haematologica
Journal of the Ferrata Storti Foundation

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Received: June 24, 2025.
Accepted: November 11, 2025.

Citation: Giorgio Alberto Croci, Daniele Cattaneo, Silvia Tabano, Ilaria Catusi, Manuela Zappa, Carlo Alberto Maronese, Niccolò Bolli, Angelo Valerio Marzano and Alessandra Iurlo. Granuloma annulare-like pseudohistiocytosis: a specific manifestation of ETV6::SYK-rearranged myeloid neoplasm with eosinophilia.
Haematologica. 2025 Nov 20. doi: 10.3324/haematol.2025.288536 [Epub ahead of print]

Granuloma annulare-like pseudohistiocytosis: a specific manifestation of *ETV6::SYK*-rearranged myeloid neoplasm with eosinophilia.

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Conflicts of interest: the Authors declare no conflict of interest.

Authors contributions: GAC, CAM, DC and AI performed the diagnosis; GAC, DC and CAM performed the critical review of the literature; AI, AVM, DC and CAM followed up and treated the patient; IC, MZ, ST and NB performed the molecular analysis; everyone else reviewed the manuscript.

Data sharing: the data that supports the findings of this study are available from the corresponding Author, upon request.

Skin manifestations of hypereosinophilic syndromes (HES) are mostly non-specific, including eczema- or urticaria-like instances. Alongside the improvement in their molecular understanding, possible clinical associations of specific entities are also emerging[1]. In 2023, a novel instance of myeloid neoplasm with eosinophilia (MLN-E) with other tyrosine kinase (TK) gene fusions, carrying t(9;12)(q22;p13) *ETV6::SYK*, was identified in a patient with a hypereosinophilic clinical picture, associated with a cutaneous manifestation interpreted as eruptive xanthogranuloma[2]. Starting from the diagnosis of a new case, we aim at discussing the clinicopathologic picture and the published literature on MLN-E, characterized by *ETV6::SYK* rearrangement.

A novel case, as evaluated during the diagnostic routine, is discussed. The study was conducted in accordance with the Declaration of Helsinki; patient consent was obtained. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded 3µm-slides via automated system (Ventana-Roche platform). Chromosome analysis was conducted on bone marrow (BM) cultures by QFQ-banding technique; at least 20 metaphases from both cultures were analyzed at a 300-band resolution level. Following karyotype, FISH analysis for *ETV6* locus and RT-PCR was performed[3] on peripheral blood (PB) and BM, to determine the presence of *ETV6::SYK* gene fusion. Targeted next generation sequencing (NGS) was conducted in PB via NGS Oncomine myeloid panel, while variant-specific Sanger sequencing was performed to assess *ASXL1* mutation in the skin. FISH analysis on cutaneous biopsy was conducted using the locus-specific probes XL *ETV6* Break Apart (MetaSystems Group, Inc., Belmont, MA) and *SYK* Break Apart (Empire genomics), following the manufacturer's instructions.

The case involves a 67-year-old woman who developed monocular diplopia and paresis, with slit-lamp examination suggestive of choroidal granulomas. The patient subsequently developed multiple, firm, partly confluent, erythematous to yellowish cutaneous plaques, some with a slightly raised border, involving the scalp and progressing to the face, back and limbs (Figure 1). The clinical picture was deemed suspicious for disseminated sarcoidosis / granuloma annulare (GA). Due to worsening of ocular signs and progression of the skin lesions, the patient visited our Institution, where a hematological workup revealed mild leukocytosis (WBC 16.62 $x10^9$/L) with severe eosinophilia (AEC 6.01 $x10^9$/L) and 1% PB blasts; hemoglobin level and platelets counts were normal. PB flow immunophenotyping showed no evidence of aberrant T-cells, specifically excluding the lymphocytic variant of HES. A concomitant PET scan showed hypercaptation in cutaneous-subcutaneous lesions, mammary glands, inguinal lymph nodes, paravertebral spaces, sinus cavities, hepatic venous branches, superior mesenteric artery, and endometrial cavity (standardized uptake value [SUV] range 5.21-19.93, with the highest values in the scalp). Skin biopsy (Figure 1c-e) revealed an interstitial accumulation of histiocytoid histiocytes with a nondescript phenotype (CD163+, MPO-, S100-, CD1a-, langerin-, ALK1-), reminiscent of the interstitial variant of GA, while BM aspirate and biopsy supported clonal eosinophilia (Figure 2a,b), as carrying dysplastic-type megakaryocytes, both with an unremarkable lymphoid infiltrate. Endometrial biopsy documented an accumulation of eosinophilic

granulocytes (Figure 2e). BM karyotype revealed t(9;12)(q22;p13), further confirmed as *ETV6::SYK* by RT-PCR in both BM and PB samples (Figure 2c,d), where *ASXL1* c.2404G>T, p.(Glu802Ter) mutation was also found by targeted NGS (VAF 15.71%). The latter was absent in the skin. RT-PCR and FISH analysis demonstrated the lack of *ETV6* and/or *SYK* rearrangement on histiocytes in the skin, the latter highlighting scattered, small-sized clonal cells, likely corresponding to granulocytes (Figure 1f).

A final diagnosis of GA-like pseudohistiocytosis / histiocytic proliferation was made, as manifestation of MLN-E and other TK gene fusions (2024 WHO Classification). Adjuvants such as ultrapotent topical corticosteroids and hydroxychloroquine were tried but proved ineffective on the cutaneous picture. The patient was then treated off-label with imatinib 400 mg QD[4] with an initial taper of prednisone, leading to partial metabolic remission, as documented by PET scan, along with gradual improvement of ocular and flattening of cutaneous lesions. Because the combination of imatinib and high-dose prednisone failed to effectively reduce AEC, along with the development of steroid-related adverse events, SYK inhibition with entospletinib was considered, but it was not approved by the manufacturer, as still an investigational drug. Due to severe, persistent eosinophilia, after one year on imatinib, the patient began off-label treatment with dasatinib 100 mg QD, achieving marked improvement in AEC within a few days, until stable normalization. Unfortunately, she died three months later from a fungal infection, likely related to the immunosuppressive state induced by prolonged treatment with high-dose steroids.

PubMed database was queried for “SYK ETV6 myeloid” and “SYK ETV6 rearrangement” and related papers, and a total of 5 cases was retrieved (Table)[2,5-8]. All patients (n=6, including ours) presented with absolute eosinophilia (range, 1.2-9.5 x10^9/L), with variable leukocytosis and anemia, and skin lesions involving the head and, to a lesser extent, the trunk and limbs. Ocular signs were present in 2 instances. The disease was defined by *ETV6* locus rearrangement in all cases, 5 of which were proved to carry the specific *ETV6::SYK* fusion. Additionally, our case harbored *ASXL1* mutation in PB, and 1 case[3] had a minor clone with a complex karyotype. Follow-up data are detailed in the table.

MLN-E are driven by a variety of TK gene rearrangements, and *ETV6* itself is a well-known actor of hematological neoplasms, including MLN-E with *ETV6::ABL1*-rearrangement, myelodysplastic syndromes/neoplasms and acute myeloid and lymphoblastic leukemia. However, the collected experience shows that *ETV6::SYK*-rearranged neoplasms are stereotyped, comprising progressive eosinophilia and an unclassifiable histiocytic proliferation, recapitulating the clinical features of disseminated sarcoidosis or, alternatively, GA.

Patients experience a protracted clinical course and a multisystem disease mimicking an immune-mediated disorder, with ocular and cutaneous involvement. Notably, our patient had been followed extensively in various Immunology departments with clinical diagnoses of “granulomatosis”, sarcoidosis, Wells syndrome, or IgG4 related disease. First, it should be noted that the SUV range of fluorodeoxyglucose-avid lesions in

our case exceeded the values commonly detected in inflammatory disorders. Also, histology of skin lesions, showing a dense, patternless accumulation of histiocytoid histiocytes with a nondescript phenotype and intermixed scattered granulocytes, fairly exceeds the common picture of GA and sarcoidosis. To some extent, the morphological pattern resembles generalized palisaded neutrophilic and granulomatous dermatitis, as clonal manifestation of chronic myelomonocytic leukemia with *SRSF2 P95* hotspot mutation[9]. A clonal skin manifestation of a myeloid neoplasm could be considered, with the atypical morphology of myelomonocytic cells suggesting leukemia cutis or the newly developed concept of myelodysplasia cutis[10]. Finally, given the clinical picture, a cutaneous manifestation of multisystem histiocytosis could be considered. This interpretation was also provided by Risch Z et al.[8], who purportedly found *ETV6::SYK* rearrangement in the skin lesion. However, we were unable to confirm the same observation in our patient: skin biopsy proved negative for clonal markers, both by Sanger sequencing for *ASXL1* and by RT-PCR and FISH analysis for *ETV6* and/or *SYK* rearrangements. On this basis, our data support an "inflammatory", albeit aberrant, manifestation of a myeloid neoplasm, similar to the histiocytoid variant of Sweet syndrome[11]. Notably, a similar pattern of cutaneous disease is currently regarded as the GA-like variant of Wells' syndrome[12], in patients lacking a clinical picture of clonal eosinophilia, thus supporting the hypothesis of an inflammatory lesion, not limited to *ETV6::SYK*+ MLN-E, but stereotypical of this peculiar molecular subset.

The field of histiocytic neoplasms is slowly shifting towards a molecularly based classification paradigm, as TK imbalances (mutations and rearrangements) are almost invariably present in driving the disease. Intriguingly, cutaneous manifestations of MLN-E are uncommon, and rather nonspecific, including erythematous eruptions, pruritus, urticaria, and eosinophilic cellulitis[1]. A peculiar association has been found between *FIP1L1::PDGFRA*+ MLN-E and lymphomatoid papulosis[13], and a single case of *FIP1L1::PDGFRA*+ MLN-E associated with generalized eruptive histiocytosis has been reported[14], with both conditions showing clinical response to TK inhibition, despite the lack of evidence of clonal relationship. Likewise, in our patient, a near-complete remission of the "histiocytosis-like" disease was achieved and maintained on imatinib, but was followed by a steady progression of the eosinophilia, with increase of t(9;12)(q22;p13)-positive metaphases, thus suggesting both a non-target specific effect of the TK inhibition on MLN-E-associated manifestations and the need for a more tailored approach. In this regard, we may only speculate on the predictive impact of the *ASXL1* mutation, a gene associated with therapeutic resistance and increased risk of progression in several myeloid neoplasms[15]. Based on the collected experience, *ETV6::SYK*+ MLN-E has been shown to be sensitive *in vitro* and, to some extent, *in vivo* to SYK inhibition (entospletinib and fostamatinib)[2,8], while a partial response to MEK inhibition with cobimetinib was recorded in another patient[7]. Finally, in the patient reported by Beauverd et al.[6], sustained remission was achieved following allogeneic stem cell transplantation (HSCT), after failing several systemic therapies for the control of blood condition, including imatinib.

ETV6::SYK-related neoplasms are exceedingly rare but easily overlooked or dismissed as inflammatory / autoimmune processes. Their recognition should prompt appropriate management, potentially benefitting from novel targeted therapies, including the oral SYK inhibitor entospletinib and, ultimately, HSCT[6,8], with the aim of ameliorating their potentially aggressive clinical course (which led to the death of our patient less than 24 months after diagnosis). This unique, GA-like presentation provides a novel, and intriguing, model of disease, and may serve as a relatively specific clue for the timely diagnosis of MLN-E harboring *ETV6::SYK* rearrangement, hopefully leading to a better prognosis for this rare and challenging subset of patients.

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Table

Clinical picture F-to-M ratio 5:1; median age 51 yrs (range: 36-67) *Current case* • steadily developing cutaneous plaques, ocular signs (monocular diplopia and paresis) • isolated eosinophilia. *Published cases* (n = 5) • skin lesions involving the head in all cases + trunk and limbs in 4 cases • ocular signs and arthralgia reported in 1 case; cutaneous pain in 1 case • absolute eosinophilia (range 1.59-9.5 x10^9/L); variable leukocytosis and anemia
Histology *Current case + published cases* (n = 4) • skin biopsy showing interstitial to diffuse dermal infiltration of spindle/histiocytoid histiocytes; very few granulocytes; non-Langerhans / non-descript histiocytic phenotype (CD68+, CD1a-, S100-, langerin-, MPO-) • bone marrow featuring megakaryocyte dysplasia, myeloid hyperplasia, and eosinophilia in all but 1 case
Molecular features • *ETV6* locus involvement in all cases; 5 cases demonstrating *ETV6::SYK* fusion • in our cases, *ASXL1* mutation found in peripheral blood, not detected in the skin • in 1 case, presence of a minor clone with complex karyotype
Therapy and follow-up *Current case* • imatinib with clinical response of the ocular and cutaneous lesions; switch to dasatinib due to steady increase of eosinophilia • died of infectious complications 1.5 years after the diagnosis *Published cases* • 1 patient, remission of skin lesions after hematopoietic stem cell transplantation • 2 cases, partial response to thalidomide or cobimetinib • 1 patient, partial response to fostamatinib, with remission after hematopoietic stem cell transplantation

Summary of major clinical and pathologic features of the collected cases of myeloid neoplasm, featuring eosinophilia and skin lesions and rearrangement of *ETV6* locus at 12p13.

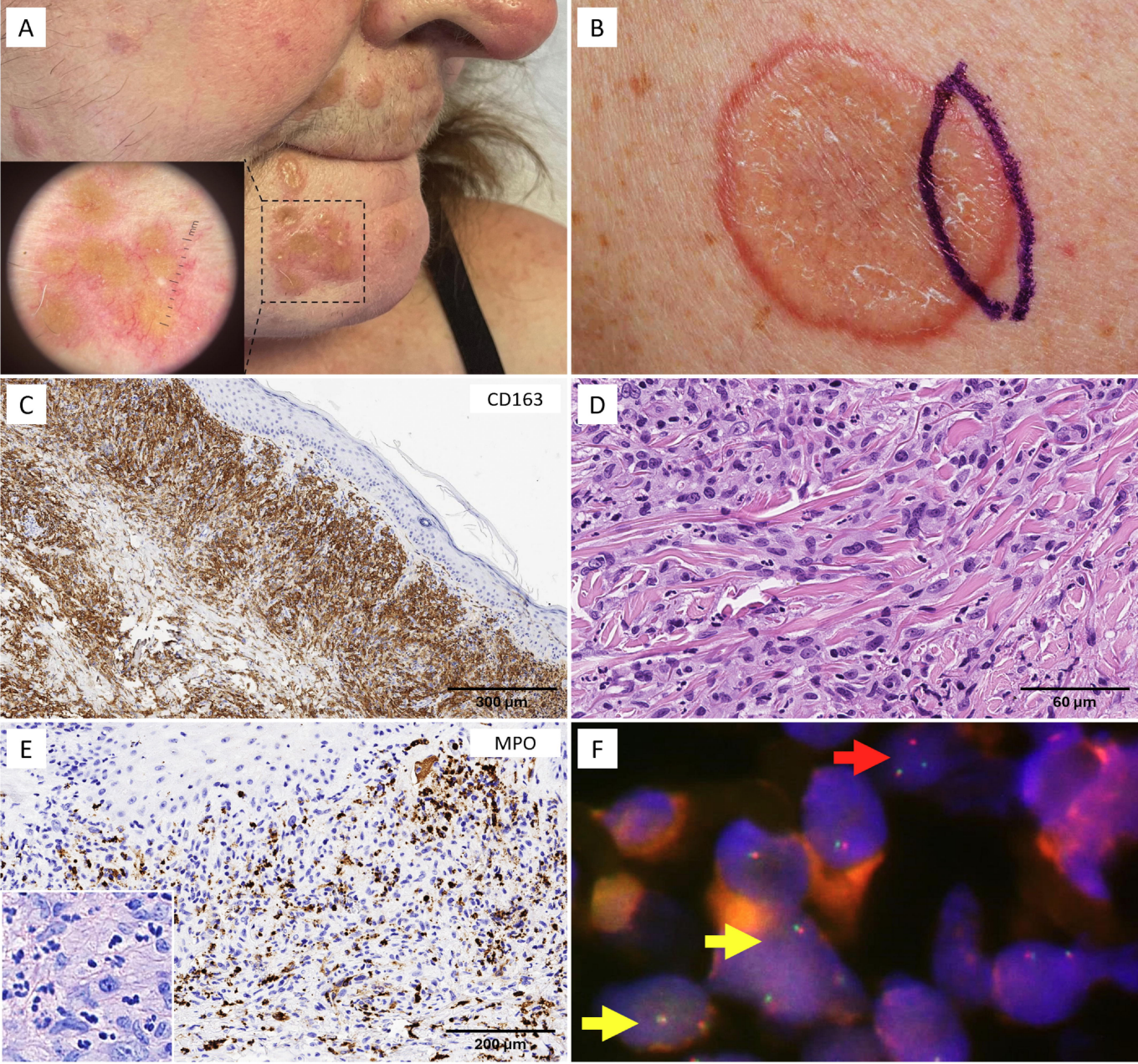
Figure legends

Figure 1 – Clinic-pathologic picture of cutaneous, histiocytic manifestation

Representative panel depicting the clinical appearance of the skin lesions, as multiple, firm, partly confluent, erythematous to yellowish plaques, some with a slightly elevated border and an intensely yellowish, depressed central area involving the face (a), scalp, and the back (b). Dermoscopy (a; inset) showed yellowish structureless areas with short, branched vessels surrounded by peripheral erythema a finding indicative of a granulomatous process. Cutaneous biopsy displaying a «busy dermis», secondary to the presence of an interstitial, patternless accumulation of "histiocytoid", CD163+ histiocytes (c. CD163, 100x; d. H/E, 400x), with foci of accumulation of granulocytes with abnormal nuclear segmentation (e. MPO, 200x and inset, Giemsa, 400x). FISH analysis (f. *SYK* break apart probe) of skin biopsy displays scattered, small-sized nuclei featuring *SYK* locus break (red arrow) consistent with granulocytes, as compared to larger cells with a wild type SYK pattern.

Figure 2 – Morphologic and molecular picture of eosinophilic neoplasm

BM aspirate and biopsy feature mild trilinear dysplasia, left shifting and hypogranularity of eosinophils, with small-sized, hypolobated megakaryocytes (a. MGG, 600x; b. H/E, 400x). Karyotype analysis (c) detected t(9;12)(q22;p13), further confirmed by RT-PCR for *ETV6::SYK* rearrangement (d. WT, wild-type probes; PB, peripheral blood; BM, bone marrow aspirate; C-, negative control). Histologic detail of endometrial biopsy (e. Giemsa, 400x) documented accumulation of eosinophils, with defective nuclear segmentation.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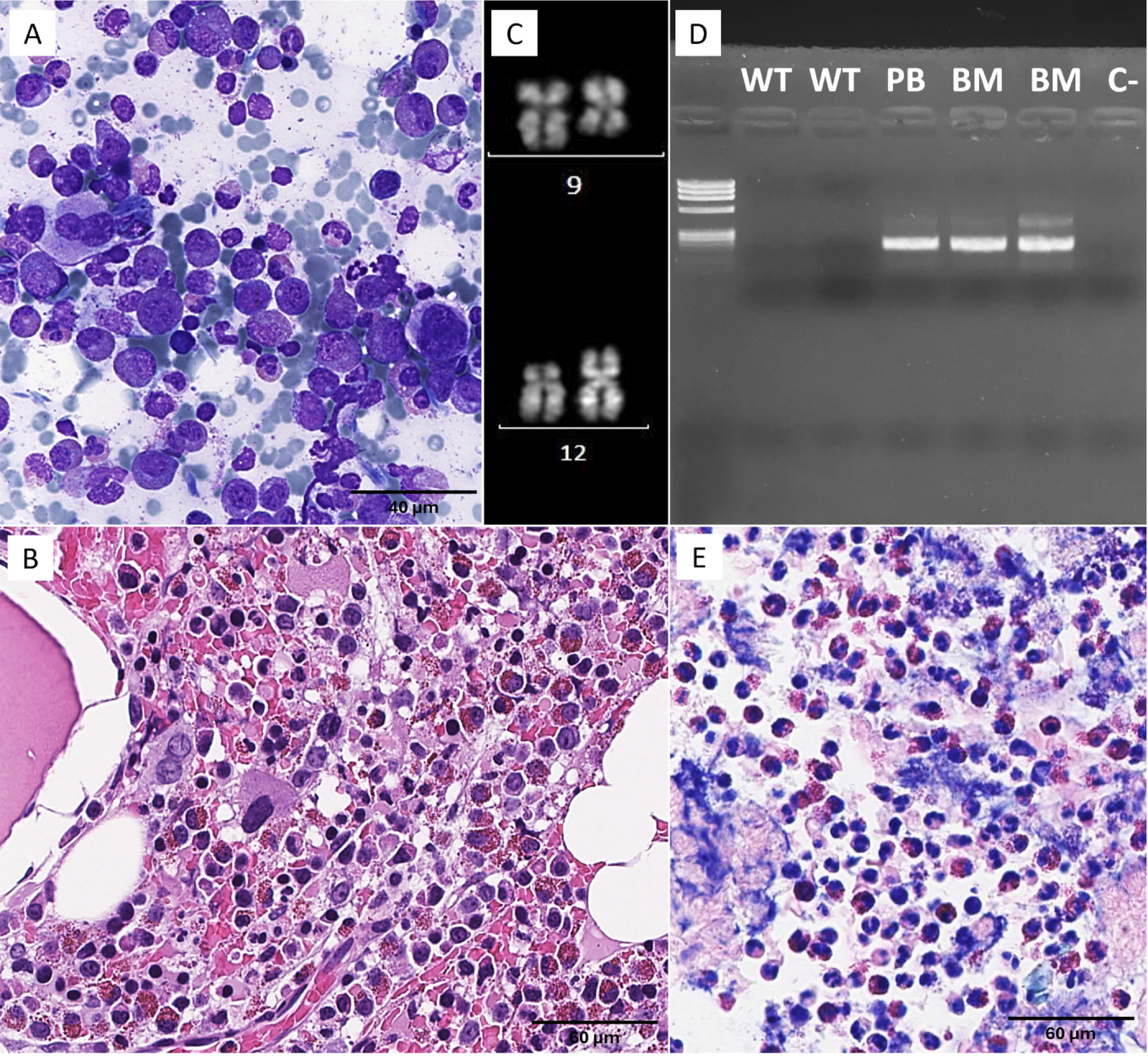
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