18A*).^{19,56–58} An additional 16 cases were identified in the literature, all more recently published (2011–2020) and mainly single case reports.⁵⁴ Interestingly, the majority presented as MPN-eo, while the

clinical presentation was more diverse in the multicentre study, in which any haematological malignancy with a 13q12 was retrospectively screened for *FLT3* rearrangement. Importantly, the 13q12 abnormality cannot be assumed to have a *FLT3* rearrangement *per se*, as other genes are located in that region.

Two cases of M/LN-eo with *FLT3* rearrangement were submitted to the EAHP 2022 BM workshop (1114, 1214). Case 1114 (recently published,⁵⁵ described a 33-year-old patient with chronic eosinophilia and an elevated serum tryptase. The BM was normocellular with eosinophilia and presence of atypical mast cells without aggregates. Cytogenetic analysis demonstrated a t(13;14)(q12;32) and a *FLT3::TRIP11* fusion by mate-pair sequencing. The natural disease course was favourable in contrast to two previously reported cases with *FLT3::TRIP11* fusion that both had aggressive disease with coexisting or progression to T-ALL.^{57,59} Case 1214 described a 58-year-old male presenting as *de-novo* B-ALL associated with mast cell infiltrates and PB eosinophilia (Figure 2). Cytogenetic and FISH studies were normal, but molecular analysis detected a *DNMT3A* and *RUNX1* mutation and a cytogenetically cryptic *FLT3::ZMYM2* fusion (RNA sequencing). A single case with *FLT3* rearrangement was received at the previous SH-EAHP 2019 workshop, presenting as nodal T-LBL and MPN-eo with minimal T-LBL engagement.³⁹

M/LN-eo with *FLT3* rearrangements appear to be sensitive to *FLT3* inhibitors irrespective of the partner genes.^{19,54,56} The importance of recognising these lies in the therapeutic potential, as illustrated by the recent case report on a 8-month-old infant presenting with features mimicking JMML.⁵

ETV6::ABL1

M/LN-eo with t(9;12)(q34.1;p13.2)/*ETV6::ABL1* occur in a range of haematological malignancies and have most commonly been reported as chronic myeloid neoplasms with clinical, laboratory and morphological features mimicking CML (or CMML) with frequent eosinophilia.^{60–64} Other frequent manifestations are T-ALL/LBL and B-ALL.⁶⁵ *ETV6::ABL1*-positive haematological malignancies are reminiscent of *BCR::ABL1*-positive neoplasms, with acute leukaemias (AL) dominating in children and young adults and MPN-like presentations in older adults.⁶⁶

A literature review identified approximately 60 cases of myeloid neoplasms with *ETV6::ABL1* fusions, including single case reports and multicentre studies (Table 2). Patients were predominantly male (3.5:1) and presented at a broad age range (0–88 years).

ALL was most commonly seen in children and adults aged < 45 years (16 of 19 reported cases), while MPN was exclusively reported in adults (median age 50 years). Morphological diagnoses included aCML/ MDS-MPN with neutrophilia, Ph-chromosome-negative MPN, MDS/MPN and, rarely, *de-novo* AML. Concomitant disease with a chronic myeloid neoplasm in the BM and T-LBL was also reported. The *ETV6::ABL1* fusion is a rare and complex rearrangement which makes routine diagnostics challenging. Karyotyping is often inconclusive and FISH can miss the fusion as the cryptic insertions are often too small to generate a visible split signal. Therefore, only targeted RT-PCR screening, a combination of both *ETV6* and *ABL1* FISH probes or RNA sequencing will reliably detect all cases. The clinical course of *ETV6::ABL1*-positive MLN-eo is highly variable and strongly associated with the disease state (chronic myeloid versus primary/secondary blast phase) and response to TKI treatment. Development of a quantitative PCR assay similar to *BCR::ABL1* fusion has been recommended for disease monitoring.

Two cases with *ETV6::ABL1* fusion were submitted to the workshop. Case 1387 (recently published in Yao et al.⁶⁰) described a patient presenting with clinical and morphological features mimicking essential thrombocytemia. Cytogenetics were normal and molecular studies were negative for MPN-related mutations and *PDGFRA/B* rearrangements. The patient progressed to a high-grade myeloid neoplasm with eosinophilia and significant myelofibrosis. FISH-analysis detected *ETV6* rearrangement, and a *ETV6::ABL1* fusion was identified by RNA sequencing in sequential samples. Case 1373 described a 40-year-old man presenting with cervical lymphadenopathy and splenomegaly. The BM showed features of a chronic MPN-eo, negative for MPN-related mutations and other somatic mutations, and the histology of the excised LN was consistent with T-LBL (Figure 3). Cytogenetic analysis revealed t(12;22)(p13;q12), suggesting a *ETV6*-myeloid neoplasm, confirmed by FISH analysis in both the BM and LN. Following chemotherapy, a control BM showed atypical mast cell infiltrates and a persisting minor cytogenetic abnormality. This rare case reflects the wide spectrum of potential disease manifestation.

M/LN WITH EOSINOPHILIA AND OTHER ALTERATIONS INVOLVING TK GENES

Other less common defined genetic alterations involving TK genes have also been discovered, such as *ETV6::FGFR2*,¹³ *ETV6::LYN*,^{12,67} *ETV6::NTRK3*,⁶⁸ *RANBP2::ALK*,⁶⁹ *BCR::RET* and *FGFR1OP::RET*,⁷⁰

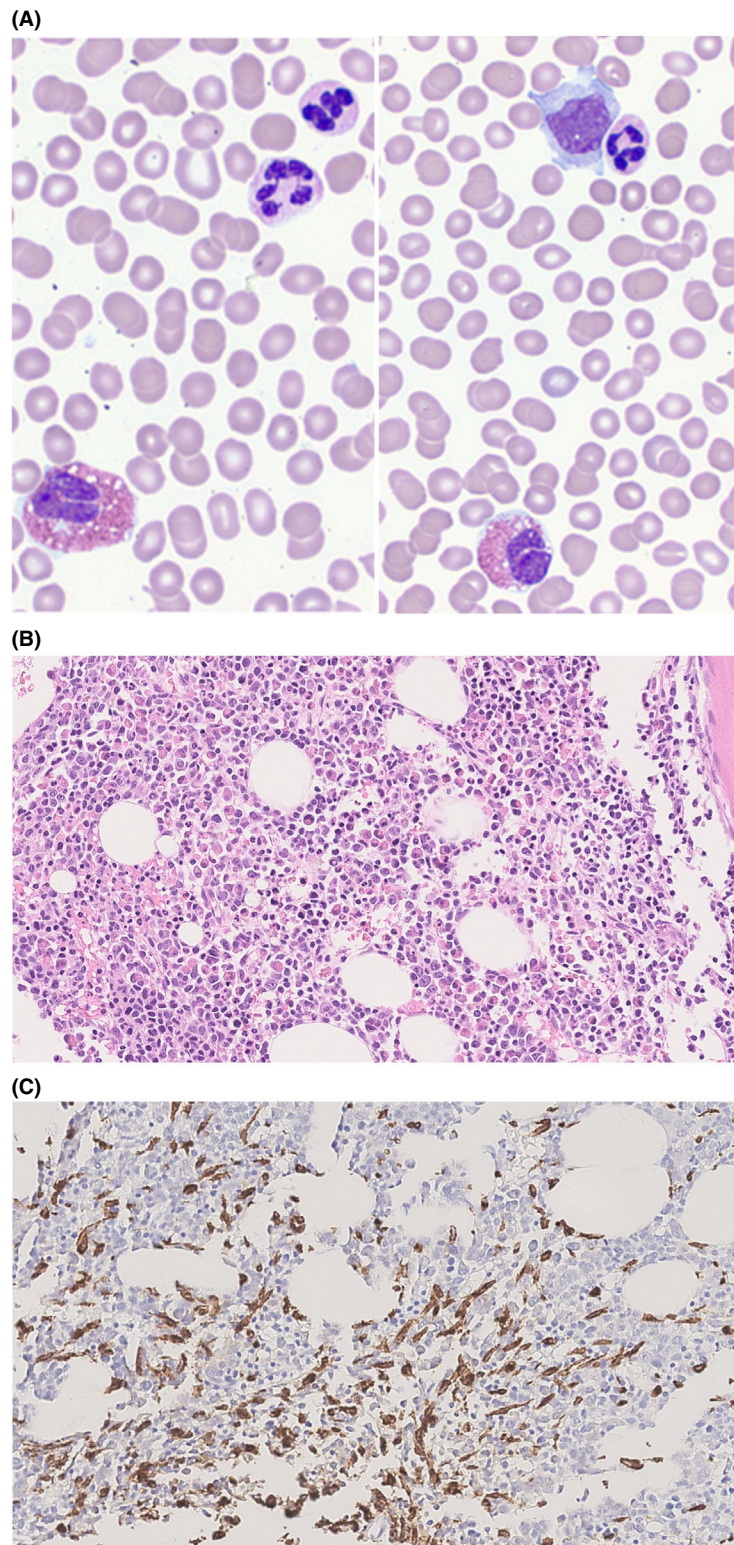


Figure 2. M/LN with *FLT3::ZMYM2* fusion, presenting as *de-novo* B-ALL with peripheral blood eosinophilia and presence of dysplastic neutrophils (A); the corresponding BM biopsy was hypercellular with blast increase, eosinophilia (B, H&E stain) and atypical, spindle-shaped mast cells (C, tryptase immunostain) (BMWS case 1214).

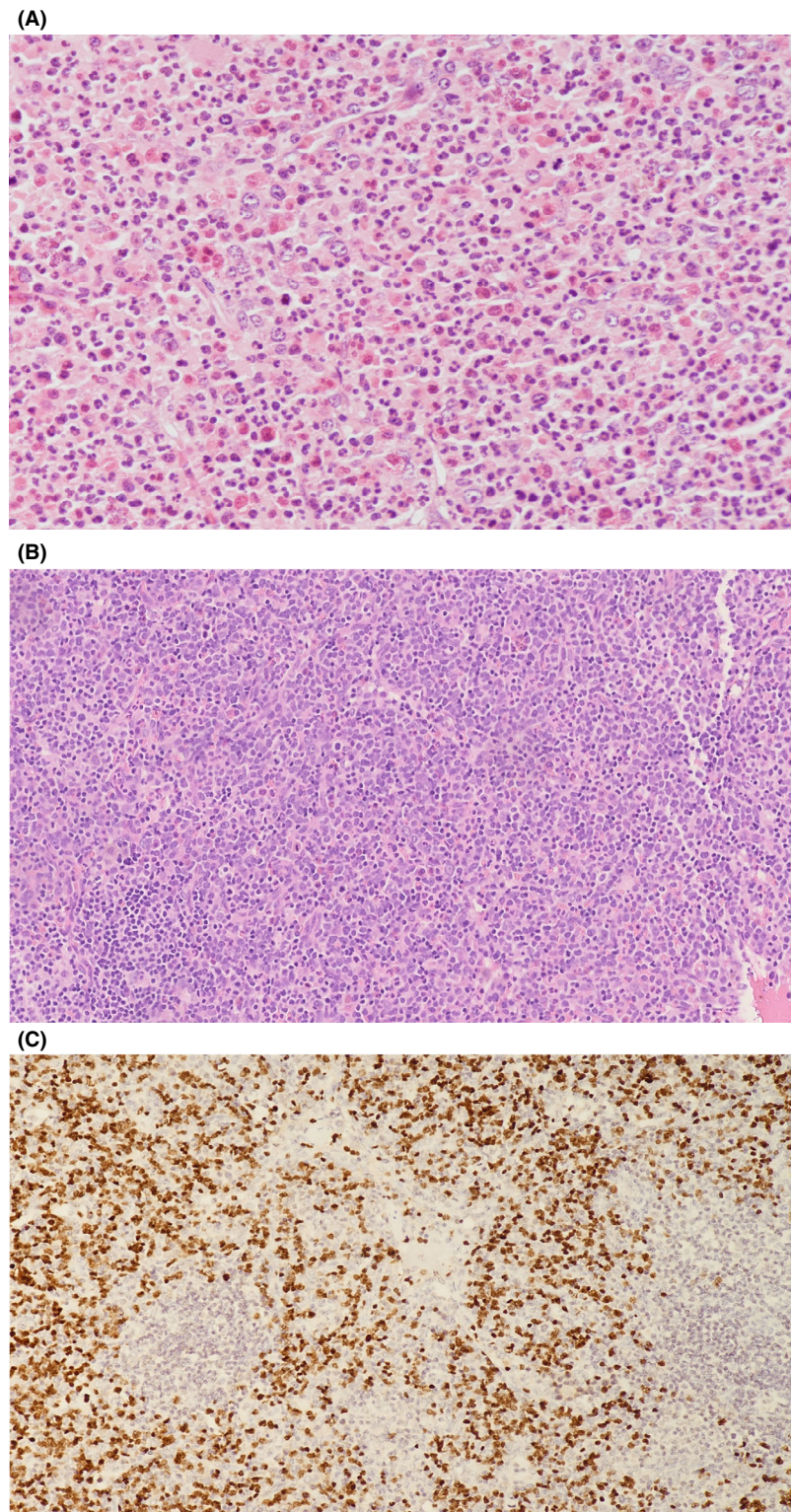


Figure 3. M/LN with *ETV6::MN1*, presenting as chronic MPN-eo with concomitant T-LBL in a cervical lymph node (BMWS case 1373). The bone marrow (BM) showed myeloid proliferation with preserved maturation and significant eosinophilia (A, H&E stain). The architecture of the cervical lymph node is effaced with sheets of immature T cells (TdT+, other IHC not shown) consistent with T lymphoblastic lymphoma. (B, H&E stain; C, IHC stain for TdT).

and these are listed as M/LN-eo with other tyrosine kinase gene fusions in the WHO-HAEM5.¹⁰

The workshop received one case with a cytogenetically cryptic *SEC31A::KIT* fusion presenting as an aggressive myeloid neoplasm (MDS/MPN-eo) with atypical mast cell infiltrates and as myeloid sarcoma in a peripheral LN and the skeleton (Figure 4, case 1388). The patient had a partial response to TKI treatment. The clinical and morphological presentation was reminiscent to other cases within the category of MLN-eo with TK gene fusions.

PAEDIATRIC CASES OF M/LN-EO WITH TK GENE REARRANGEMENT

Approximately 30 paediatric cases of M/LN-eo with various TK gene fusions have been identified in the literature, including several reports in infants (Table 3).^{4,5,7,9,71–73} The majority were *PDGFRB*-rearranged M/LN-eo with similar clinical

presentations as in adults, such as leucocytosis, hepatosplenomegaly and MPN-like BM morphology, mimicking CEL.^{71,72,74} Abraham *et al.* reported two patients with systemic manifestations, and initial investigations included skin and liver biopsies which showed eosinophilic inflammation. Cutaneous involvement at initial presentation has also been reported by others.^{7,8} All *PDGFRB*-rearranged M/LN-eo had an excellent response to imatinib treatment.

Other studies reported on *FGFR1*-rearranged M/LN-eo in children.^{4,75–78} Macdonald *et al.* (1995) reviewed 27 published cases with the '8p11 myeloproliferative syndrome' (*FGFR1* rearrangement); seven were aged ≤ 18 years at presentation. As in adults, concomitant manifestation of a chronic myeloid neoplasm and nodal T-LBL was reported, including demonstration of the cytogenetic abnormality in immunophenotypically diverse lineages.^{4,76} RT-PCR assays were used for measurable residual disease (MRD) assessment during follow-up of patients who

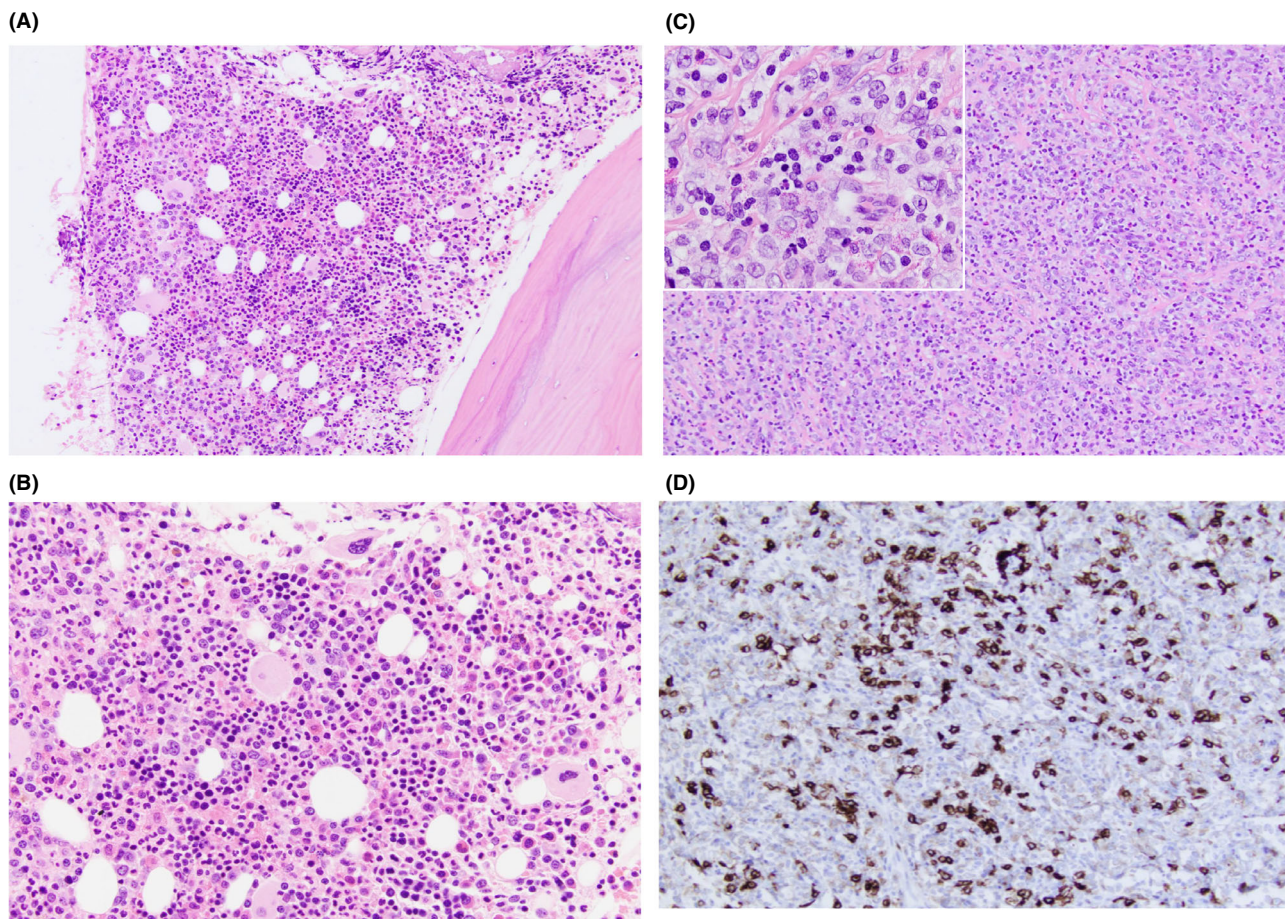


Figure 4. M/LN with *SEC31A::KIT* fusion, presenting as MDS/MPN (A,B, H&E stain) with mild eosinophilia and atypical mast cell infiltrates (not shown); concomitant myeloid sarcoma in a supraclavicular lymph node (C, H&E stain; in magnification: immature myelomonocytic forms, staining positive for CD117, D; BMWS case 1388).

were in clinical remission.⁴ However, the clinical course of *FGFR1*-rearranged M/LN-eo was often aggressive, with frequent relapses and/or lymphoblastic transformation.^{7,77}

Very recently, two paediatric cases with *FLT3* rearrangement were reported. Spitzer *et al.* described an *ETV::FLT3* fusion-driven M/LN-eo with T-lymphoid and myeloid differentiation in a 8-month-old male infant who presented with features mimicking JMML.⁵ Importantly, the high percentage of myeloid blasts/blast equivalents and the detection of an immature T-cell population by FCM, together with pronounced eosinophilia, pointed to an alternative diagnosis. Combined chemotherapy and *FLT3* inhibitor treatment followed by ASCT resulted in complete clinical and cytogenetic remission. The other case presented as *de-novo* T-LBL associated with PB eosinophilia.⁶ An extensive molecular work-up detected a *ZMYM2::FLT3* translocation that reclassified the disorder as M/LN-eo. Targeted treatment (sorafenib) resulted in rapid, lasting response.

These reports emphasise the importance of performing genetic analysis in the diagnostic work-up of unexplained hypereosinophilia with suspected malignancy, also in children. This should not be restricted to specific fusions; additional analyses such as array CGH and RNA-sequencing and/or whole

transcriptome sequencing should be considered. Sensitive molecular assays can also be applied for MRD monitoring and NGS can provide additional information on underlying driver mutations. Taken together, extensive clinical and laboratory investigation is recommended and often needed in order to identify gene fusions as soon as possible for targeted therapy. In addition to the aforementioned molecular assays, these investigations should include imaging and functional tests to evaluate possible organ damage, biopsy sampling from extramedullary disease manifestations, chromosome analysis and FISH analysis with break-apart probes targeting 4q12 (*PDGFRA*), 5q31~5q33 (*PDGFRB*), 8p11~8p12 (*FGFR1*) and 9p24 (*JAK2*).

Summary

The M/LN-eo represent a rare and challenging group of haematological neoplasms with variable clinical and morphological presentation and course of disease. Extensive laboratory work-up is needed and fusion NGS, when available, can be a highly effective tool in the identification of cases that are not suspected clinically and when performed as part of a routine evaluation of haematopoietic neoplasms (Figure 5). Importantly, eosinophilia is frequently

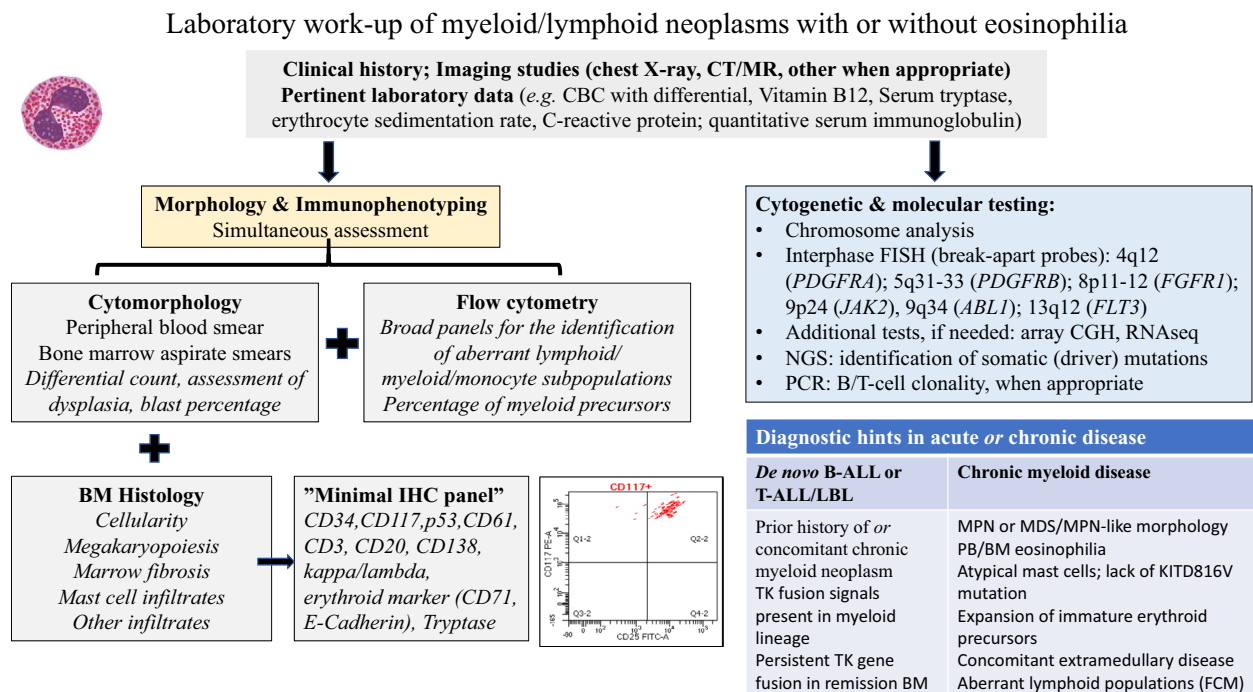


Figure 5. Overview of the laboratory work-up of myeloid/lymphoid neoplasms.

observed but not invariably present, and is not a prerequisite criterion for the diagnosis of this group of disorders; therefore, eosinophilia should not be the only driving force triggering the investigation for M/LN-eo. As discussed in this paper, cases may lack 'classic' presentation of a chronic myeloid neoplasm with eosinophilia (case 1214), present with disparate stages of disease (chronic versus acute or transformed; case 1452) or disparate lineages (cases 1240, 1214, 1373), with primary extramedullary (nodal/extranodal) presentation (case 1351), or may be detected first during follow-up and/or after treatment of the original diagnosis (case 1387). As a rule, in cases that present as *de-novo* B-ALL or as T-ALL/LBL, the TK fusion genes should involve the myeloid lineage in addition to lymphoblasts in order to be classified as M/LN-eo-TK.

Present and previous BM workshop cases and published case reports underscore the diagnostic value of BM biopsies and/or biopsies from other sites in patients with extramedullary disease, in addition to the cytomorphological examination of PB and BM aspirate smears, not only at initial diagnosis but also during follow-up for the detection of residual or concomitant disease (1373). Moreover, flow cytometric immunophenotyping in addition to immunohistochemistry can assist in the detection of aberrant (sub)populations as indicators for clonal disease (cases 1354, 1114) and multilineage involvement.³⁰

It is also known that an abnormal mast cell proliferation can be seen in M/LN-eo with any of the recurrent fusion genes. Approximately half the workshop cases (six of 13) had aberrant mast cell infiltrates at diagnosis (1420, 1351, 1214, 1388, 1114) or during follow-up (case 1373).

The definite diagnosis of M/LN-eo relies upon the identification of a characteristic activating kinase fusion. However, conventional cytogenetic analysis may be normal, and FISH analysis does not always detect the rearrangement. Therefore, in spite of being rare diseases and in spite of the relatively common existence of reactive causes of eosinophilia, broad cytogenetic and molecular testing is indicated in the routine diagnostic work-up of suspicious haematopoietic neoplasms in all patients, given the dramatic therapeutic responses to targeted kinase inhibitors and the added mutational and prognostic information.

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Conflicts of interest

The authors have no conflicts of interest.

Ethics approval

The authors confirm that this manuscript fulfills ethical standards.

Data availability statement

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

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