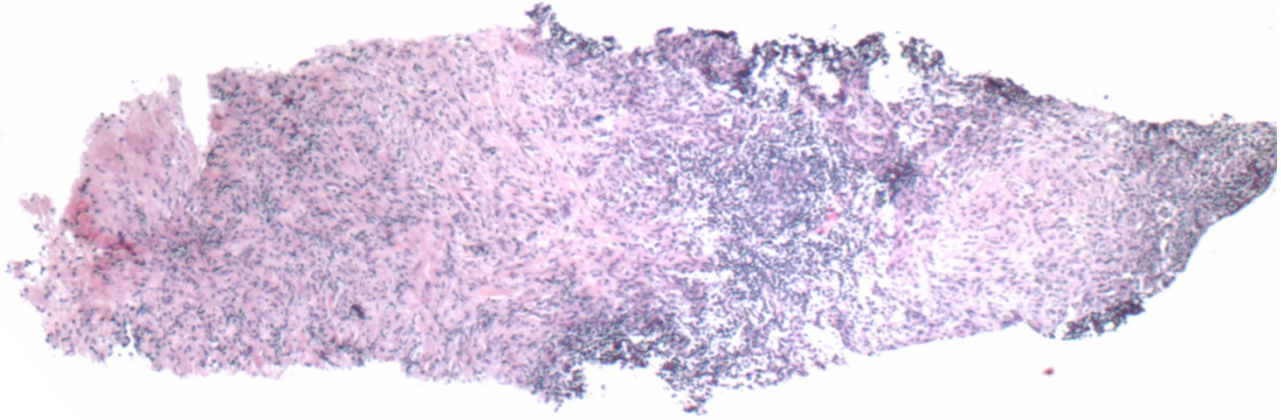
2017 Workshop of the Society for Hematopathology/European Association for Haematopathology
Molecular Genetics of Hematopoietic Neoplasms • Chicago, Illinois
Session 4: Genetic Testing in the Diagnosis of Myeloid Neoplasms, Excluding Acute Leukemias

Case # SH2017-0156

Unmasking of Multiorgan Involvement by Systemic Mastocytosis



Panel Diagnosis: Systemic Mastocytosis with an Associated Hematologic Neoplasm
(Chronic Myelomonocytic Leukemia-0)

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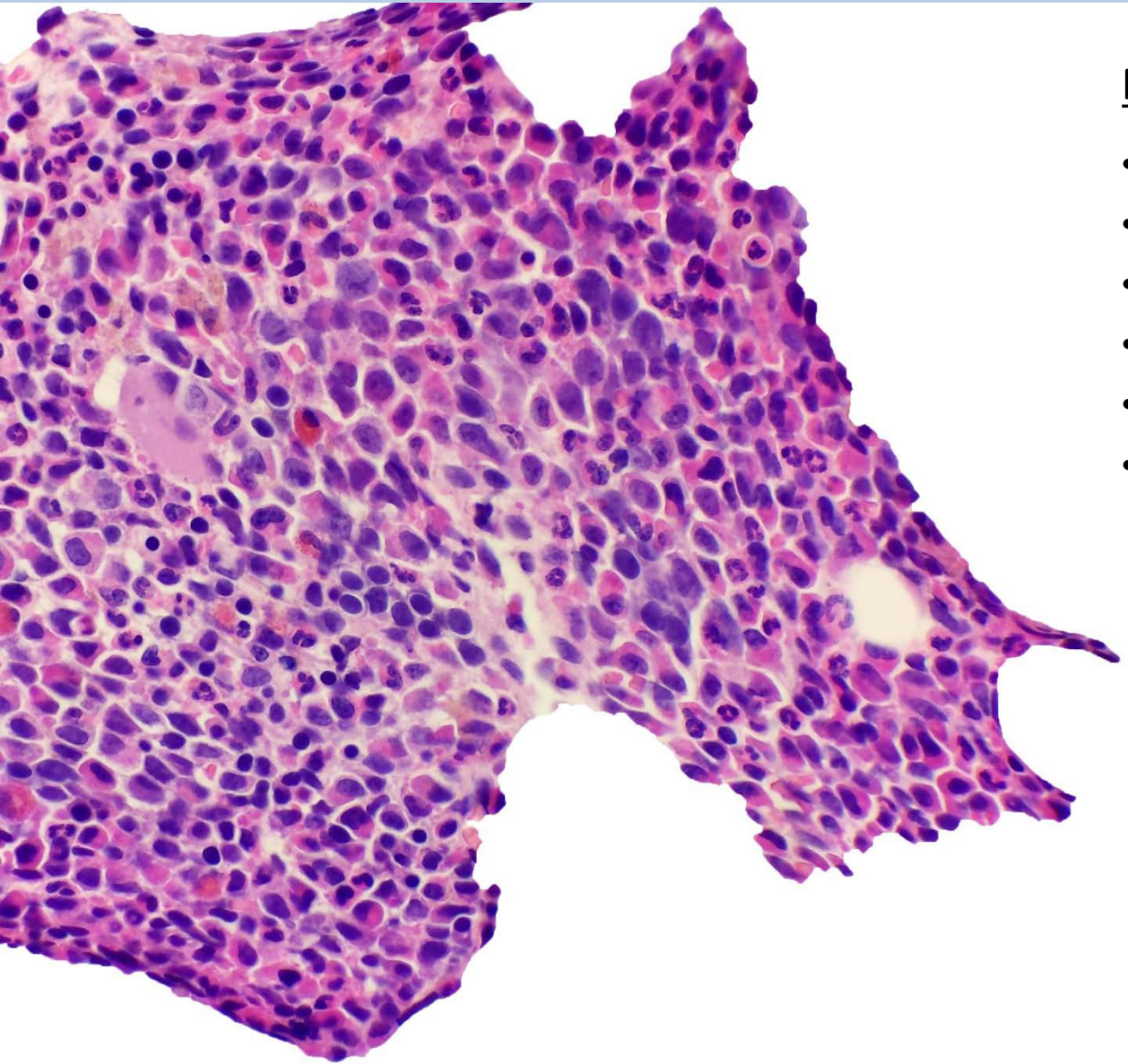
Clinical History

Patient: 72-year-old male, retired physician

- Presentation: LUQ pain w/ self-palpated splenomegaly, fatigue and weight loss
- Imaging (CT):
  - Splenomegaly (16.8 cm; no focal lesions)
  - Retroperitoneal adenopathy (≤ 2.6 cm)
  - Abdominal varices (c/w portal hypertension)
- CBC-Diff:
  - WBC 10.7 K/uL (H)
  - ANC 5.9 K/uL
  - AMC 2.8 K/uL (H)
  - HCT 35.8 % (L)
  - MCV 90.0 fL
  - PLT 139 K/uL (L)
- Labs:
  - ALT 13 U/L
  - AST 18 U/L
  - ALP 519 U/L (H)
  - Tbili 3.9 mg/dL (H)
  - ALB 3.3 g/dL (L)
  - PT-INR 1.5 (H)
- Pathology workup:
  - Bone marrow core biopsy
  - Lymph node core biopsy
  - Liver core biopsy
- Referred to DFCI for Hematology-Oncology consultation based on the BM findings:

"suspicious for a myeloproliferative neoplasm"

Microscopic Findings: Bone Marrow Biopsy



Preliminary Findings:

- Markedly hypercellular (90%)
- Myeloid hyperplasia
- Megakaryocytic dysplasia
- Mild reticulin fibrosis
- No increase in CD34+ blasts
- No ring sideroblasts

Ancillary Studies:

- Cytogenetics:
  46,XY[20]
- MDS/MPN FISH:
  No abnormalities

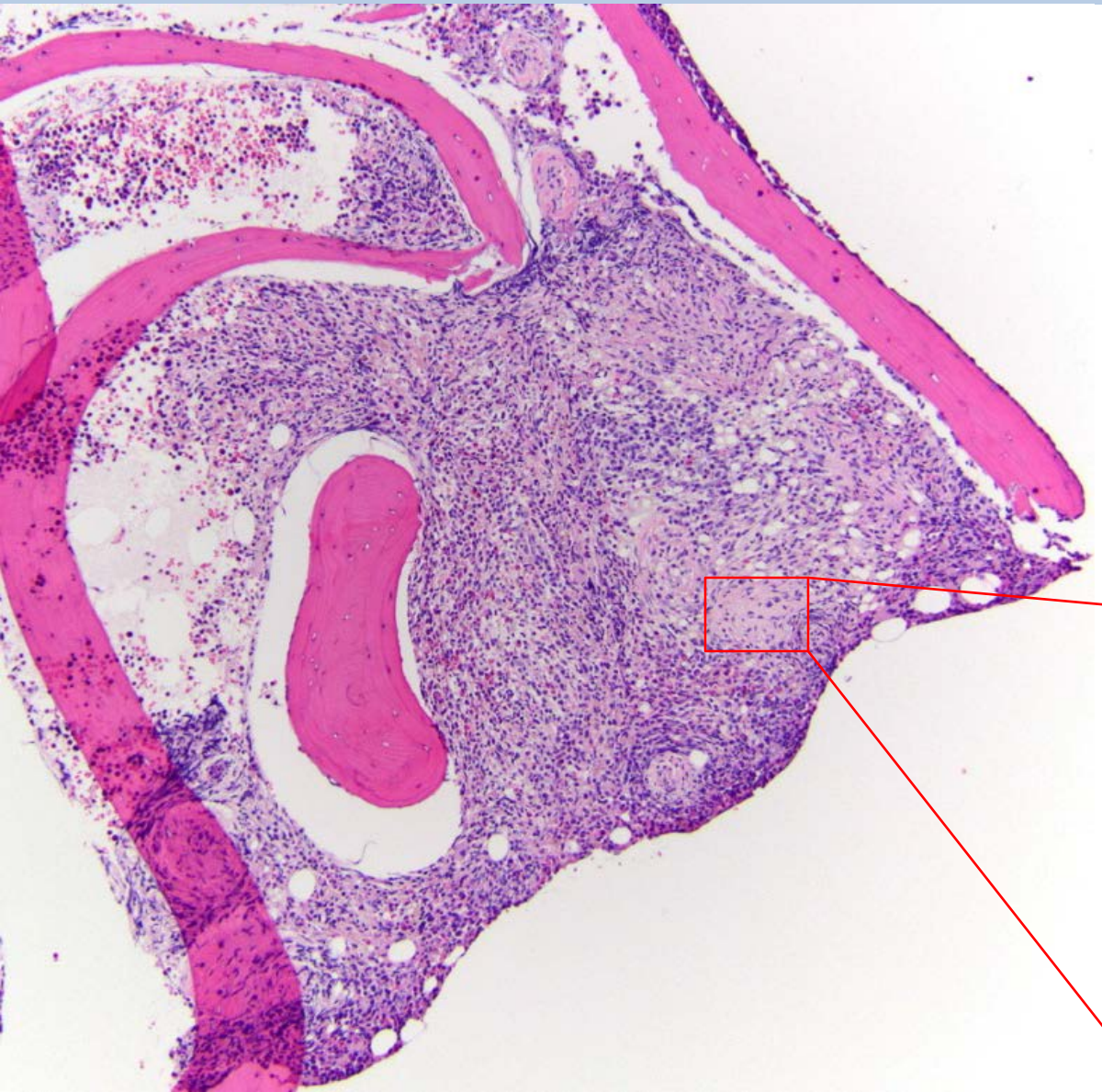
Molecular Genetic Findings

- Molecular analysis:
  - Performed on peripheral blood during initial consultation
  - "Rapid Heme Panel" (95-gene NGS assay):

- Results:
  - Pathogenic Single Nucleotide Variants and Small Insertions/Deletions:
    - ASXL1 NM_015338 c.1926_1927insT p.G642fs* - in 70.6% of 119 reads
    - **KIT NM_000222 c.2447A>T p.D816V - in 41.8% of 593 reads**
    - TET2 NM_001127208 c.2596C>T p.Q866* - in 45.4% of 1442 reads
    - TET2 NM_001127208 c.3765C>G p.Y1255* - in 46.7% of 302 reads

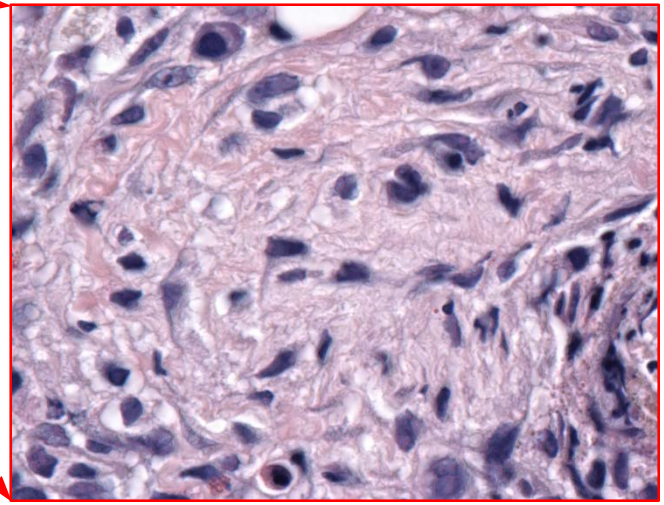
- Concurrent CBC-Diff:
  - WBC 6.7 K/uL
  - ANC 2.4 K/uL
  - AMC 2.5 K/uL (H)
  - HCT 35.7 % (L)
  - MCV 95.5 fL
  - PLT 138 K/uL (L)

Microscopic Findings: Bone Marrow Biopsy

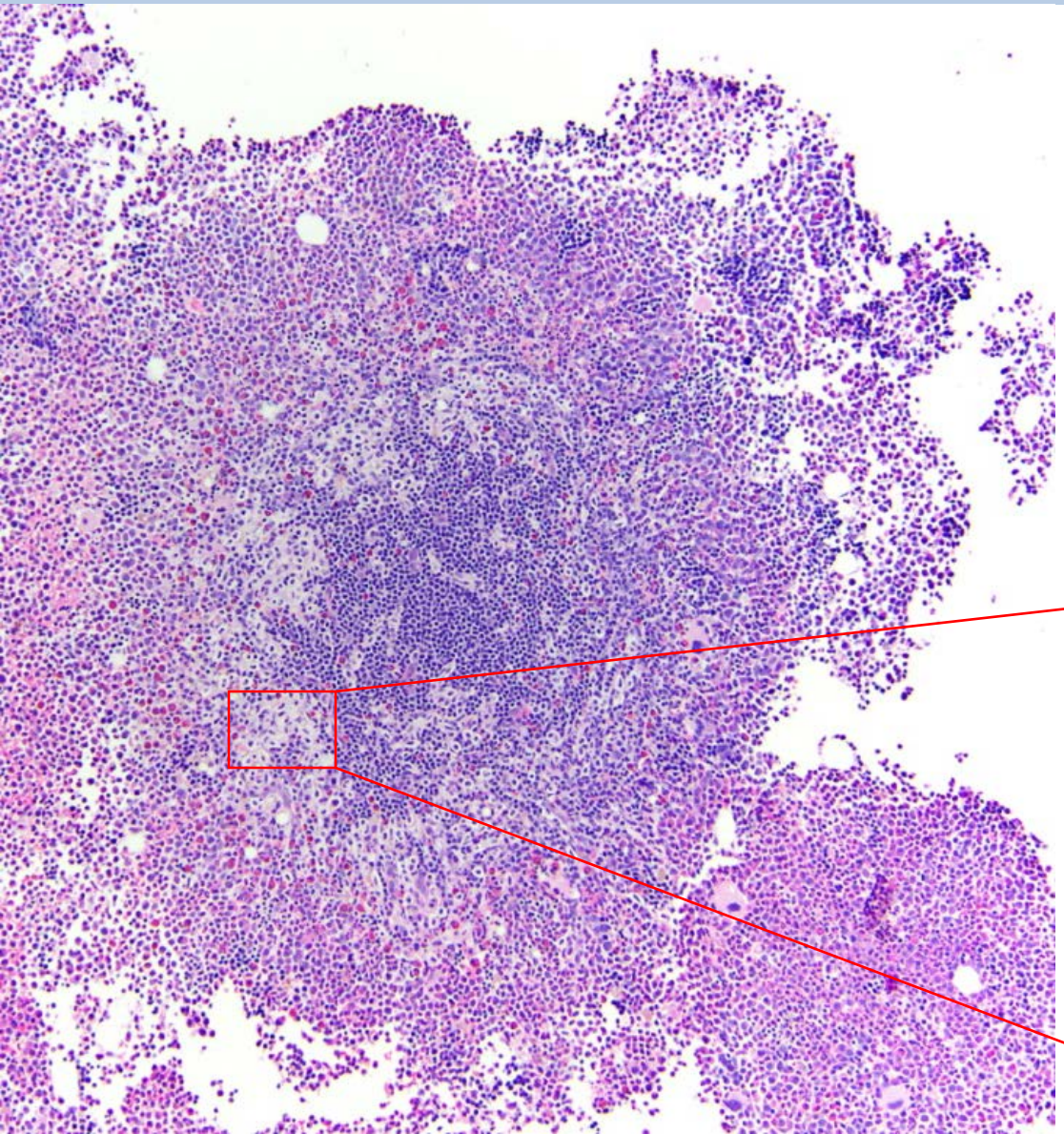


Deeper Levels:

- **Scattered fibrotic foci containing intermediate-sized cells with elongated nuclei, condensed chromatin, indistinct nucleoli and abundant pale cytoplasm with well-defined cell borders**

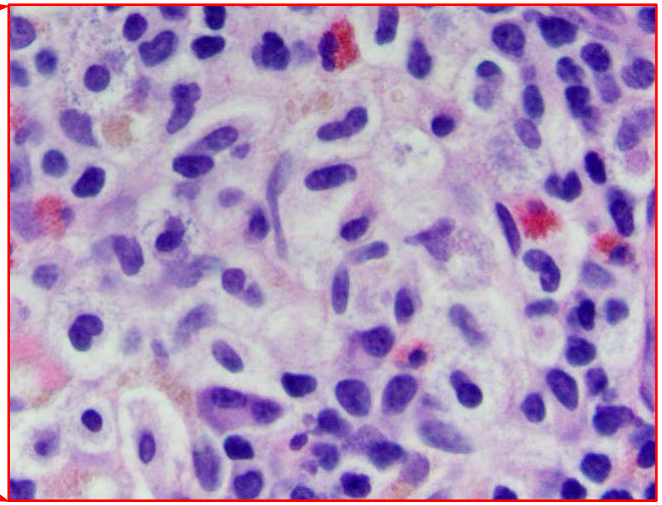


Microscopic Findings: Bone Marrow Clot Preparation

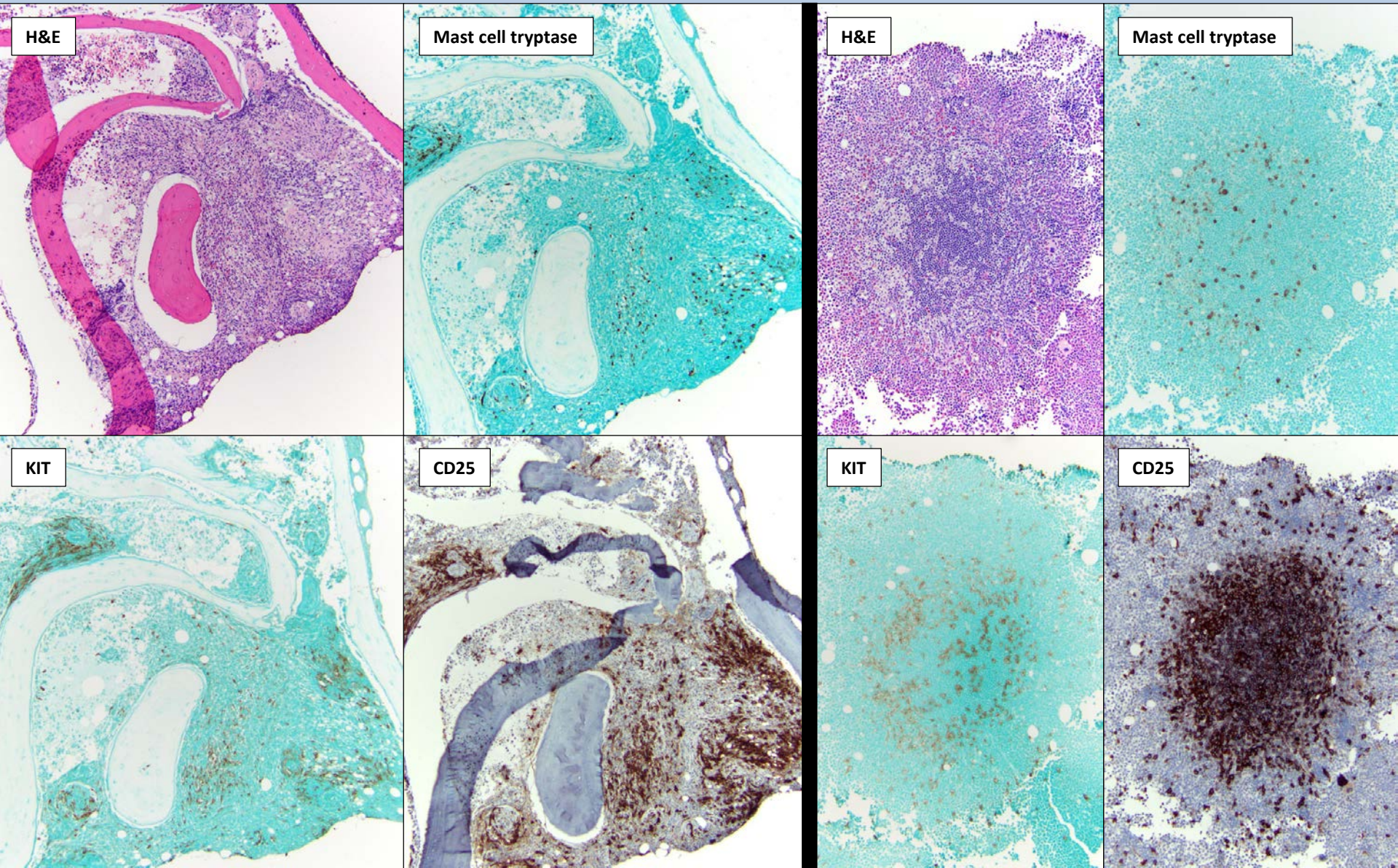


Deeper Levels:

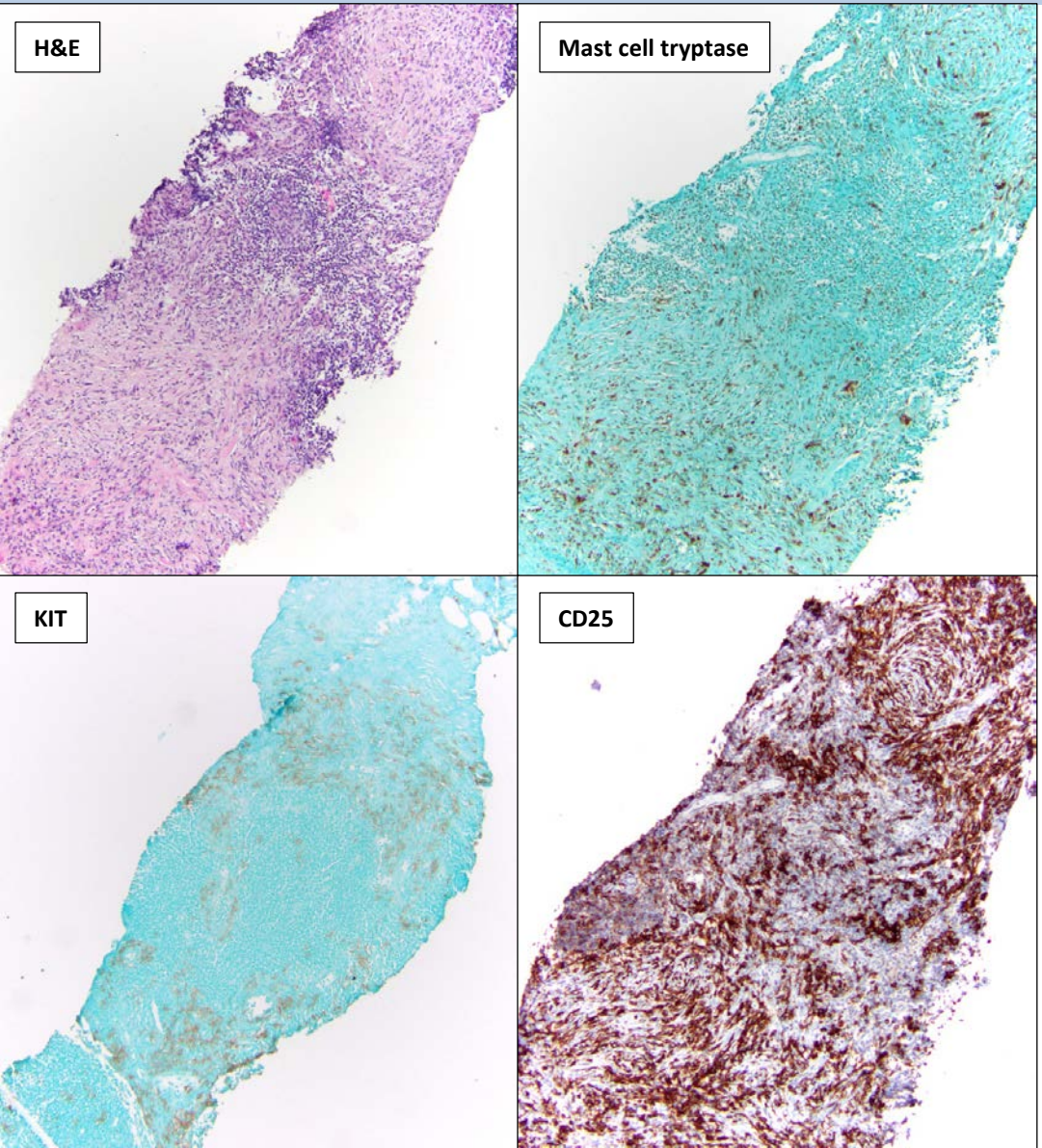
- **Large lymphoid aggregate surrounded by intermediate-sized cells with elongated nuclei, condensed chromatin, indistinct nucleoli and abundant pale cytoplasm with well-defined cell borders**



Immunohistochemistry: Bone Marrow Biopsy/Clot Prep



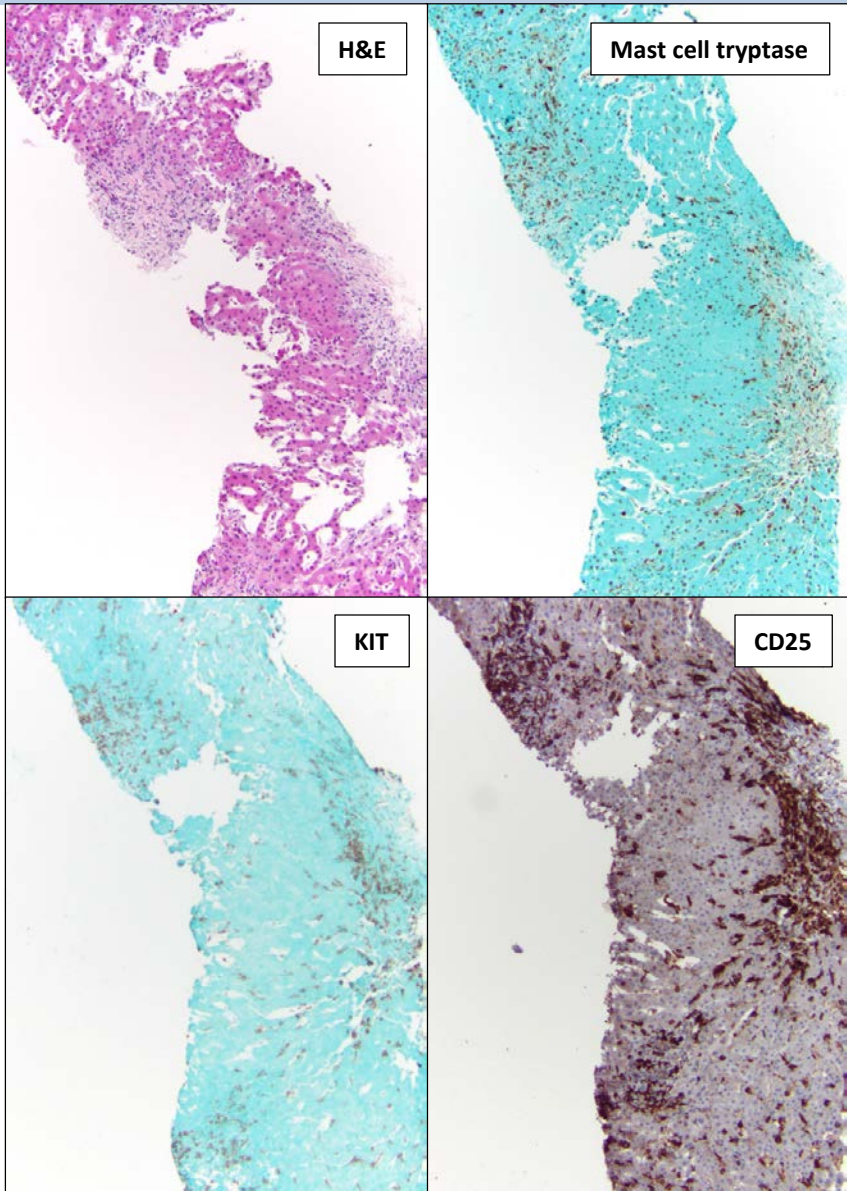
Lymph Node Core Biopsy



- Requested for additional evaluation of unexplained lymphadenopathy following bone marrow workup
- Outside Interpretation:
  - Flow cytometry: no abnormal T-cells, polyclonal B-cells
  - Histology: No evidence of lymphoproliferative disorder or malignancy
  - “Area of irregular fibrosis with bland spindle cells consistent with myofibroblasts”; “could be reactive in nature”
- Post-molecular interpretation:
  - SYSTEMIC MASTOCYTOSIS

Liver Core Biopsy

- Requested for additional evaluation of unexplained cholestatic liver injury and portal hypertension w/ varices & progressive ascites
- Hepatology workup: Negative serological evaluation (ANA, LKM, AMA, A1AT, IgG4, HepC, etc.)
- Outside Interpretation:
  - Chronic biliary tract disease with prominent portal fibrous expansion, patchy mononuclear cell infiltrates and ductular reaction
  - No granulomas, bile duct inflammation or concentric periductular fibrosis
  - Differential: primary biliary cirrhosis vs. sclerosing cholangitis (2° to CMML?)
- Post-molecular interpretation:
  - SYSTEMIC MASTOCYTOSIS



Clinical Follow-Up

Patient: 72-year-old male, retired physician

- Unifying Diagnosis:
  - Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)
    - SM component: Aggressive systemic mastocytosis (ASM)
    - AHN component: Chronic myelomonocytic leukemia (CMML-0)
  - Serum tryptase level elevated at 88 ng/mL (ref. <11.5 ng/mL)
- Treatment:
  - Midostaurin:
    - Multi-kinase inhibitor capable of inhibiting KIT D816V
    - Effective in patients with advanced systemic mastocytosis
    - Initiated October 2016
  - Plan to delay CMML-directed therapy for as long as possible
- Outcome:
  - "Continuing to get better on a regular basis" per recent clinic note
    - Reduction in ascites and organomegaly
    - Improved appetite with intentional weight gain
    - Increased physical activity level

Diagnostic criteria for Systemic Mastocytosis

(2008 WHO Classification of tumors of hematopoietic and lymphoid tissues)

- **Requires the major criterion and 1 minor criterion OR ≥ 3 minor criteria**

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:

1. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology or, of all mast cells in bone marrow aspirate smears, >25% are immature or atypical mast cells.
2. Detection of an activating point mutation at codon 816 of *KIT* in bone marrow, blood or another extracutaneous organ.
3. Mast cells in bone marrow, blood or other extracutaneous organs express CD2 and/or CD25 in addition to normal mast cell markers.
4. Serum total tryptase persistently exceeds 20 ng/mL (unless there is an associated clonal myeloid disorder, in which case this parameter is not valid).

Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)

- **Diagnosis:**
  - Requires clear morphologic evidence of :

    (1) Systemic mastocytosis (not pure cutaneous mastocytosis)

    (2) An associated clonal hematologic non-MC lineage disease
    - Associated hematologic neoplasms (AHN) include:
      - Common: MDS, AML, MPN, MDS/MPN (typically CMML)
      - Rare: NHL, PCN
  - Morphology is heterogeneous and largely dependent on the type of AHN
  - May be difficult to establish in specimens where one component predominates
  - SM may be identified retrospectively following therapy for the AHN
  - 2nd most common subtype of SM (after indolent systemic mastocytosis)
  - True incidence is likely underestimated

Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN)

- **Clinical:**
  - Presentation and course generally dominated by the AHN
  - Major exception is aggressive systemic mastocytosis, characterized by high disease burden with organomegaly and organ dysfunction
- **Genetics:**
  - *KIT* mutations, especially KIT D816V, present within the MC component of the majority of SM-AHN
  - *KIT* mutations variably present in the non-mast cell component of SM-AHN (CMML > AML > MPN > LPD)
  - KIT D816V thought to function as a “differentiation inducer” or “phenotype modulator”, rather than as a strong oncogenic driver
- **Differential Diagnosis:**
  - Non-mast cell myelogenous tumors with signs of mast cell differentiation
    - Tryptase-positive AML
    - Myelomastocytic leukemia

KIT mutations in systemic mastocytosis & other hematopoietic malignancies

- **Systemic mastocytosis (all subtypes):**
  - >90% of cases possess gain-of-function mutations in the *KIT* proto-oncogene
    - Result in stem cell factor-independent activation of KIT
    - Vast majority are somatic
    - Rare germline mutations associated with familial mastocytosis
    - Majority cluster in exons 11 and 17
    - Mutations in exons 8, 9, and 10 encountered infrequently
  - Hallmark D816V mutation is seen in >80% of cases
    - Affects the second intracellular tyrosine kinase domain (exon 17)
    - D816V is resistant to imatinib
    - Responsive to other kinase inhibitors (e.g. midostaurin)
  - Postulated cell of origin is a pluripotent CD34+ hematopoietic progenitor cell
    - KIT mutations may be confined to mast cells or present within additional hematopoietic lineages

KIT mutations in systemic mastocytosis & other hematopoietic malignancies

- **Other hematopoietic malignancies:**
  - *KIT* mutations are also seen in AML with t(8;21) or inv(16)
    - 20% of core-binding factor AML
    - Impart poor prognosis
  - *KIT* mutations are rarely reported in other myeloid malignancies (<5%)
    - e.g. MDS, MPN, other acute leukemias
    - Often viewed as a marker of molecular progression
    - Unknown how frequently such mutations represent undetected involvement by systemic mastocytosis

Case Considerations

- **PROPOSAL #1:**

  KIT mutation analysis should be included in the molecular diagnostic workup of all newly diagnosed myeloid neoplasms, in part to assist with the recognition of otherwise unsuspected/undetected systemic mastocytosis.

- **PROPOSAL #2:**

  Additional testing for systemic mastocytosis should be performed in all patients with newly diagnosed myeloid neoplasms harboring *KIT* mutations (e.g. IHC panel, serum tryptase measurement).

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Panel Diagnosis:

Systemic Mastocytosis with an Associated Hematologic Neoplasm
(Chronic Myelomonocytic Leukemia-0)

Acknowledgements:

Afshin Shameli, M.D.

Geraldine Pinkus, M.D.

Jason Hornick, M.D., Ph.D.