

SS-05 National Societies: Wolf in sheep's clothing or vice versa?

## Case presentation #4

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# Case presentation

- A 61-year-old male
- UC for Abdominal Surgery: for splenectomy
- 1 month before:
  - Incidentally diagnosed splenic tumor during routine US examination because of ill-defined abdominal discomfort.
  - CT: focal 42mm hypodense lesion with peripheral postcontrast signal. Interpreted as SECONDARY NEOPLASM (DDx: Primary splenic neoplasm can not be excluded)
  - Physical examination: No symptoms or signs of interest, except PRODUCTIVE CAUGH ( CT Thorax: negative)
  - Gastrointestinal Endoscopy: negative

- Laboratory findings:
  - Conjugated bilirubin 7,25 (Ref. up to 6,8)
  - Globulins 25,1 (Ref. 27-35)
  - Tumor markers (CA 72-4, CEA, CA 19-9, CA125) :  
negative
  - Hemogram and coagulation status: Ref. ranges
  - Enzymes and metabolites: Ref. ranges
- Medical history: None of interest

# Case presentation

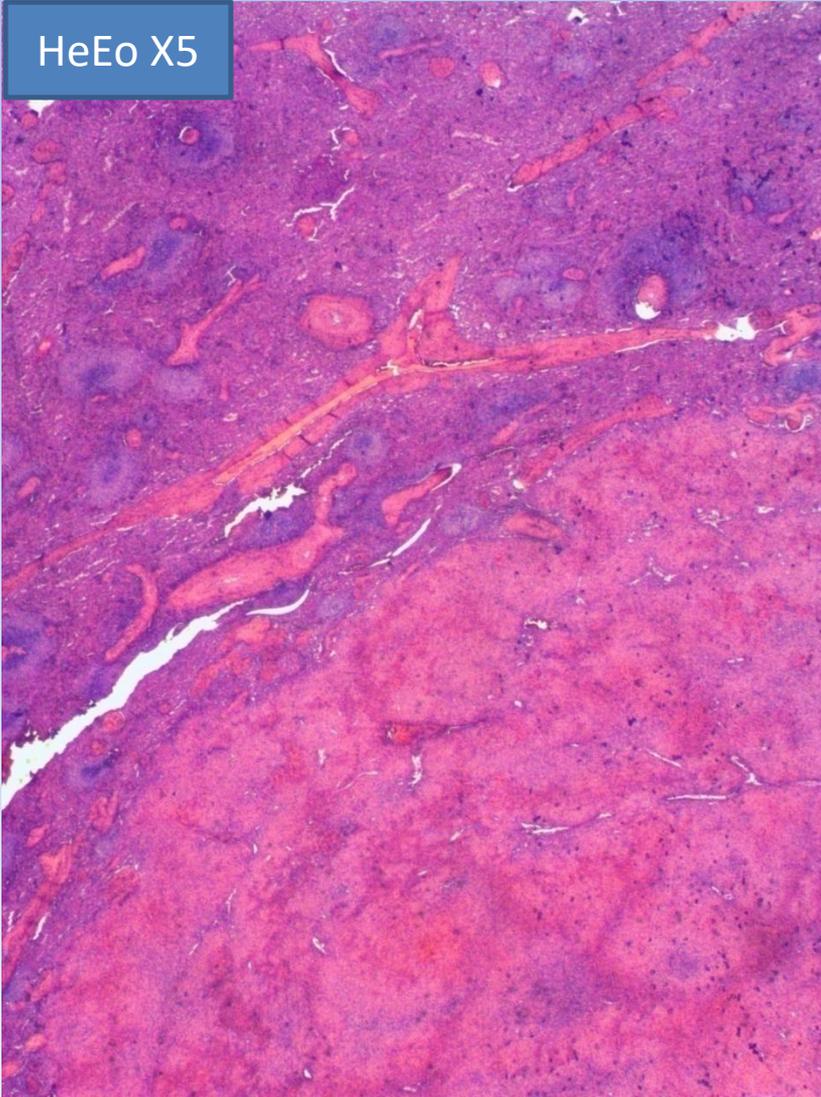
- Macroscopic examination:
  - Spleen 225 g (11x9,5x4,5 cm)
  - Cut surfaces:
    - well demarcated solid greyish-livid tumor; 3,5x3x3 cm
    - Surrounding splenic tissue unremarkable



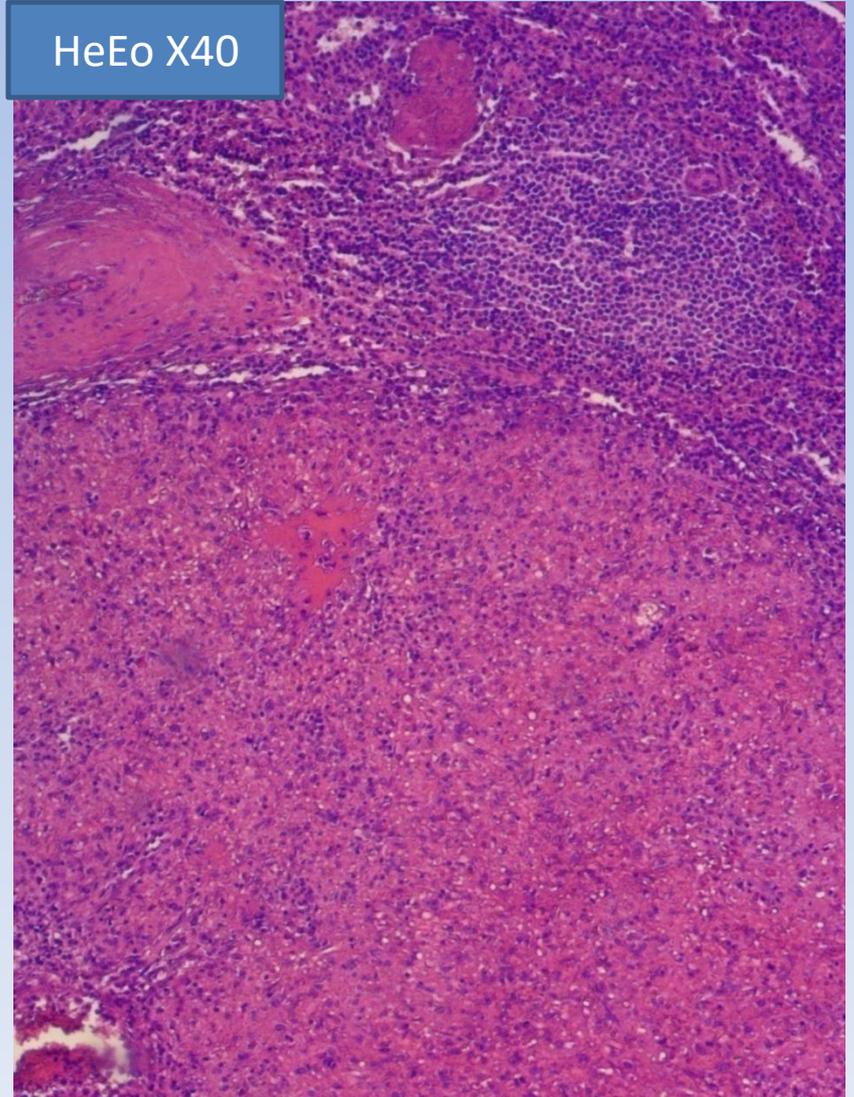
# Case presentation

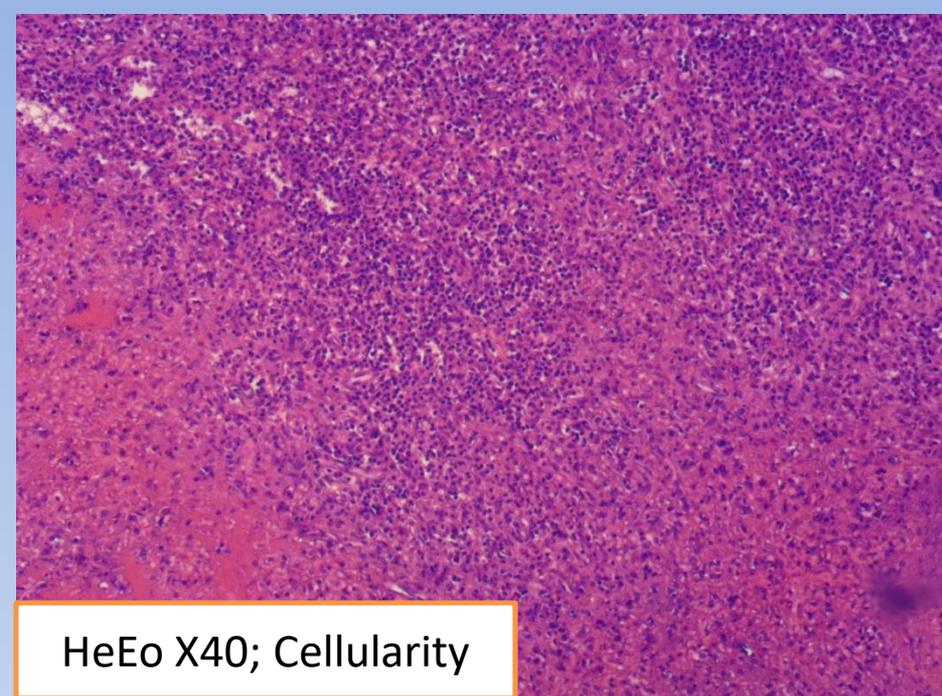
- Microscopic examination

HeEo X5

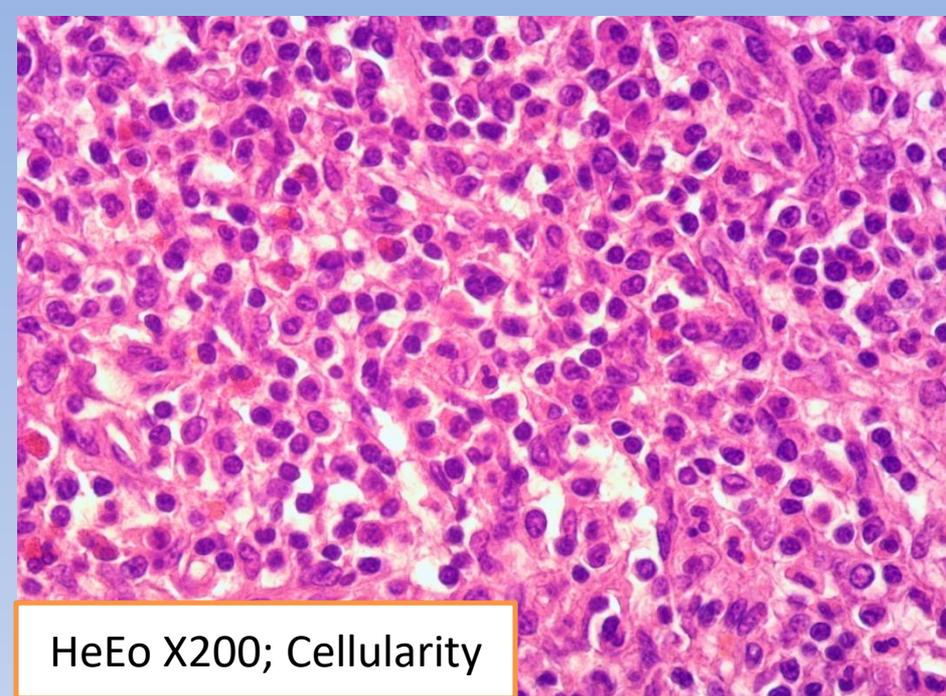


HeEo X40

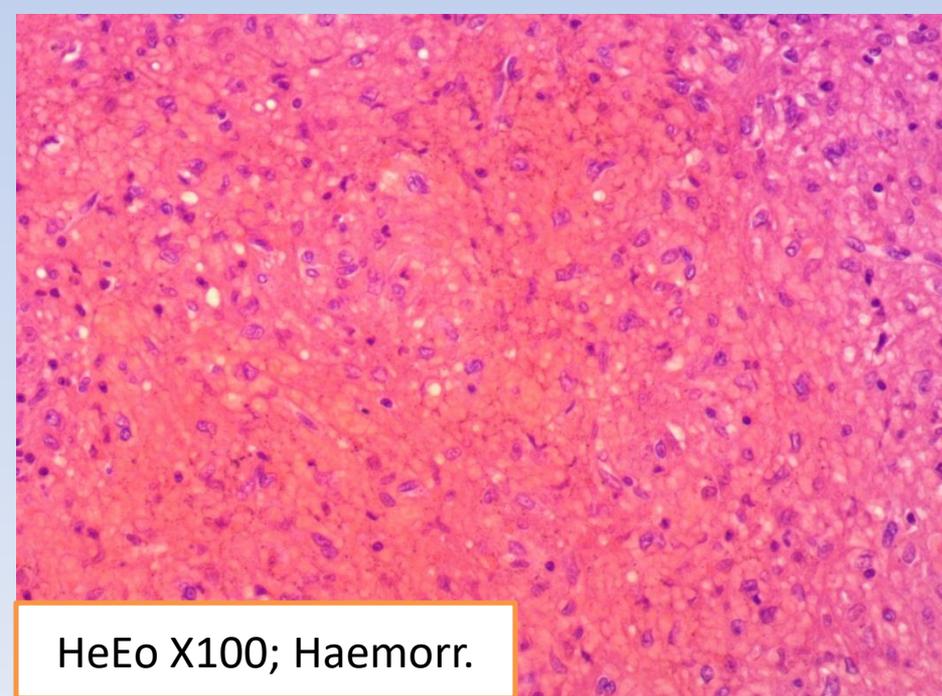




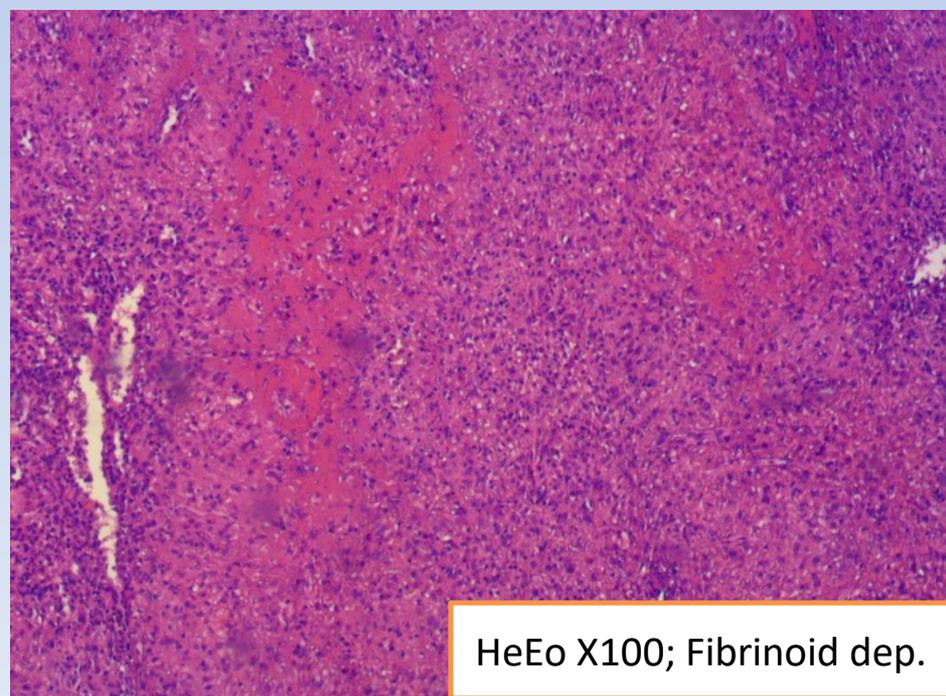
HeEo X40; Cellularity



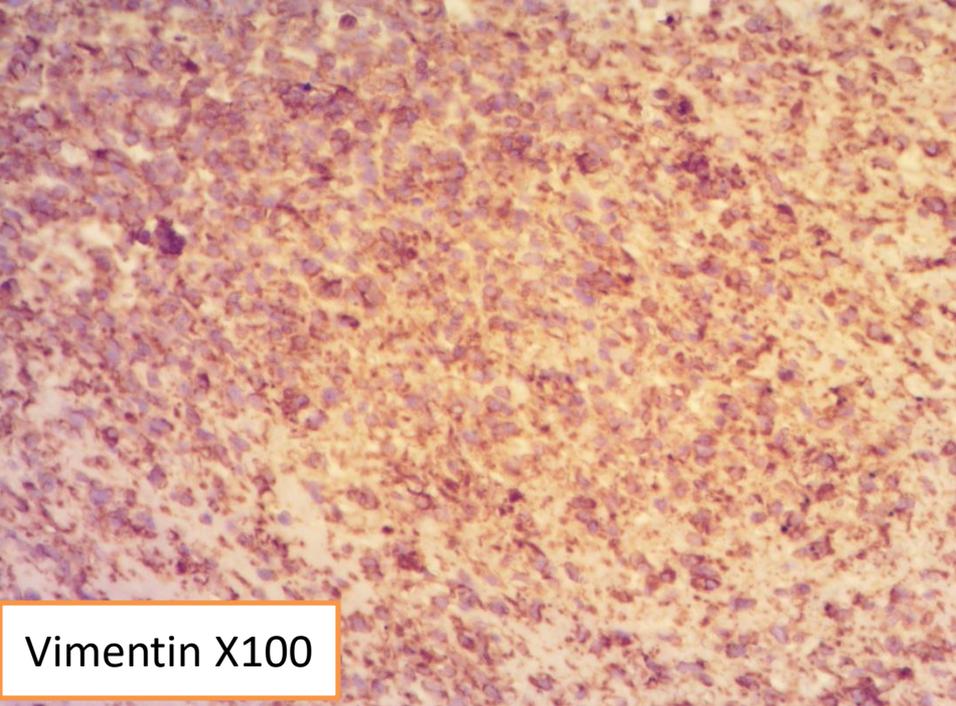
HeEo X200; Cellularity



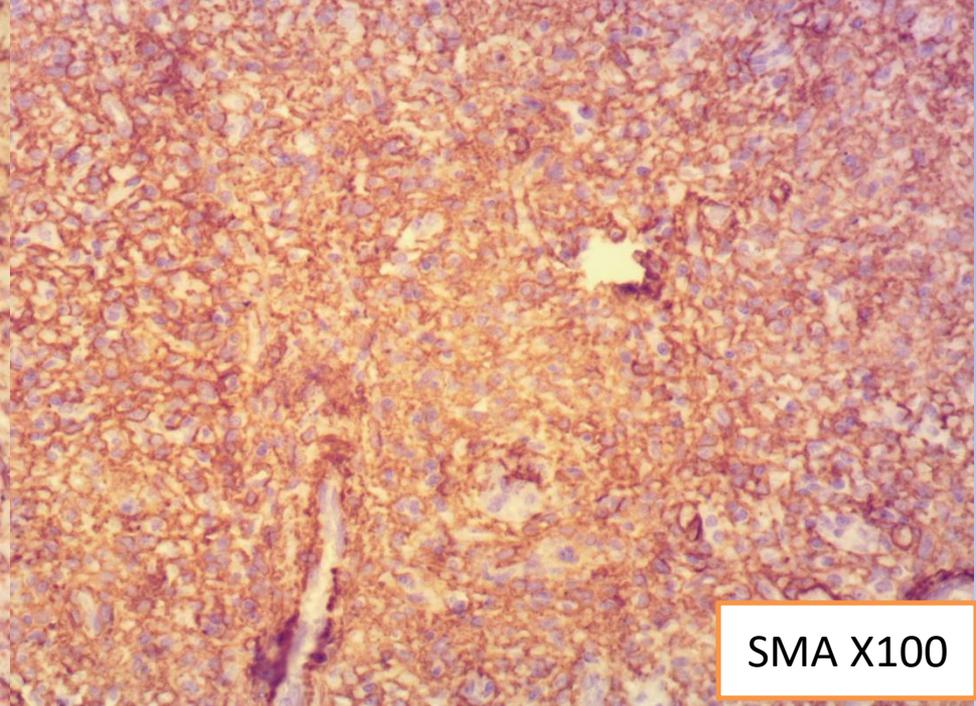
HeEo X100; Haemorr.



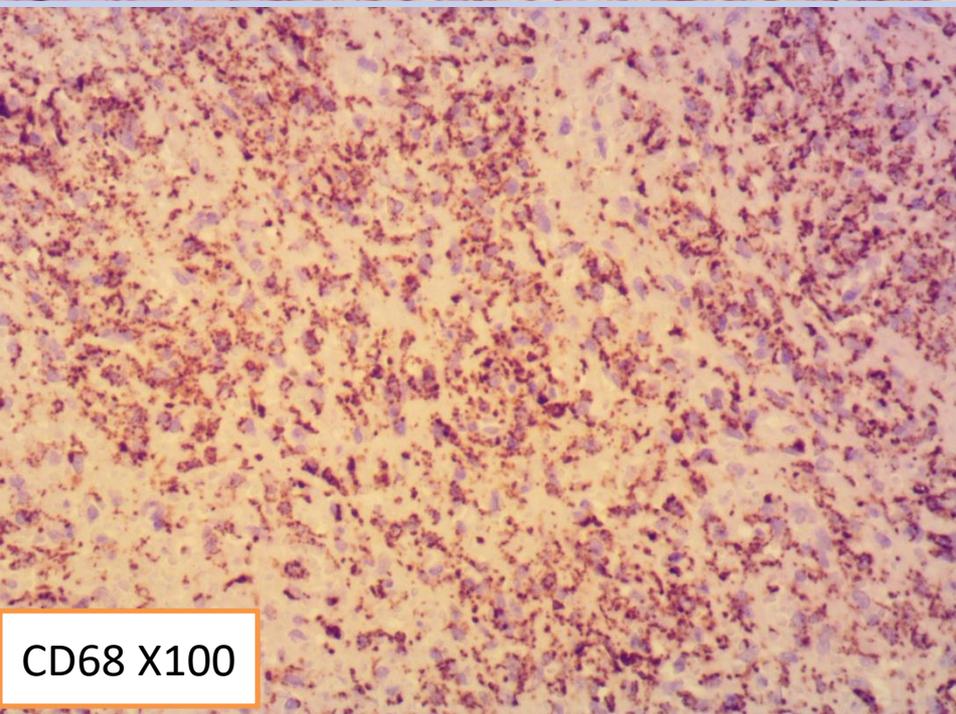
HeEo X100; Fibrinoid dep.



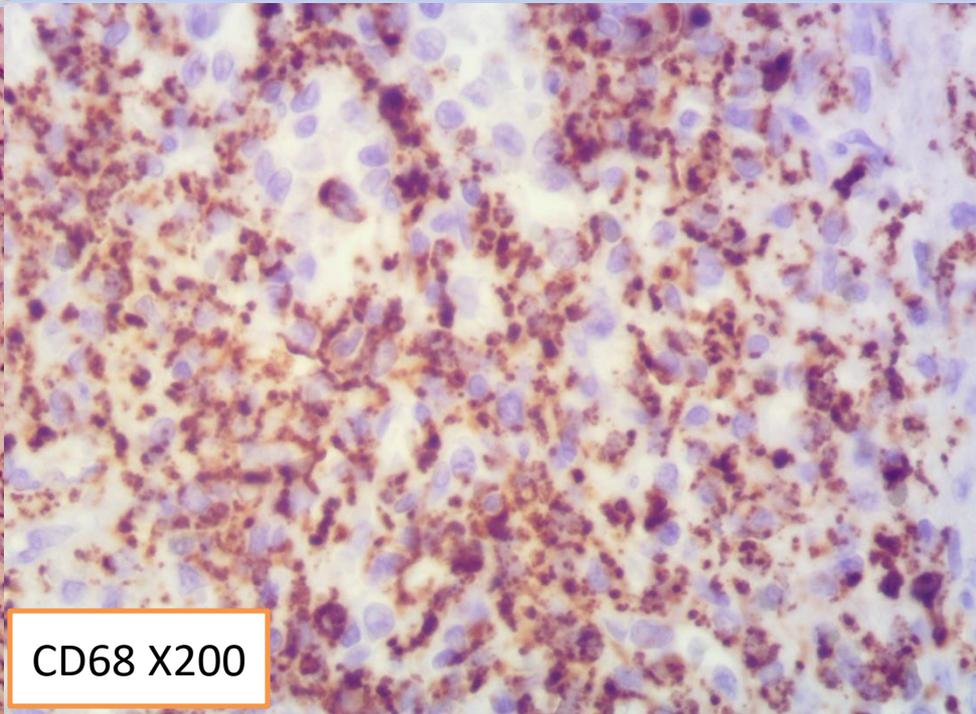
Vimentin X100



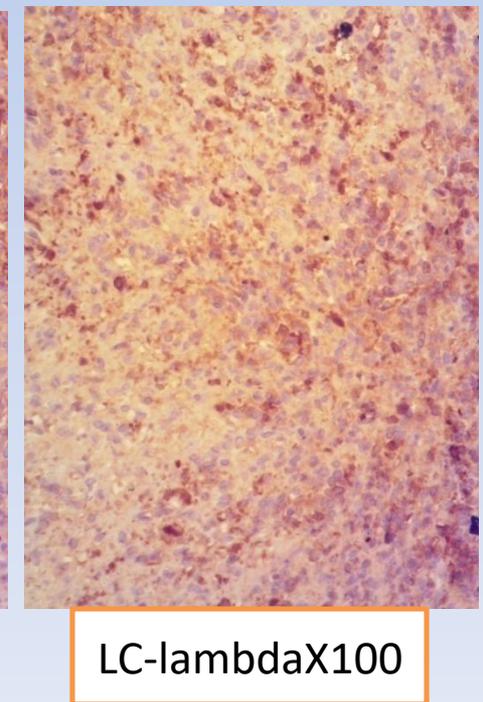
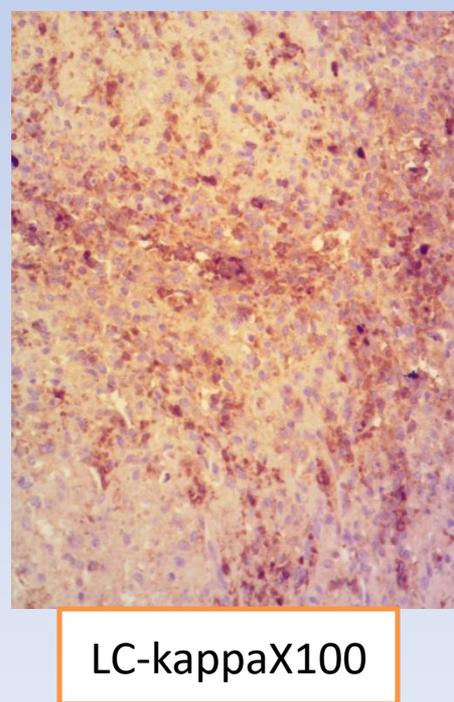
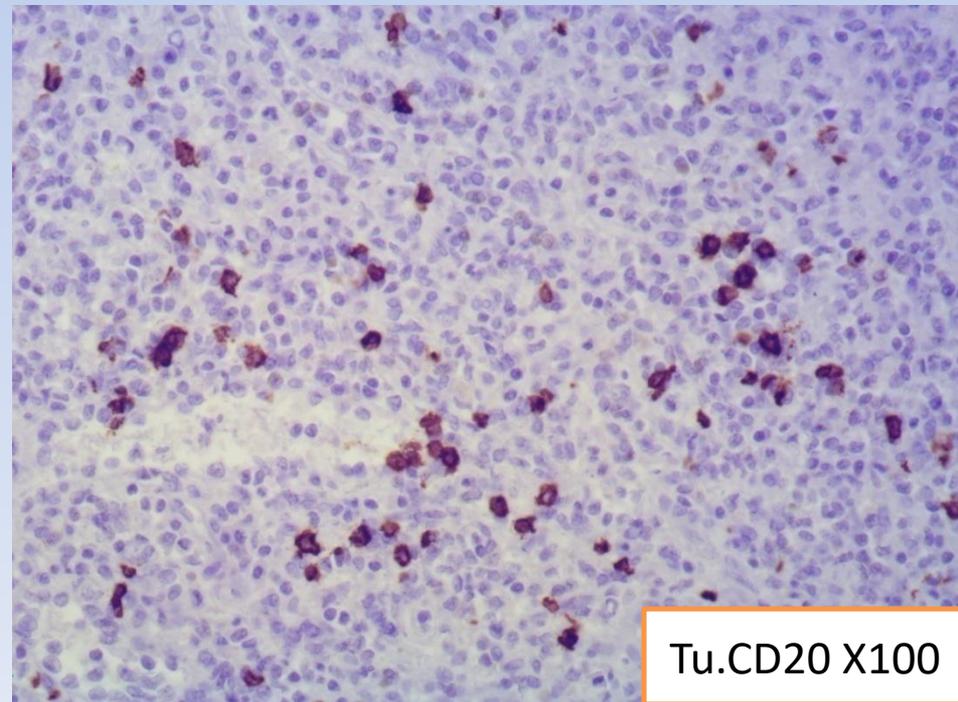
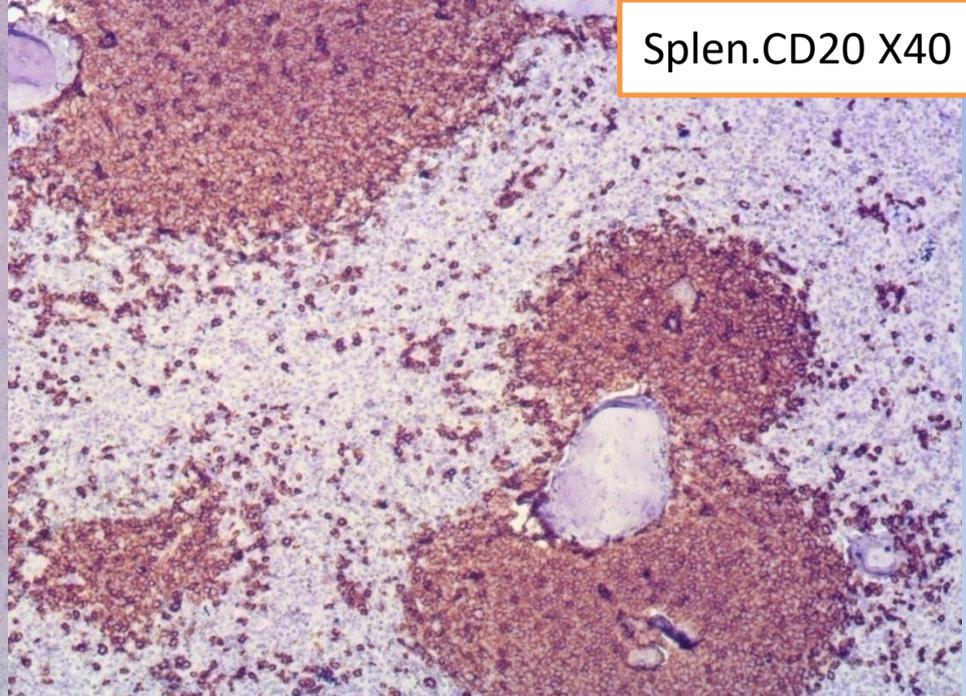
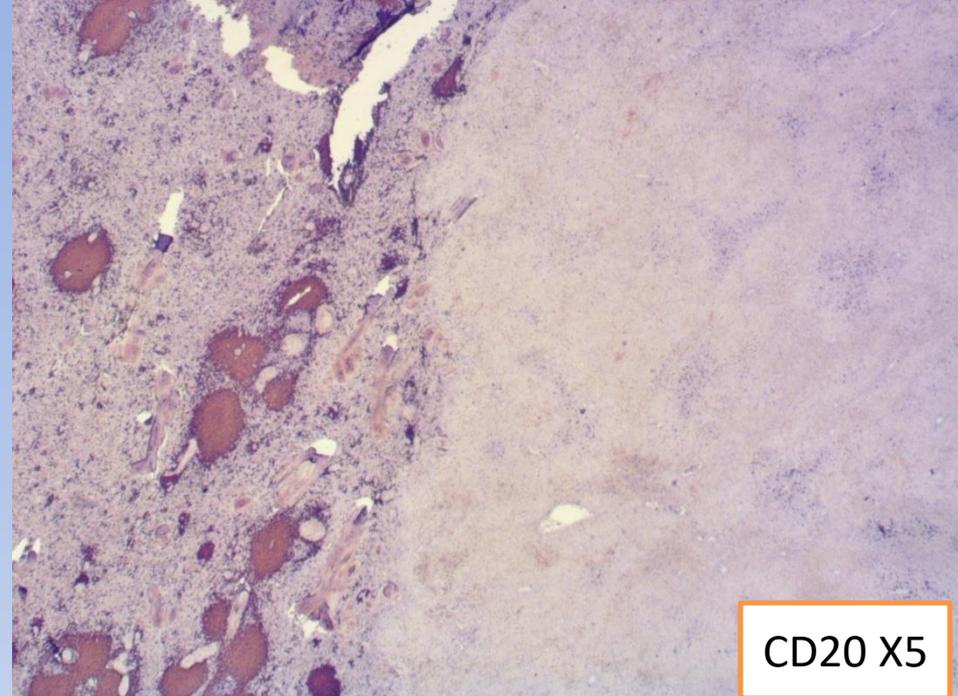
SMA X100

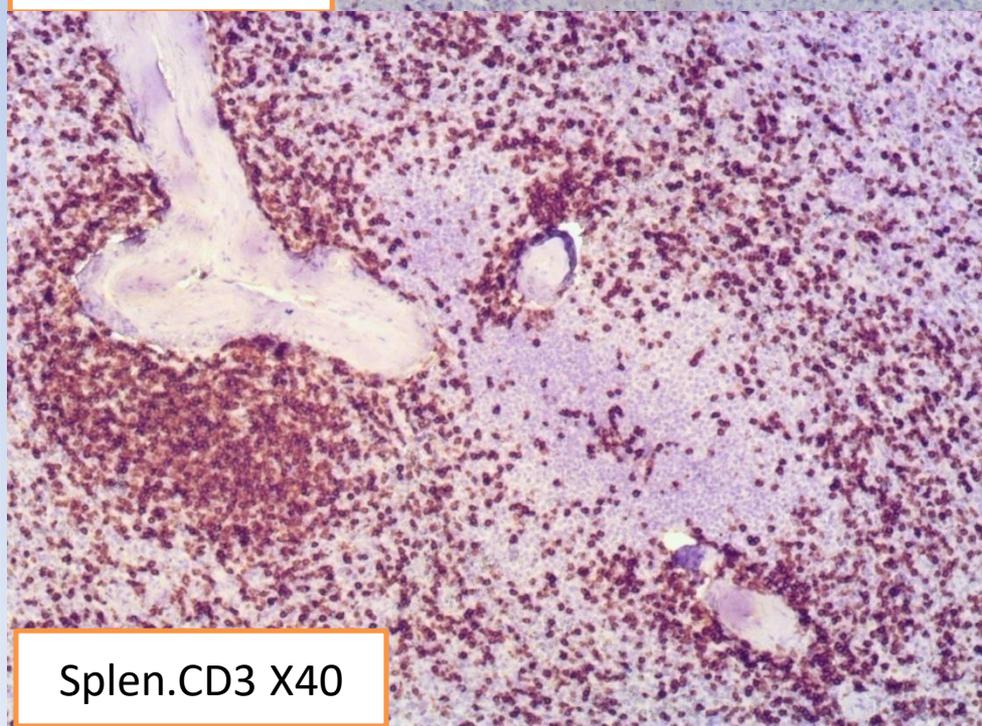
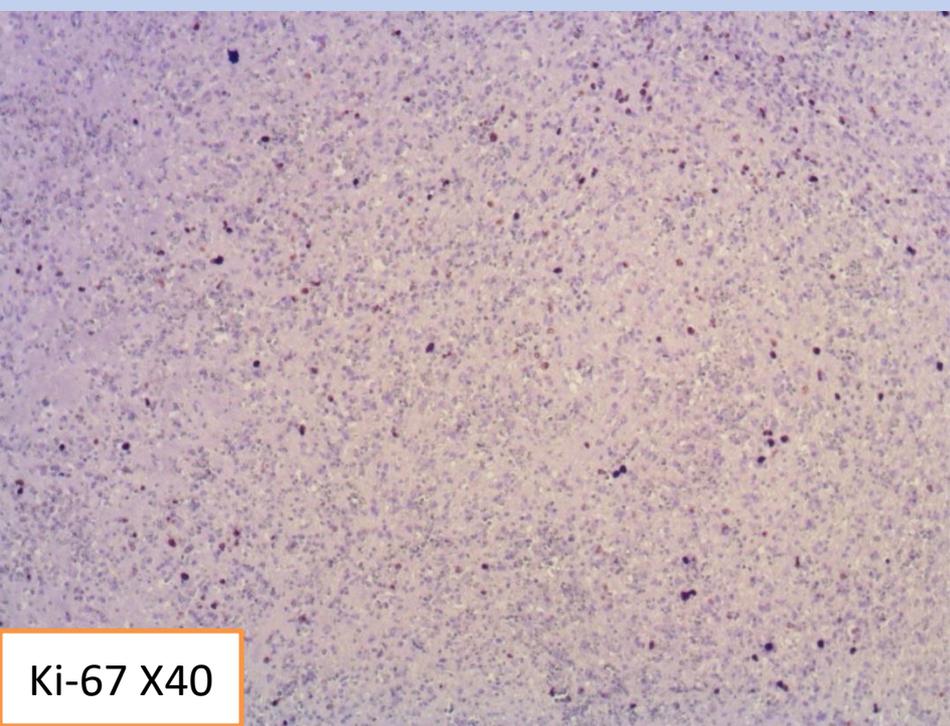
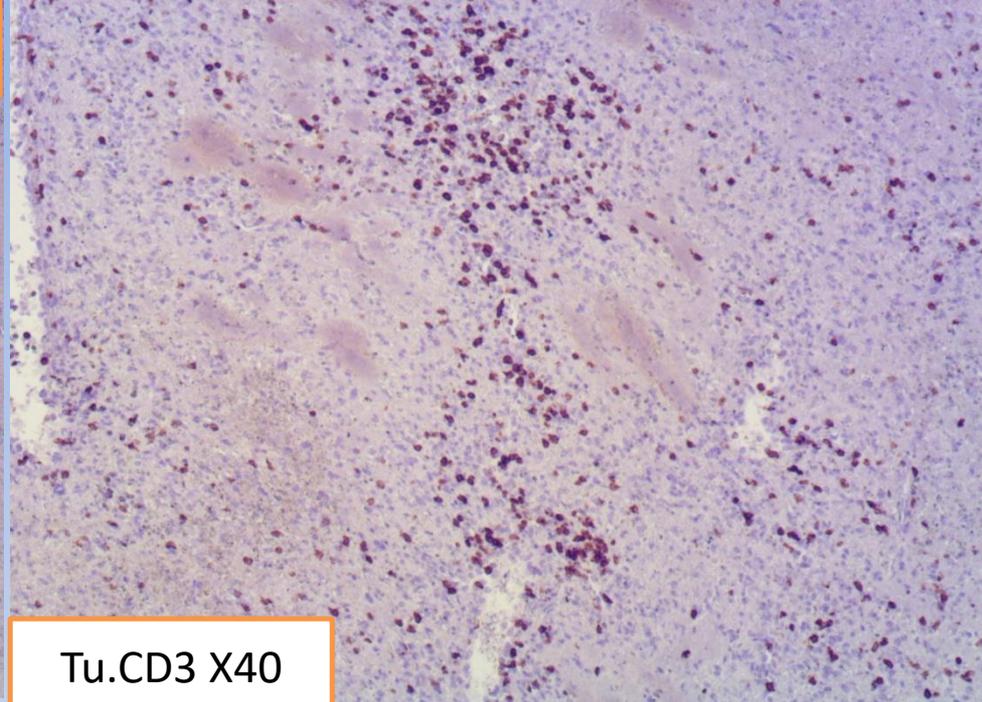
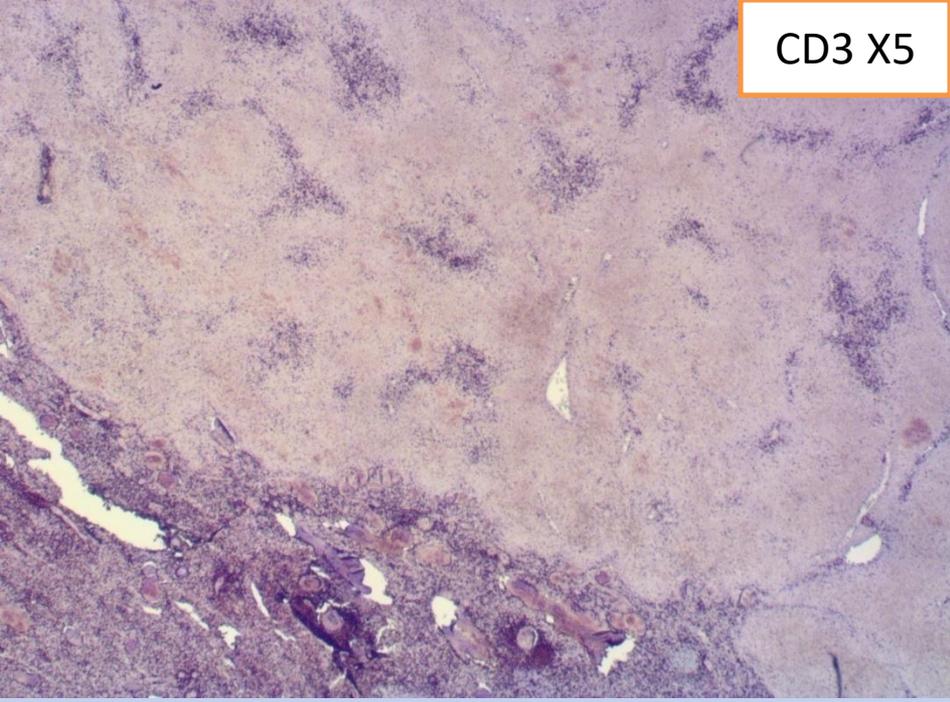


CD68 X100



CD68 X200





# Case presentation

- Negative stains
  - Crystal violet
  - Congo red
  - Ziehl-Neelsen
  - EBV
  - HHV8
  - ALK1
- Additional tests
  - EBER: not performed
  - NGS - Miseq DX (TruSight Tumor 15: AKT1, BRAF, EGFR, ERBB2, FOXL2, GNA11, GNAQ, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, RET, TP53):
    - **TP53** (c.215C>G; p.Pro72Arg) polymorphism
    - Low confidence missense SNVs
      - **AKT1**: c.73C>T, **highly pathogenic** but only 1,6% variant fraction;
      - **ERBB2**: c.2024C>T, **potentially pathogenic**, 1,26% variant fraction;
      - **ERBB2**: c.1957C>T, **potentially pathogenic**, 1,09% variant fraction;
      - **ERBB2**: c.1972C>T, **potentially pathogenic**, 1,49% variant fraction;
      - **TP53**: c.917G>A, **potentially pathogenic**, 1,3% variant fraction)

# Histopathological diagnosis

- *Inflammatory Myofibroblastic Tumor  
(Inflammatory Pseudotumor of spleen)*
- In the postoperative follow-up (11,5 months) the patient has uneventful recovery.

# Discussion

- IMT/IPT is a rare tumor/pseudotumor of unknown origin
- Rare; < 150 cases reported in adults in spleen; < 10 cases in children
- More common in women
- Associated with fever of unknown origin, splenomegaly **or an incidental finding**
- Actual pathogenesis unknown
- Possible factors include **bacterial infection, neoplastic processes, immunological derangement (Some cases are EBV+ )**
- May present with B symptoms including weight loss, fever and abdominal pain

# Discussion

- **DDx:**
  - **Splenic hamartoma:** Splenic hamartoma is composed exclusively of **red pulp elements**. It lacks follicles or fibrous trabeculae.
  - **Follicular dendritic cell tumor:** SMA -; CD21+, CD35+
  - **Mycobacterial infection in immunocompromised patients:** spindle cells form nodules in red pulp, spindle cells are **CD68+**, contain **acid fast bacilli in cytoplasm**

# Discussion

- IMT vs. IPT
  - Opposing IPT: none of the usually reported conditions associated with IPT (i.e. IBD, Chronic bacterial infection, Immunologic disturbances, Malignant neoplasms, Previous abdominal surgery, Ventriculoperitoneal shunt, Irradiation, Corticosteroids, etc.)
  - Probably IMT? but ALK- and unknown EBER status (although EBV negative)

NOW... Re-call “**AKT1: c.73C>T, highly pathogenic 1,6% variant fraction**”?

# Ready or Not, Here I Come: Inflammatory Myofibroblastic Tumors With Kinase Alterations Revealed Through Molecular Hide and Seek

Kurtis D. Davies, PhD,<sup>a</sup> Victor M. Villalobos, MD, PhD,<sup>b</sup> Dara L. Aisner, MD, PhD<sup>a,\*</sup>

In this issue of the *Journal of Thoracic Oncology*, Chang et al<sup>1</sup> report findings from their study that sought to characterize the prevalence and mechanisms of kinase activation in thoracic inflammatory myofibroblastic tumor (IMT) samples. They used several distinct molecular testing approaches to query for variants in 33 IMT patient samples, a relatively large cohort when considering the rarity of the disease. Remarkably, all 33 samples showed genetic or altered transcriptional activation of one of four different receptor tyrosine kinases (RTKs): ALK receptor tyrosine kinase (*ALK*), *ROS1*, ret proto-oncogene (*RET*), or neurotrophic receptor tyrosine kinase 3 (*NTRK3*). This study has significant implications for our understanding of IMT at the genetic level, and it establishes exciting possibilities for clinical management of the disease. In addition, it highlights important considerations for molecular testing paradigms that have become increasingly critical for the clinical management of many different types of cancer.

IMTs occur predominantly in younger populations and can appear in any anatomic site with a predilection to arising in thorax and abdomen. They have an intermediate biology risk due to their high rates of local

alternative transcription initiation (ATI) variant that has been observed in roughly 11% of melanoma samples and less frequently in other cancer types.<sup>5</sup> The remaining samples were positive for either *RET*, *ROS1*, or *NTRK3* rearrangement/fusion (3.0%, 18.2%, and 9.1% of the cohort, respectively). *ALK*, *ROS1*, *RET*, and *NTRK3* fusion events are all well-described oncogenic drivers of NSCLC (and all have been observed in other cancer types as well). The *ALK* ATI event has also been described in NSCLC, but to date has not been extensively studied. As was observed in this IMT cohort, fusion events in NSCLC tend to exist exclusively of each other (and, in the case of NSCLC, exclusive of other known drivers such as mutations in *EGFR*, *KRAS*, and *BRAF*). However, in contrast to NSCLC, for which the combined prevalence of these fusions is roughly 10% or less, 100% of the IMT cases in this study were positive for kinase activation via rearrangement/fusion or ATI. Thus, it appears from this and other studies (including the finding of platelet derived growth factor receptor beta [*PDGFRB*] fusion in IMT) that IMT may be largely defined at the molecular level by RTK activation.<sup>6</sup> The finding that a diagnostic entity that is morphologically diverse yet classically determined by

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Disclosure: Dr. Davies has received personal fees from ArcherDx. Dr. Villalobos serves on advisory boards with Abbvie, Lilly, Janssen, Epizyme, Agios, Ignyta, and Nanocarrier. Dr. Aisner has received personal fees from Bayer Oncology, Genentech, AbbVie, and Bristol-Myers Squibb.

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# Take - home message

- Although the incidence of splenic IPT/IMT is low, awareness of its existence is necessary, since their occurrence can sometimes lead to serious complications and may pose a DDx problem.
- The prognosis is favorable following splenectomy.
- Careful microscopic examination of the specimen is mandatory, including additional tests, due to possible misdiagnosis.
- Comprehensive research is needed including larger number of genes on retrospective cases that have proven to be malignant or benign during follow up.

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**Merci beaucoup**