VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La **DIAGNOSTICA EMATOPATOLOGICA** nell'**ERA** della **MEDICINA** di **PRECISIONE**

When Disease Hides Behind Therapy

Carlo Pescia

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Milano

Bologna, Aula Prodi | 11-12 maggio 2026

COI: None to declare

CLINICAL PRESENTATION

Male patient, 74 years old. Past medical history: hypertension, prostatic hypertrophy, COPD, **immune thrombocytopenic purpura** (ITP, known from 1999). **2010**: Bone marrow trephine was normal; aspirate not evaluable; karyotype normal.

ITP treated with steroids (Methylprednisolone) and with Revolade (Eltrombopag) started 6 months prior to presentation at our centre.

- **December 2024**: admission to the ER of our hospital for fainting, nausea and lack of appetite
- CBC revealed: Hb 13.3 g/dL, MCV 94 fL, GB 24180/mmc with N 21970/mmc, Mo 900/mmc (3%) and L 11300/mmc, PLT 43000/mmc
- Gastroscopy: duodenal ulcer (Helicobacter pylori+)
- Thorax CT: pulmonary embolism

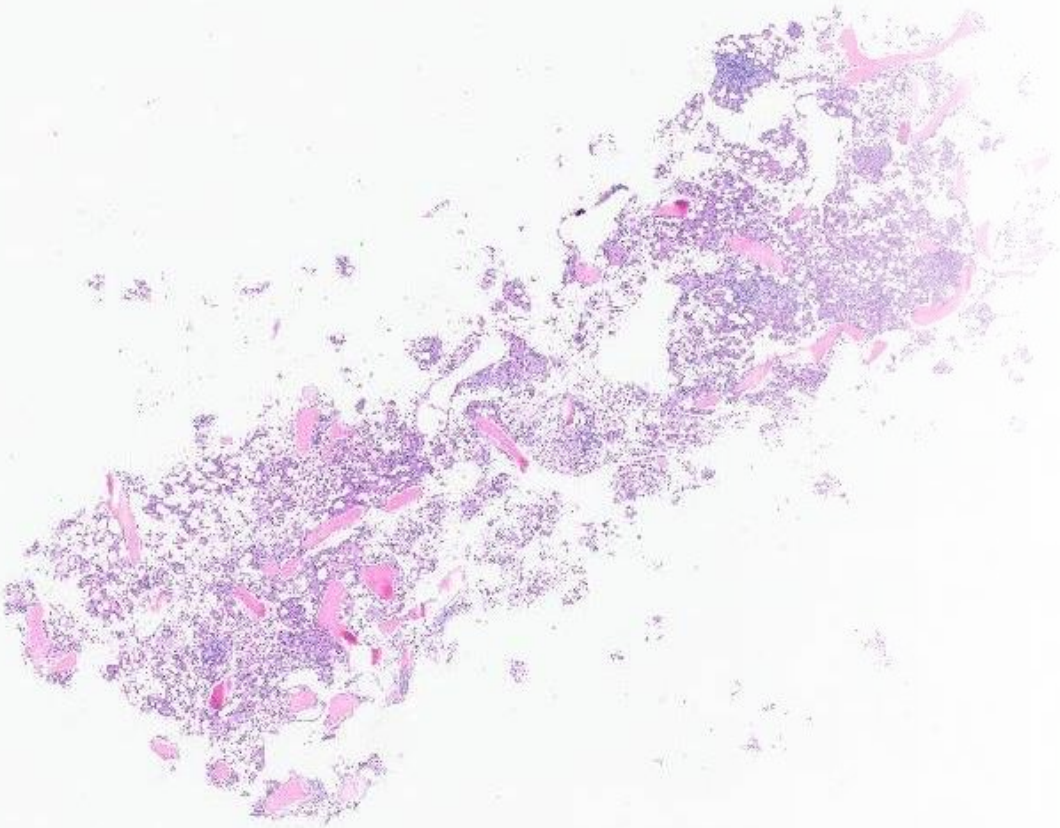
Due to CBC alterations suspicious for a myeloid neoplasm, a bone marrow trephine biopsy, bone marrow aspirate and flow cytometry were performed.

BONE MARROW ASPIRATE MORPHOLOGY

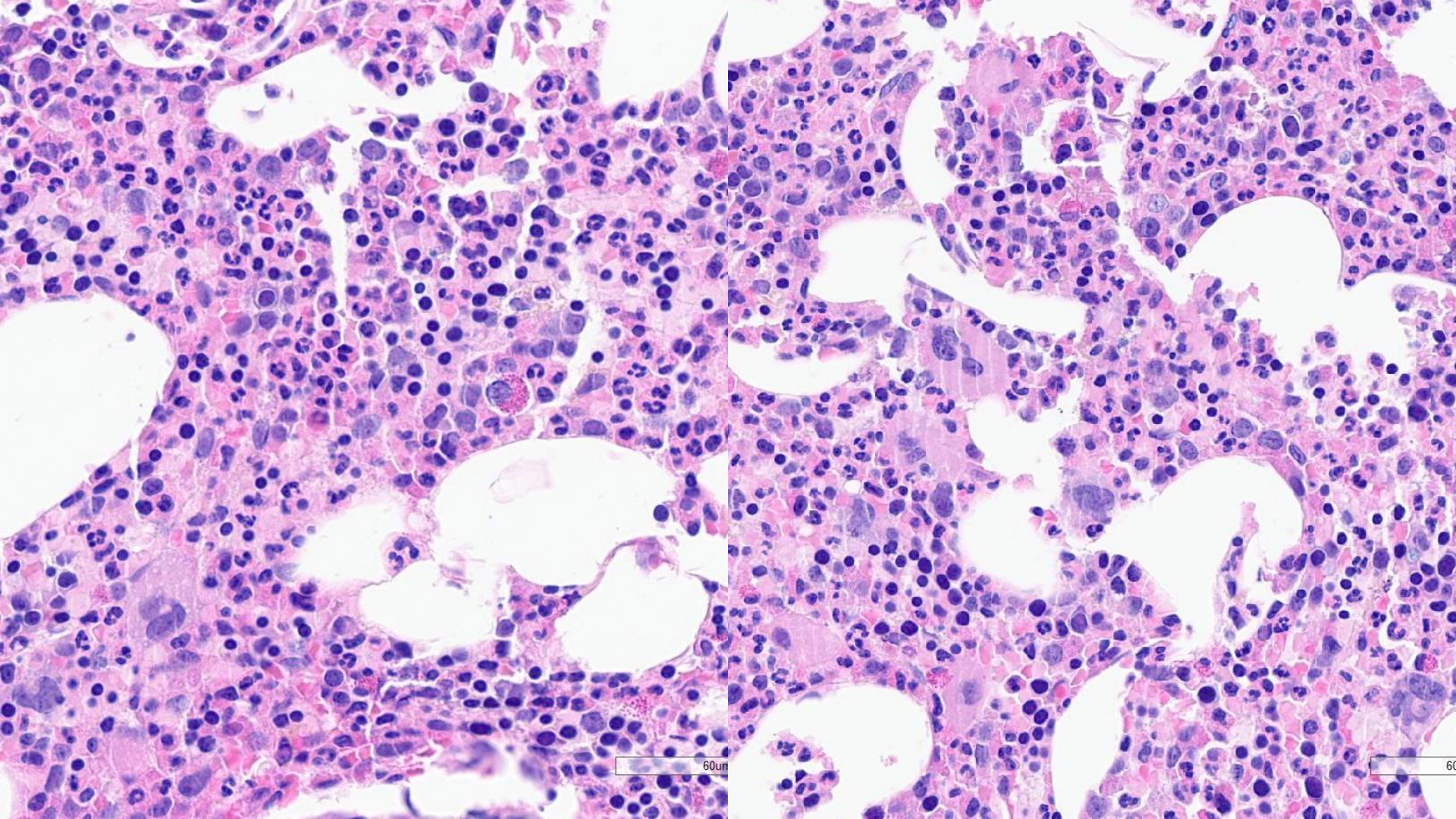
Hypercellular bone marrow, with increase in megakaryocytes (mostly hyperlobated) and increase in mast cells.
Mild dyserythropoiesis; normal maturing granulopoietic lineage with no increase in blasts (1.9%)

BONE MARROW ASPIRATE FLOW CYTOMETRY

No increase in blasts (1%)



Bone Marrow
December 2024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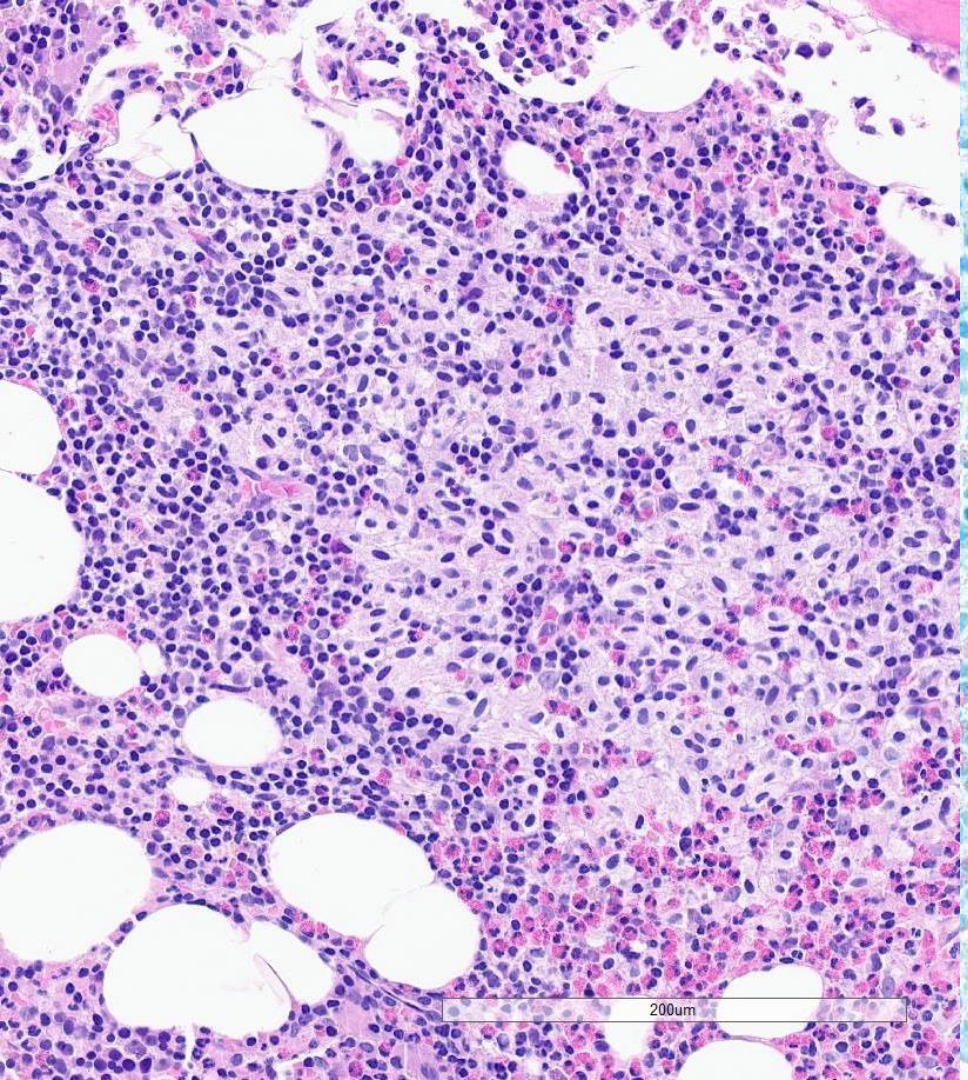
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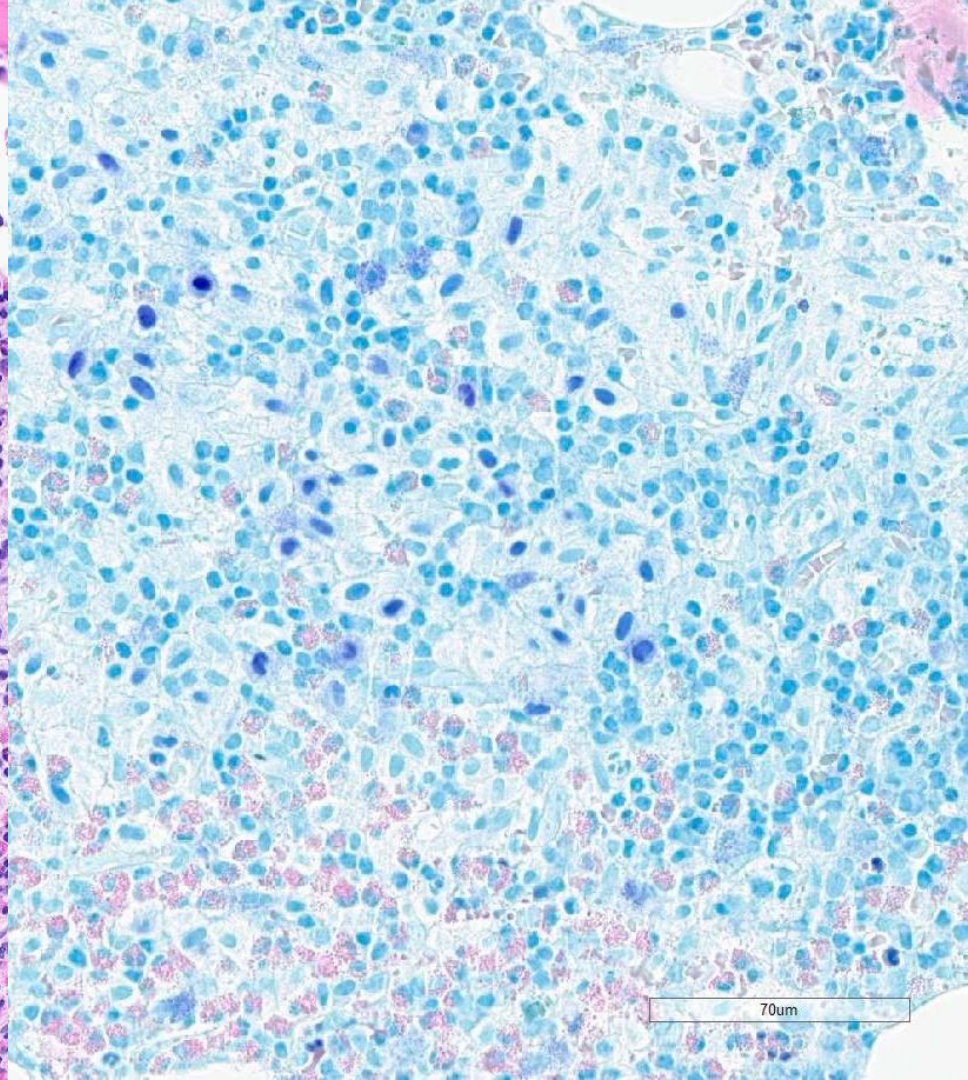
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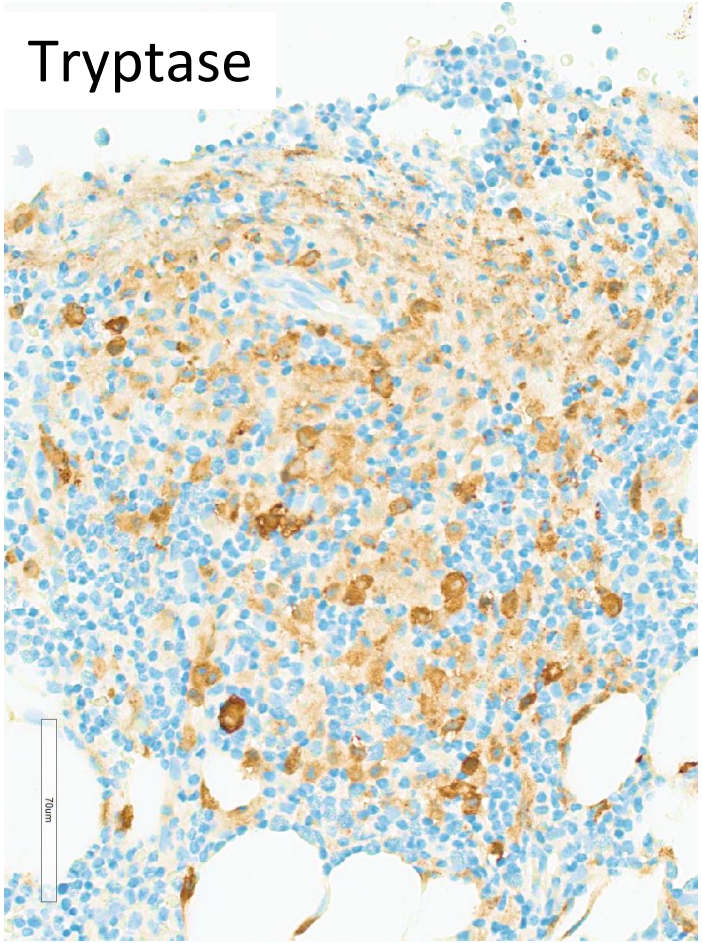
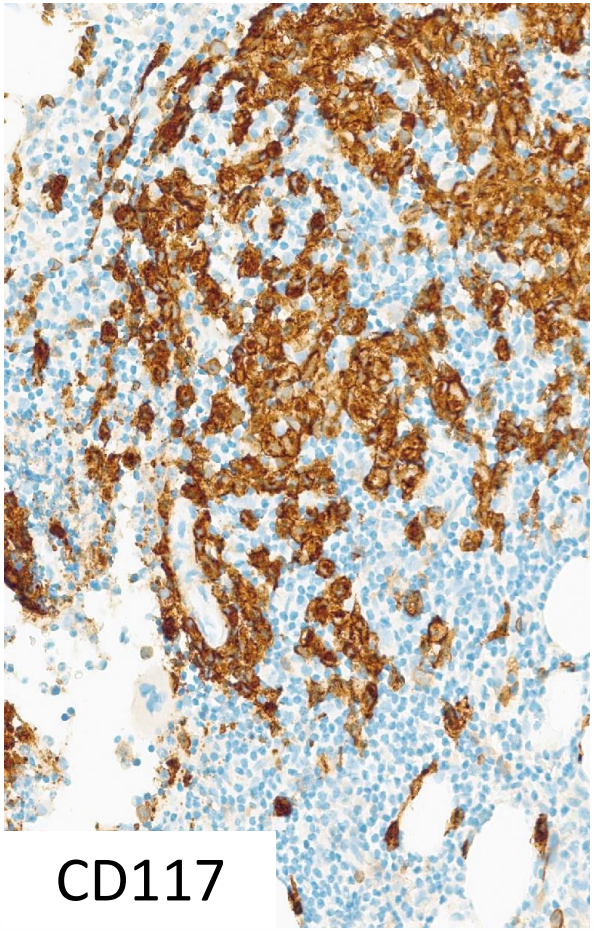
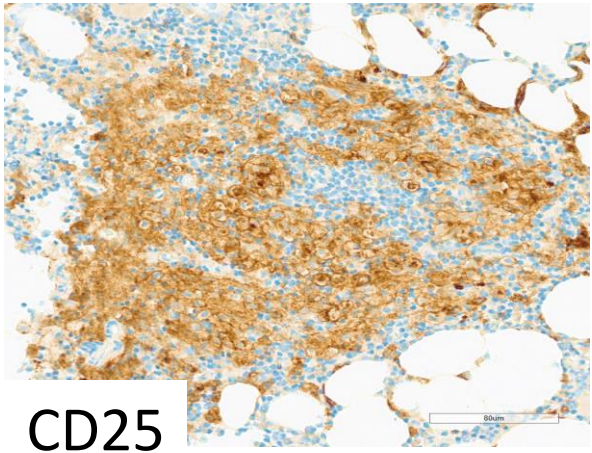
Tryptase





CD117



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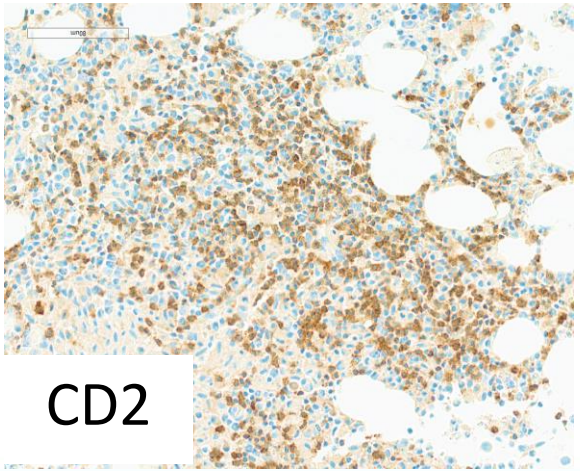

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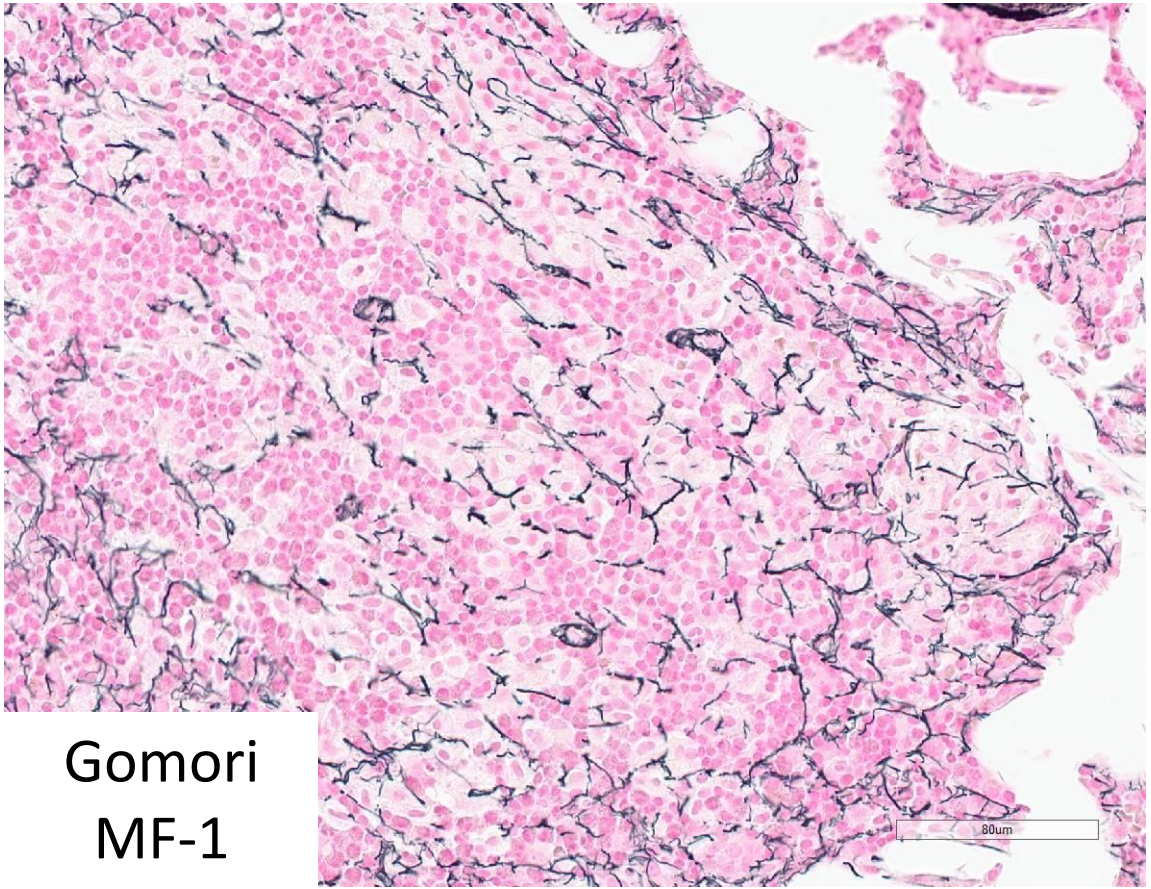


Gomori
MF-1

DIAGNOSTIC CRITERIA FOR SYSTEMIC MASTOCYTOSIS (WHO 5th ed.)

#32136

Diagnostic criteria for systemic mastocytosis {34901755}

Major criterion:

- Multifocal dense infiltrates of mast cells (≥ 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organ(s)

Minor criteria:

- Atypical mast cell morphology, including spindle shape or immature morphology, present in > 25% of all mast cells on bone marrow smears or in other extracutaneous organ(s)[a]
- Mast cells aberrantly express one or more of the following antigens: CD2, CD25, CD30
- *KIT* p.D816V mutation or other activating *KIT* mutation[b] detected in peripheral blood, bone marrow, or other extracutaneous organ(s)
- Baseline serum tryptase concentration of > 20 ng/mL in the absence of an associated myeloid neoplasm; in the case of a known HαT, the tryptase level could be adjusted[c]

The diagnosis of systemic mastocytosis can be made if the major criterion and at least one minor criterion are fulfilled, or if at least three minor criteria are fulfilled.

CRITERIA FOR CMML DIAGNOSIS (WHO 5th ed.)

Essential criteria

1. Persistent absolute ($\geq 0.5 \times 10^9$/L) and relative ($\geq 10\%$) peripheral blood monocytosis
2. Blasts constitute < 20% of the cells in the peripheral blood and bone marrow[a]
3. Not meeting diagnostic criteria of chronic myeloid leukaemia or other myeloproliferative neoplasms[b]
4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions (e.g. *PDGFRA*, *PDGFRB*, *FGFR1*, or *JAK2*)[c]

NOT MET

Desirable criteria

1. Dysplasia involving ≥ 1 myeloid lineages[d]
2. Acquired clonal cytogenetic or molecular abnormality[e]
3. Abnormal partitioning of peripheral blood monocyte subsets[f]

Requirements for diagnosis

- Essential criteria must be present in all cases
- If monocytosis is $\geq 1 \times 10^9$/L: one or more desirable criteria must be met
- If monocytosis is $< 1 \times 10^9$/L: desirable criteria 1 and 2 must be met

DIAGNOSTIC CRITERIA FOR MDS/MPN NOS (WHO 5th ed.)

#32938

Diagnostic criteria for myelodysplastic/myeloproliferative neoplasm (MDS/MPN) NOS

Peripheral blood:

- A combination of cytopenia(s) and proliferative feature(s)

NOT MET (thrombocytopenia was attributed to ITP)

Bone marrow cytology:

- A combination of cell dysplasia and proliferative features { 22195406 ; 18480833 ; 15217205 }

Molecular analyses of blood or bone marrow:

- A combination of mutations seen in proliferative and dysplastic myeloid malignancies

To be excluded:

- Therapy-related myeloid neoplasms
- Disease-defining gene fusions such as *BCR*::*ABL1* or rearrangement of *PDGFRA*, *PDGFRB*, *JAK2*, or *FGFR1*
- Biallelic *TP53* mutations
- Other MDS/MPN entities, including chronic myelomonocytic leukaemia, MDS/MPN with neutrophilia, and MDS/MPN with *SF3B1* mutation and thrombocytosis

DIAGNOSIS

SYSTEMIC MASTOCYTOSIS (SM).

Given the presence of 1 B-finding ("Signs of myeloproliferation and/or myelodysplasia not fulfilling criteria for AHN"), the absence of C-findings, a serum tryptase level of 17 ng/mL, and **no skin lesions**, the case could be framed within the group of **Indolent Systemic Mastocytosis (ISM) without skin lesions** (according to WHO and ICC criteria)

+ **Thrombopoietin (TPO) receptor agonists (TPO-RAs) side effects?**

Karyotype: normal

NGS (suboptimal material) revealed only a presumably oncogenetic **TET2** exon 11 mutation with 45% VAF.

- *ISM without skin lesions:* at most one B finding[a,b] and/or basal serum tryptase ≥ 125 ng/mL and/or dense SM infiltrates in an extramedullary organ

CLINICAL MANAGEMENT AND FOLLOW UP

The most critical clinical parameter remained the **persistent thrombocytopenia (PLT 15-25000/mmc)**, occasionally symptomatic.
No treatment for SM was started.

To control the thrombocytopenia, the patient **shifted from Eltrombopag to Avatrombopag in March 2025**, with mild increase in PLT (up to 40.000/mmc).

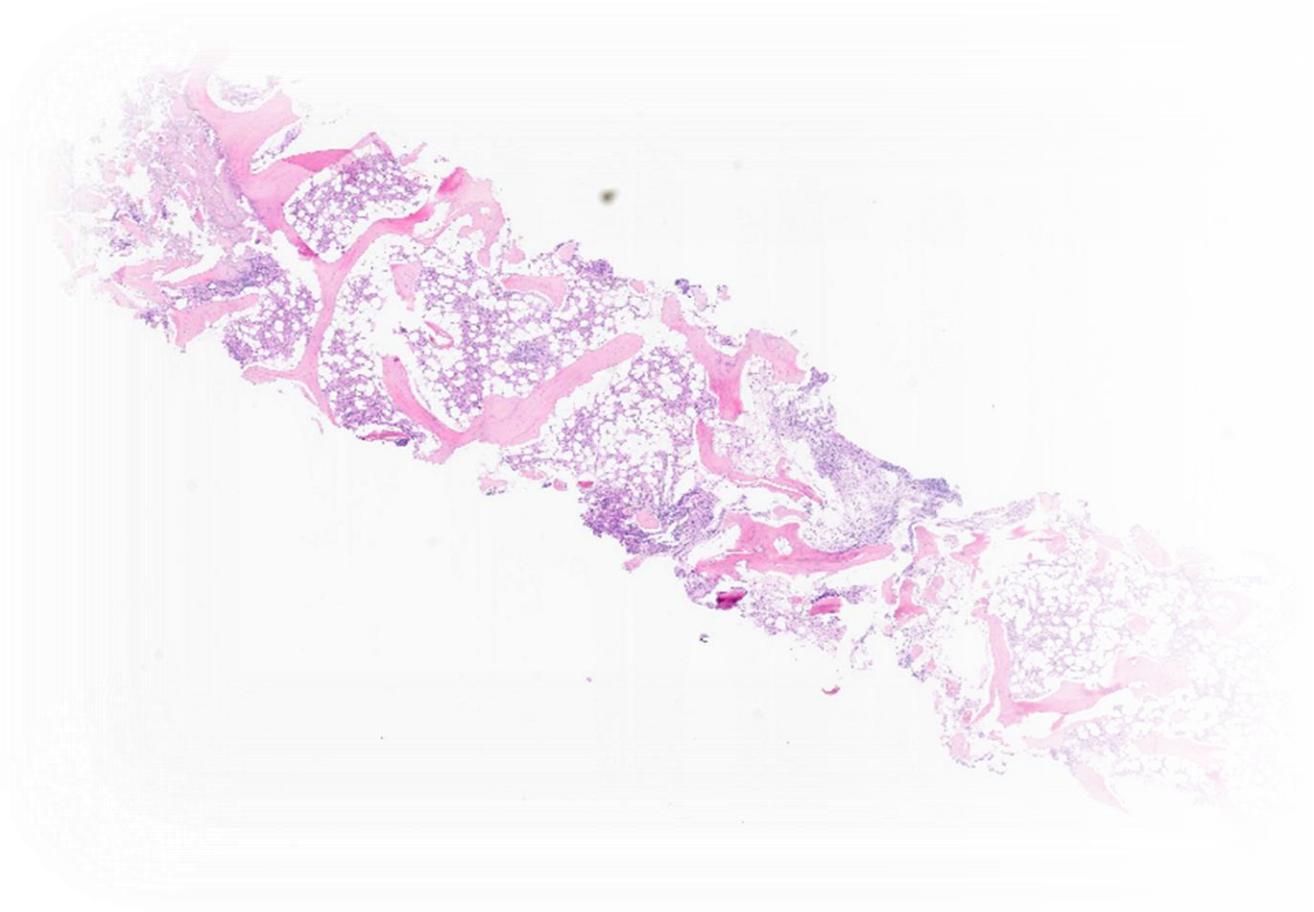
In September 2025, the patient complained of sudden-onset diffuse pruritus, without skin lesions suggestive of cutaneous mastocytosis.

LAST FOLLOW UP

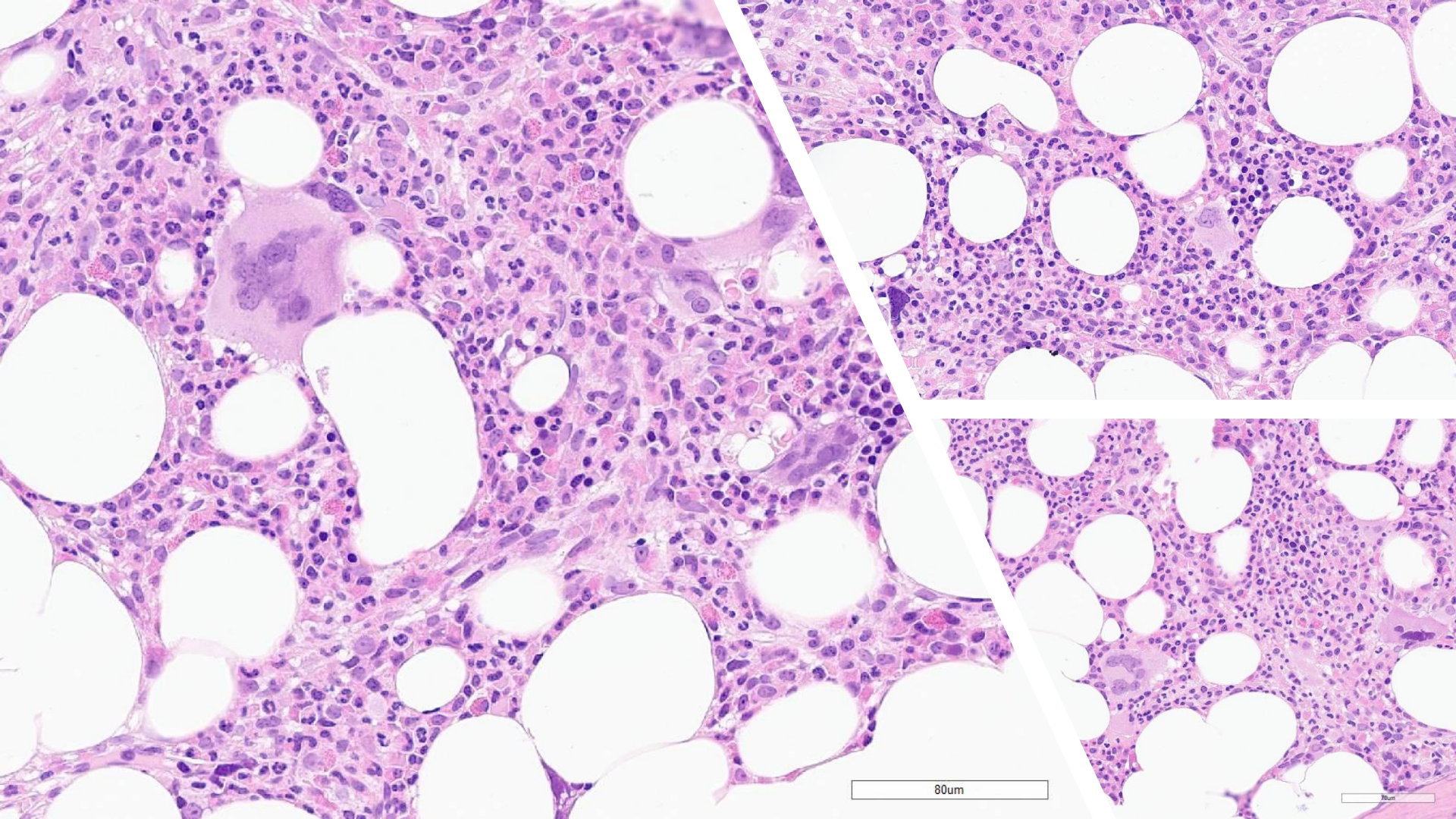
Follow up CBC performed in January 2026 showed **Hb 10.5 g/dL**, MCV 96 fL, GB 16270/mmc with N 12460/mmc, L 2010/mmc, **M 1350/mmc (8%)**, **PLT 90000/mmc**, **LDH 631 U/L**; tryptase <20 ng/ml.

A **second bone marrow trephine** was performed to exclude SM evolution or onset of AHN.

Bone marrow aspirate and flow cytometry was not evaluable (dry tap).



Bone Marrow
February 2026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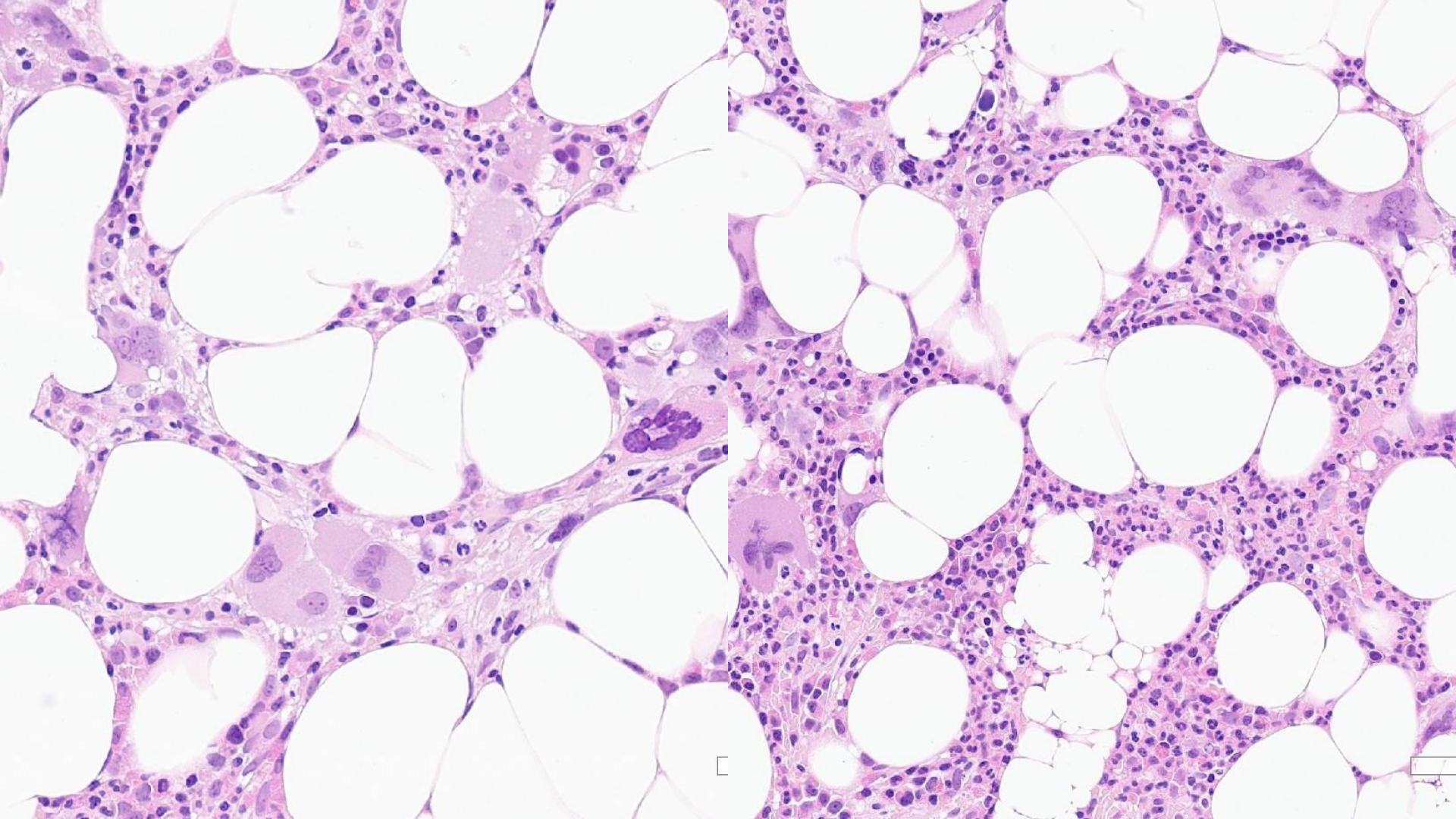

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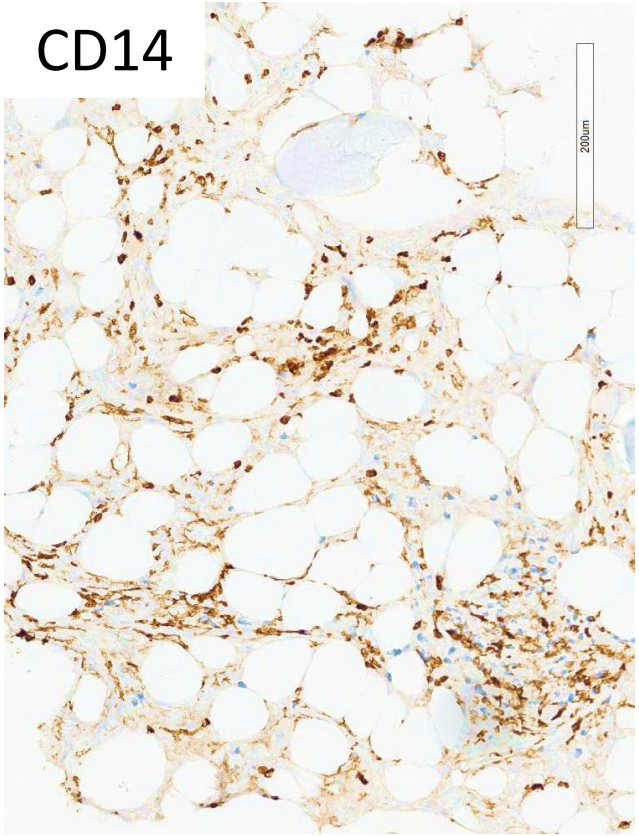

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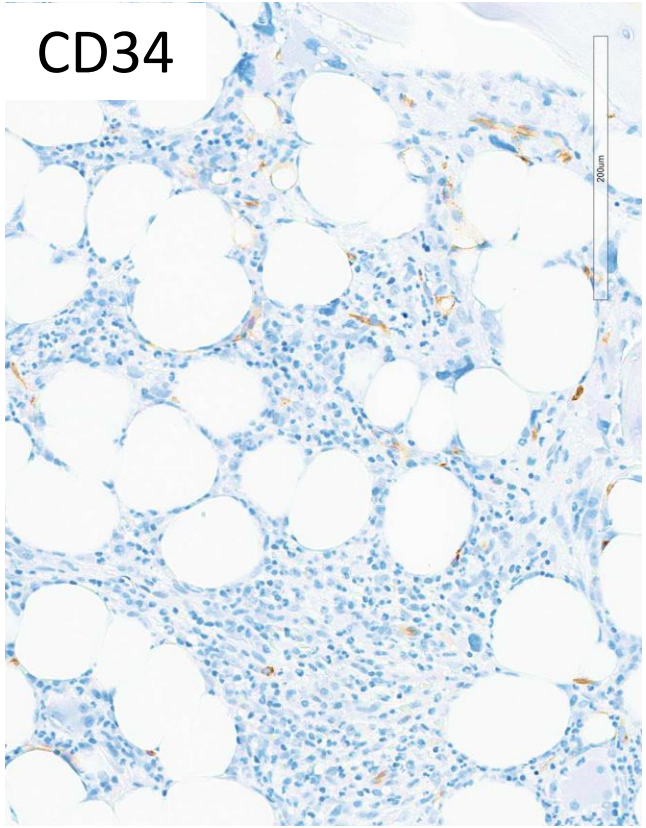

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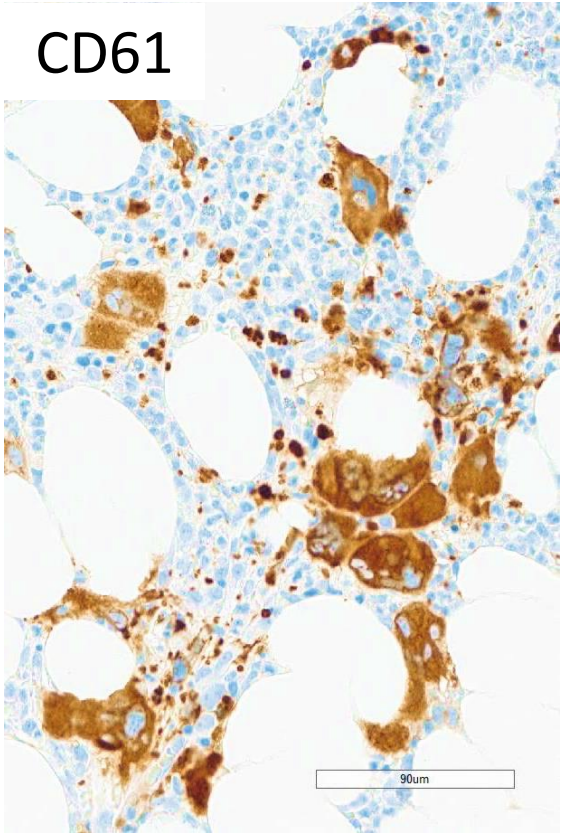

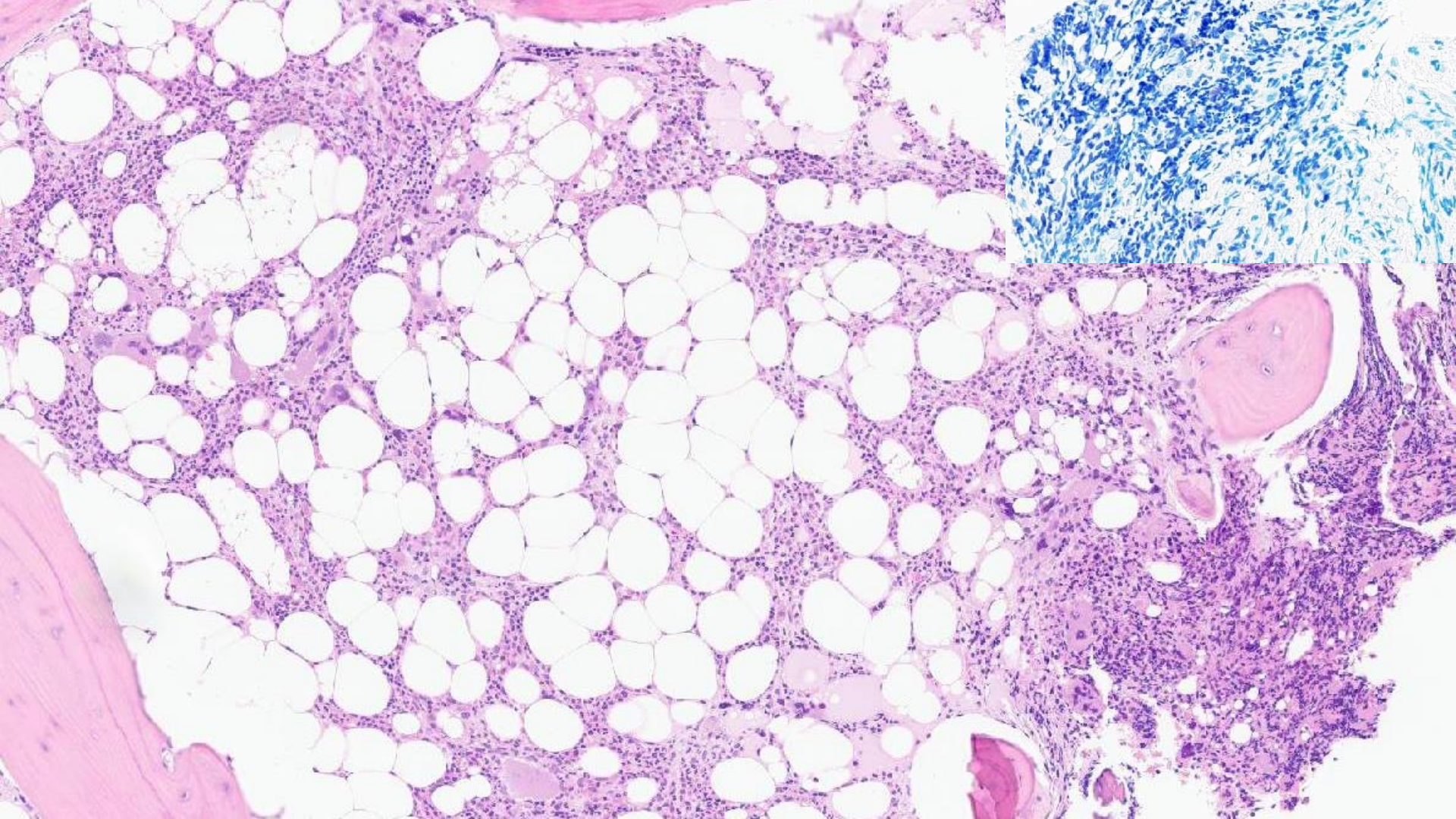

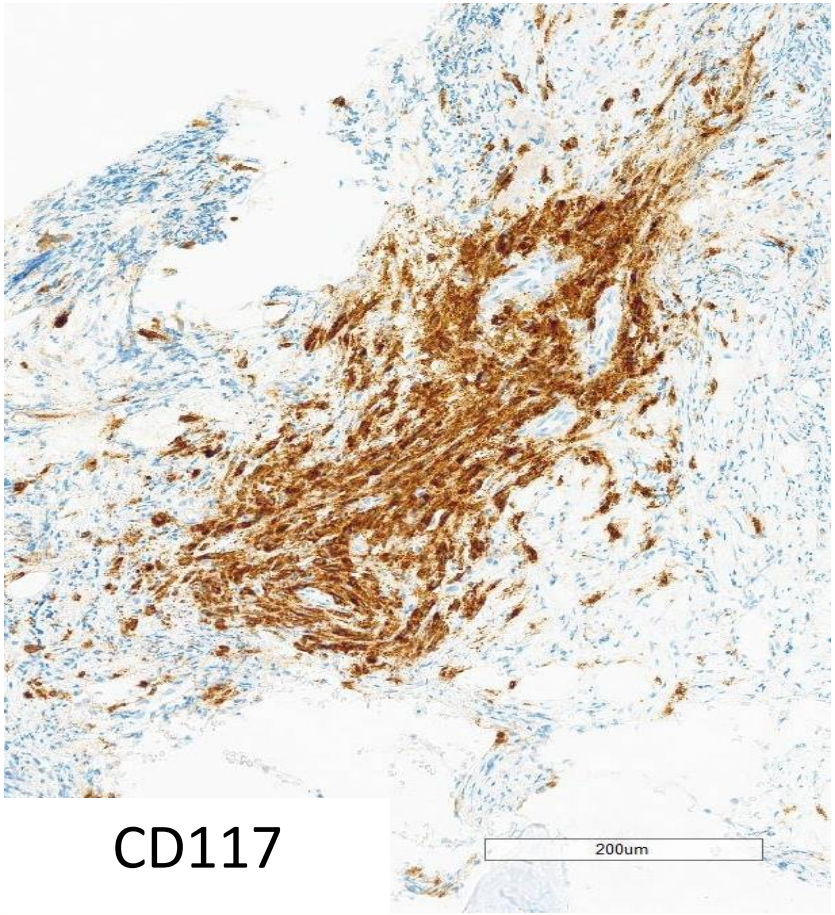

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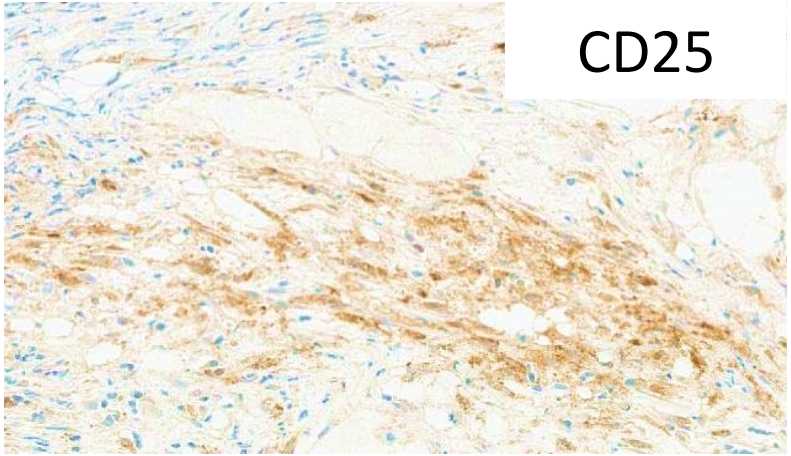

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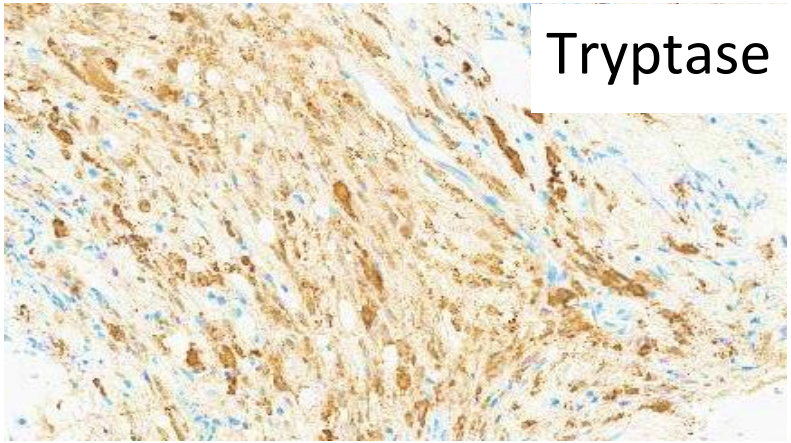
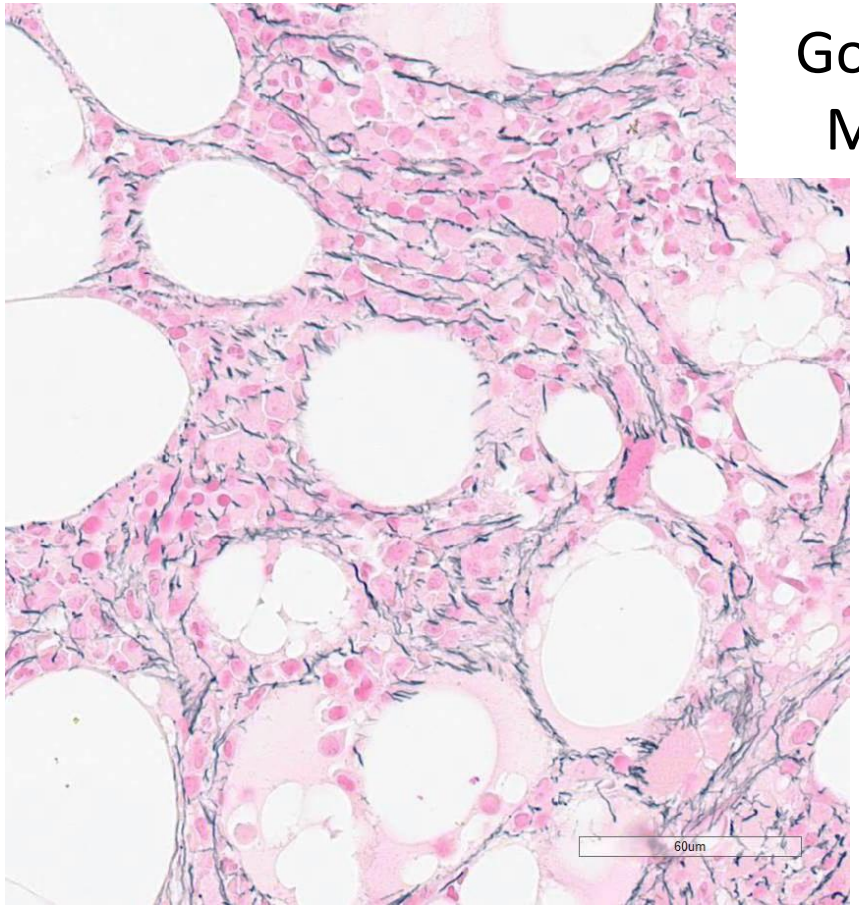
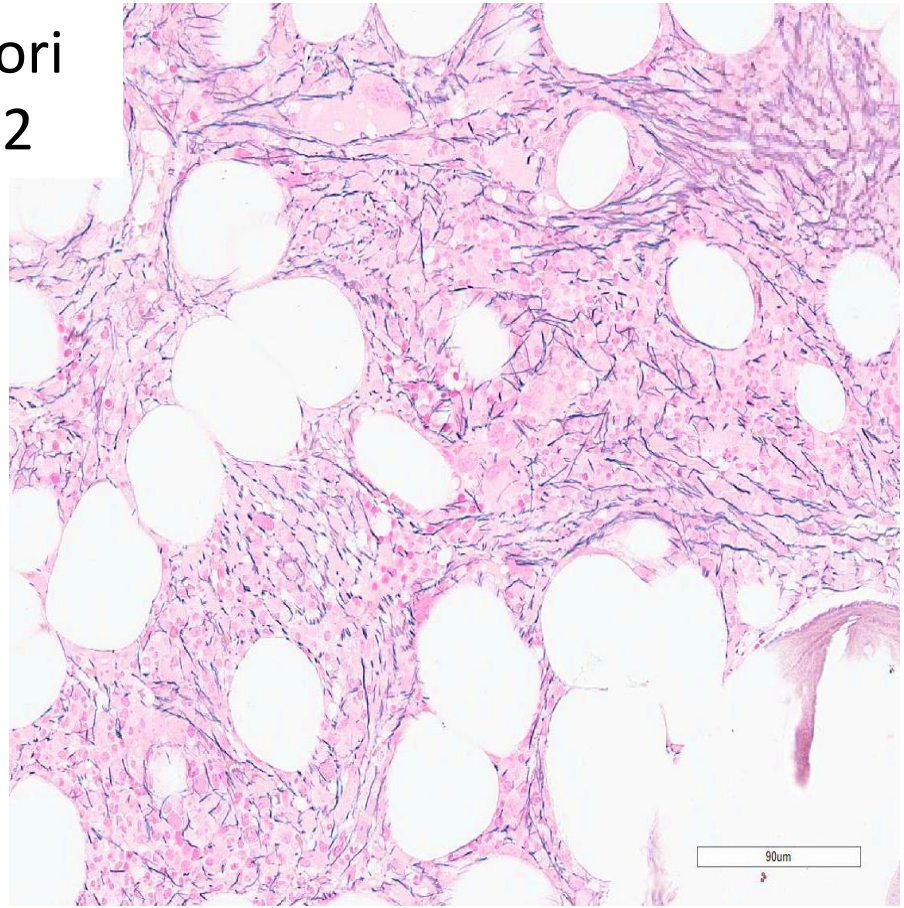


Tryptase

Gomori
MF-2





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STILL MISSING?

Desirable criteria

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DIAGNOSIS

The clinical and histological findings could be consistent with systemic mastocytosis associated with a hematologic neoplasm (**SM-AHN**), with clinical features suggestive, although not diagnostic, of **oligomonocytic chronic myelomonocytic leukemia (CMML).**

The overall stromal and megakaryocytic changes, showing PMF-like features, are consistent with side effects related to thrombopoietin receptor agonists (**TPO-RAs)**.


Vol. 99 No. 5 (2014): May, 2014 > Bone marrow fibrosis in 66 patients with immune...

ARTICLES

Bone marrow fibrosis in 66 patients with immune thrombocytopenia treated with thrombopoietin-receptor agonists: a single-center, long-term follow-up

Waleed Ghanima , Julia Turbiner Geyer , Christina S. Lee , Leonardo Boiocchi , Allison A. Imahiyerobo , Attilio Orazi , James B. Bussel

Vol. 99 No. 5 (2014): May, 2014 https://doi.org/10.3324/haematol.2013.098921


Modern Pathology

Volume 25, Issue 1, January 2012, Pages 65-74

Article

Thrombopoietin receptor agonist therapy in primary immune thrombocytopenia is associated with bone marrow hypercellularity and mild reticulin fibrosis but not other stromal abnormalities

Leonardo Boiocchi [1,2], Attilio Orazi [3], Waleed Ghanima [3,4], Melissa Arabadjief [3], James B Bussel [3], Julia Turbiner Geyer [1]

INTERESTING FEATURES

The identification of the AHN component has been presumably delayed by the long history of thrombocytopenia treated with **TPO-RAs, which are known to induce stromal and MK abnormalities similar to those of MPNs.**

These modifications (MK morphology alterations, bone marrow hypercellularity and **fibrosis**) can **mask and/or delay the diagnosis** of underlying myeloid disorders.

The high VAF of the **TET2** mutations suggests a pre-existing myeloid clone, which could have led to MDS/MPN onset.

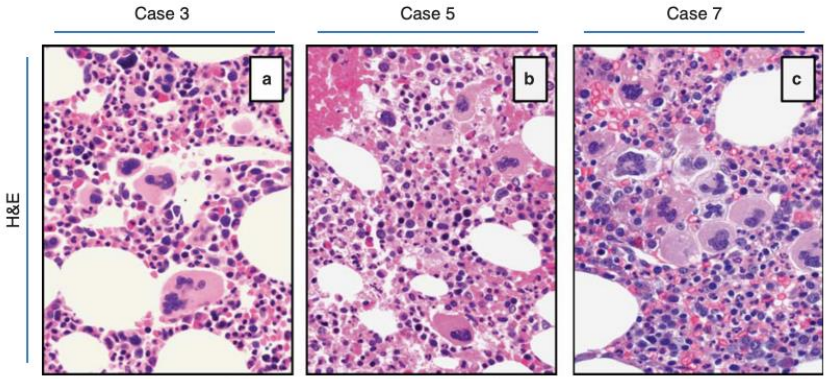
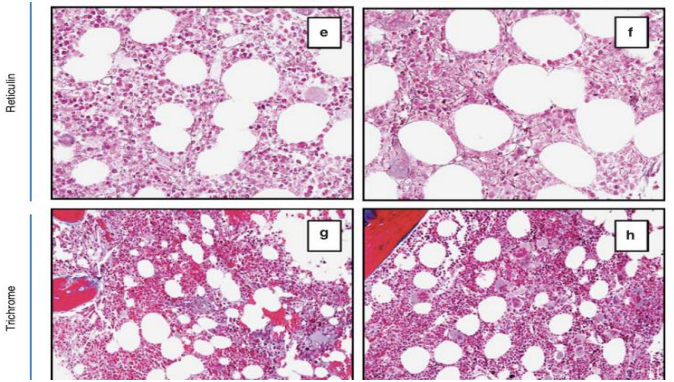


Figure 2 Megakaryocytic alterations observed in course of treatment with thrombopoietin receptor agonists. H&E sections of on-therapy bone marrow biopsies from patient 3 (**a**), 5 (**b**) and 7 (**c**). Megakaryocytes showed some myeloproliferative neoplasm-like features, including a marked degree of pleomorphism with an increased proportion of large cells displaying nuclear hyperlobulation and/or abnormally condensed chromatin; there was also a tendency of megakaryocytes to form clusters (**c**).



Leonardo Boiocchi, et al., Modern Pathology, Volume 25, Issue 1,2012

INTERESTING FEATURES

Open question: is it possible to diagnose an oligomonocytic CMML in this case? Or is it best to consider it an MDS/MPN unclassifiable?

- The diagnosis of SM-AHN **(Advanced SM)** significantly impacts on prognosis and treatment, but it can be difficult and hindered as in this case by previous treatments.

Our case suggests the importance of careful integration of clinical, laboratory, histological and molecular data for a better longitudinal approach to SM-AHN diagnosis, particularly in the setting of pre-existing cytopenias

Thank you for your attention