Myeloproliferative disorder, ET-like, associated with germline *SH2B3* mutation

Case SH2017-0042

Society for Hematopathology/European Association for Hematopathology 2017

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Case Summary

Family History/background

- Eastern European Ashkenazi Jewish background
- Older brother with many similar medical conditions

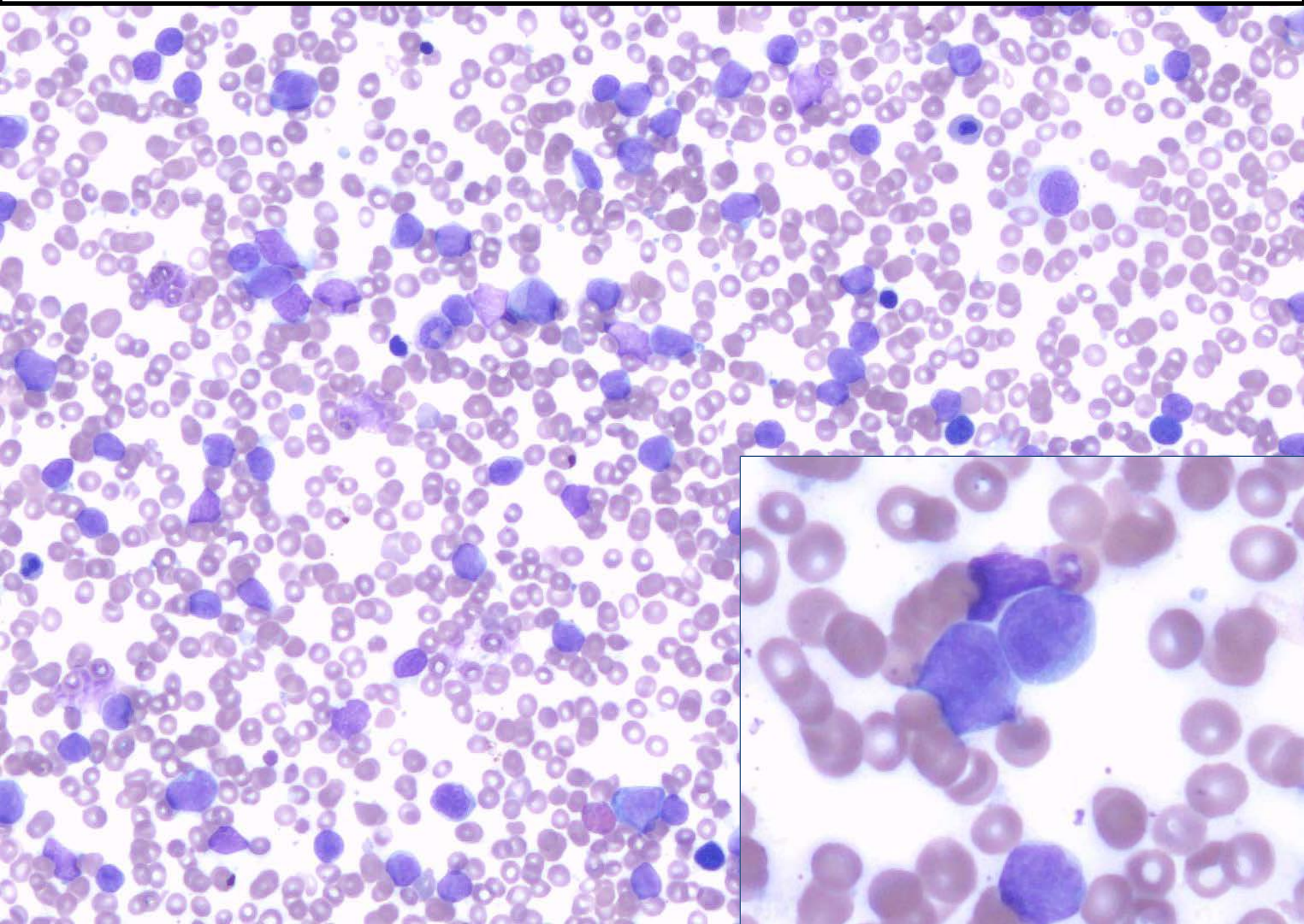
Chronic medical conditions from birth:

- Small for gestational age
- Mild developmental/growth delay
- Hepatitis (autoimmune)
- **Progressive Splenomegaly**

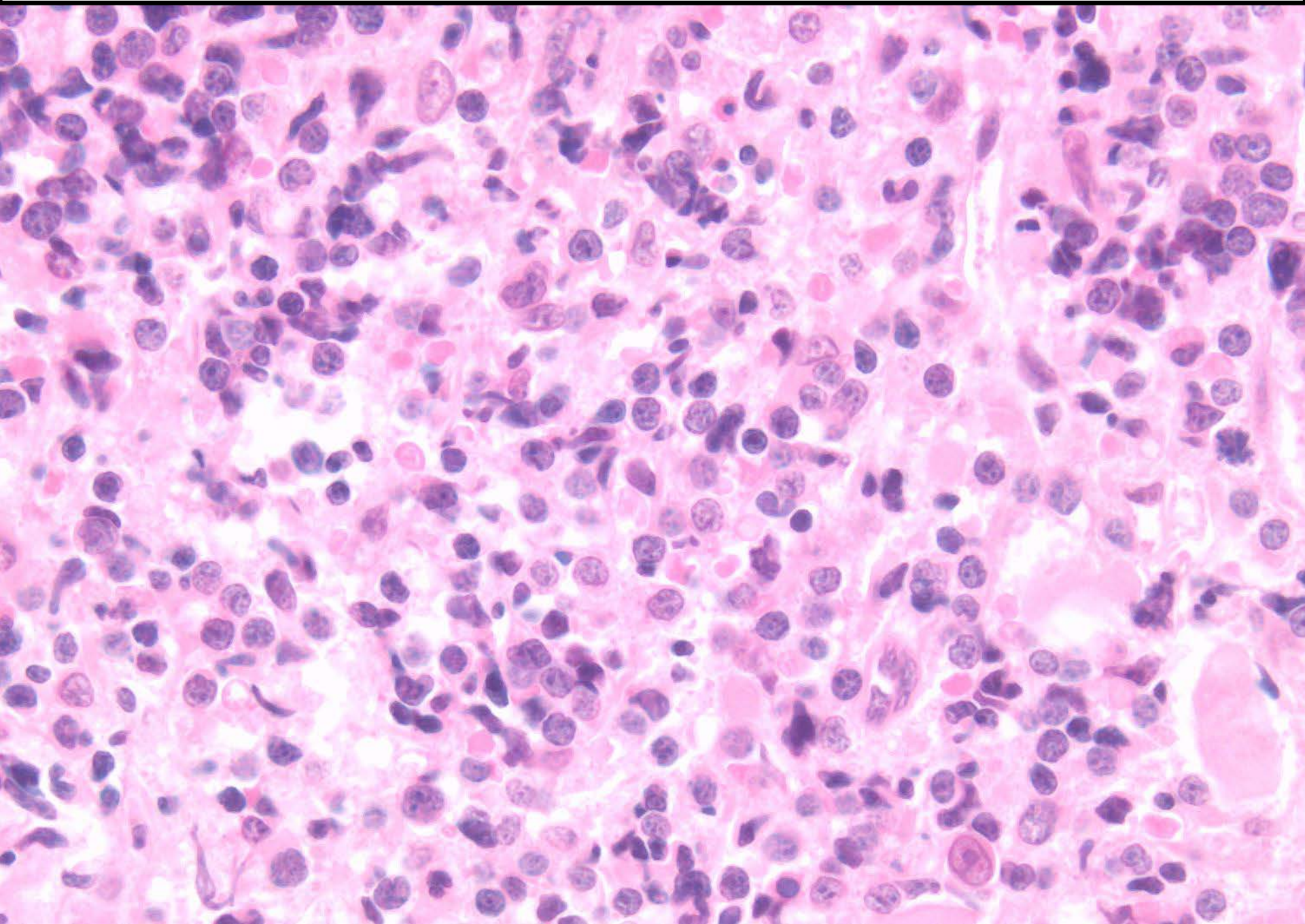
1 year of age:

- Irritability, fever, decreased PO intake
- Abnormal CBC:
  - WBC: 5, Hgb 5.5, Plt 55
- Bone marrow biopsy:

B-ALL, Bone marrow aspirate and biopsy



B-ALL, Bone marrow aspirate and biopsy



Case Summary

B-ALL:

- Flow cytometry immunophenotype:
  - TdT, CD45(dim), HLA DR, CD38, CD34, CD19, CD10, CD22(dim)
- Cytogenetics: 46,XX
- FISH: *CDKN2A* deletion in 42.6% of cells
- *Targeted mutational studies (NGS) were not performed

Treatment and Course:

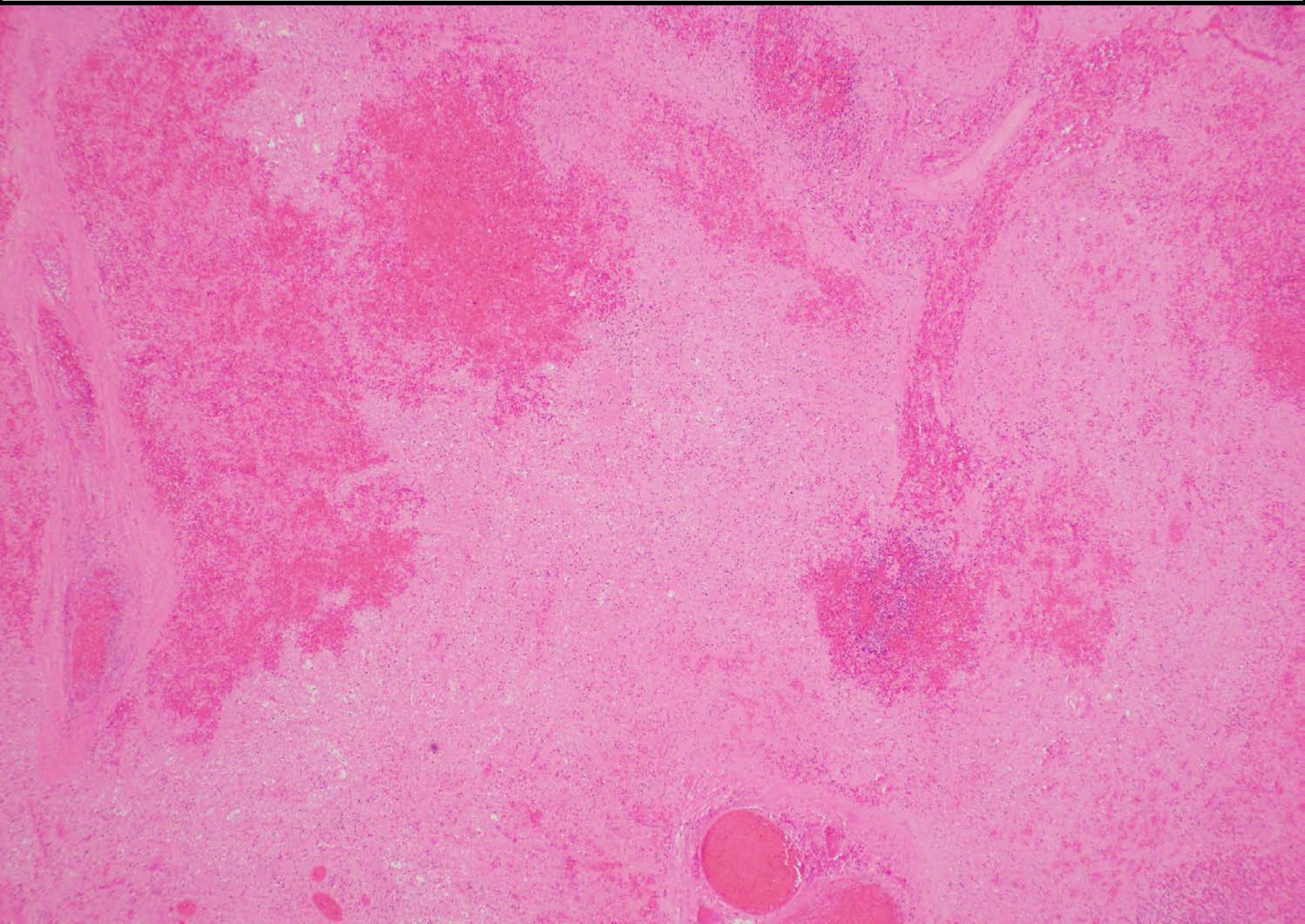
- Initial classification: Standard Risk
- Treated according to DFCI Consortium 05-001 Protocol
- Remains in complete remission up to present day

Case Summary

6 years of age:

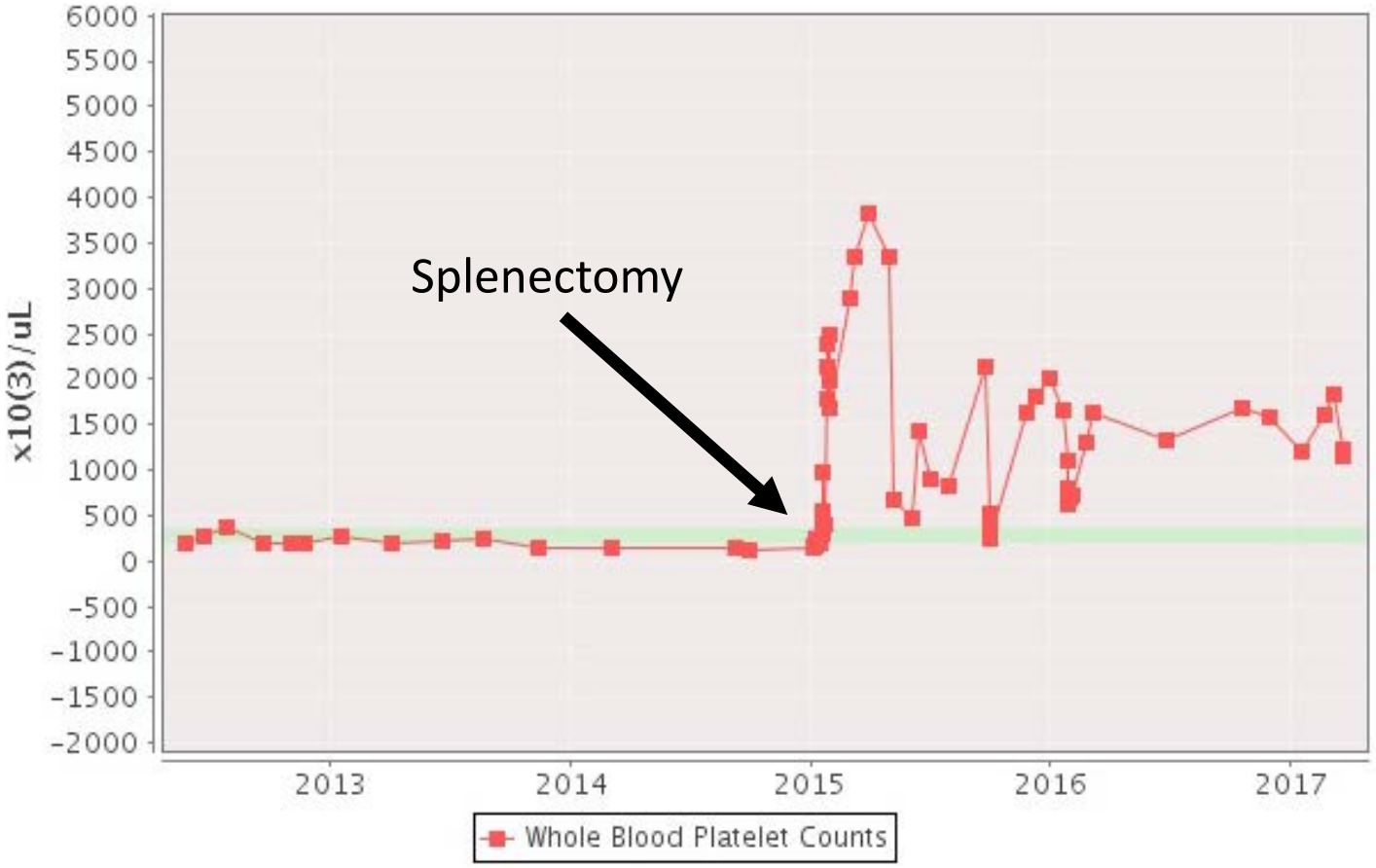
- Progressive splenomegaly (from birth) reached **30 cm** in size, required intervention:
  - Embolization:
    → complicated by multiple thromboses
  - Emergency splenectomy:

Spleen

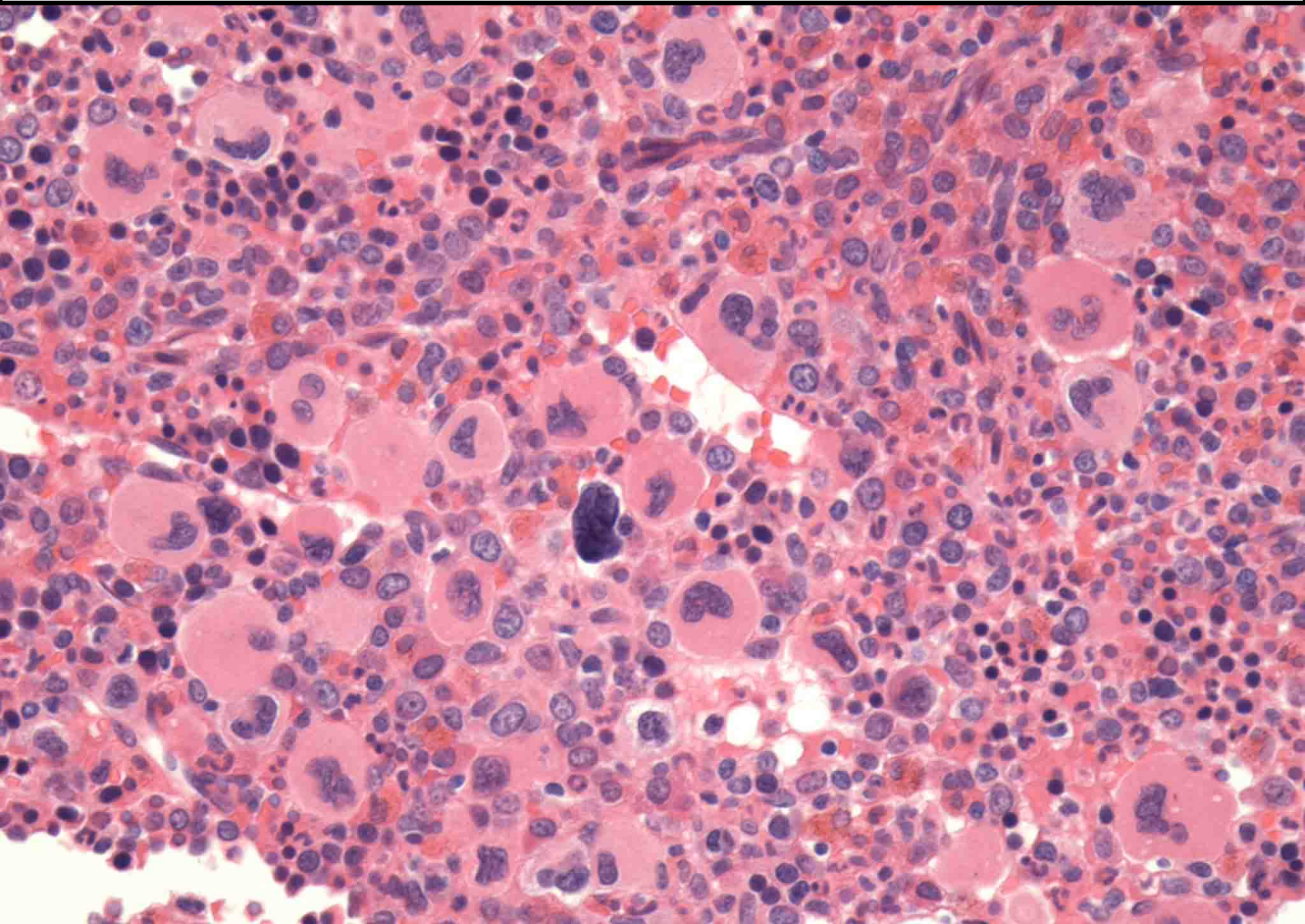


Case Summary

- Marked acute increase in Plt count following splenectomy (**188,000/µl → > 3,500,000/µl)**



Bone marrow biopsy



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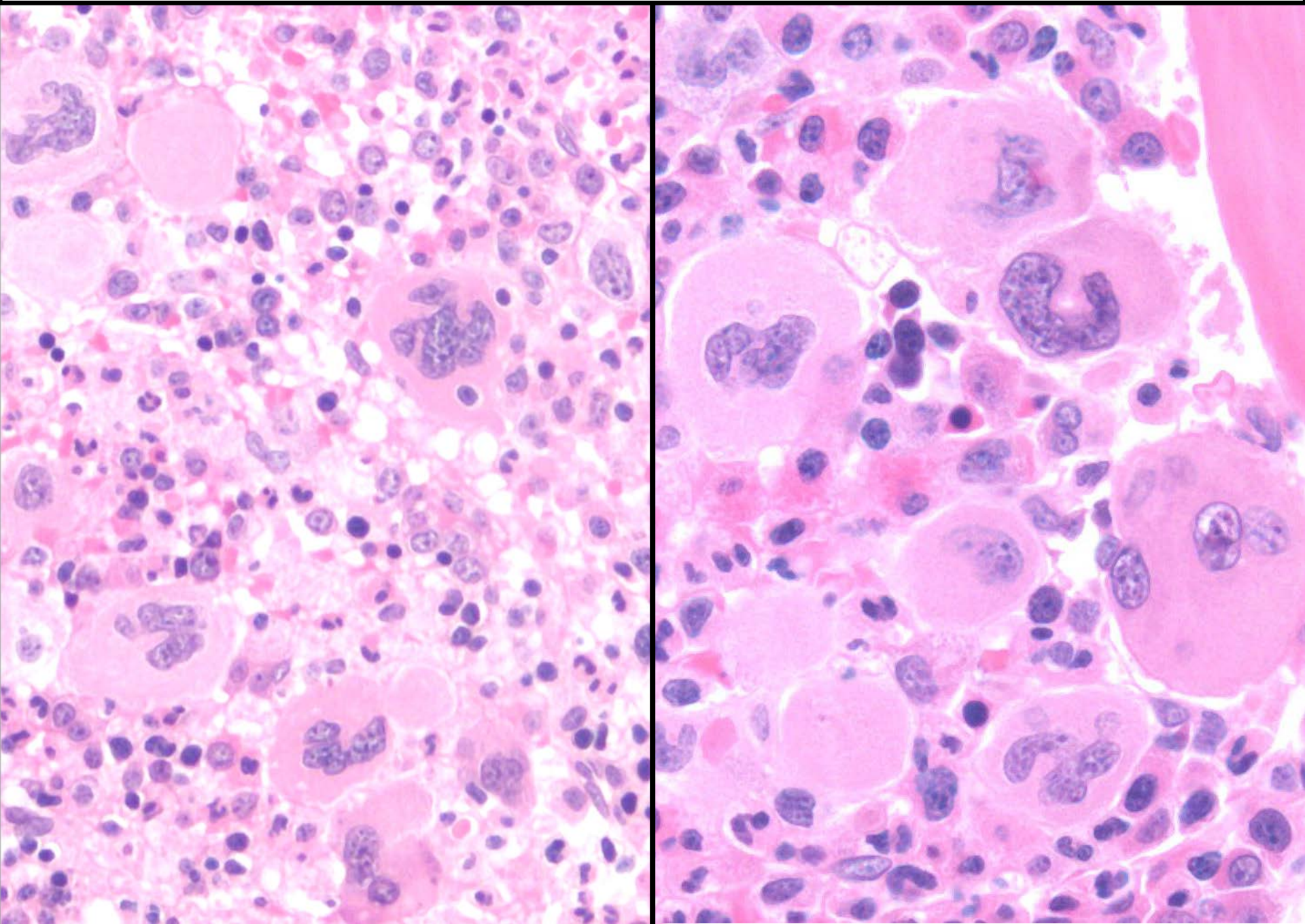
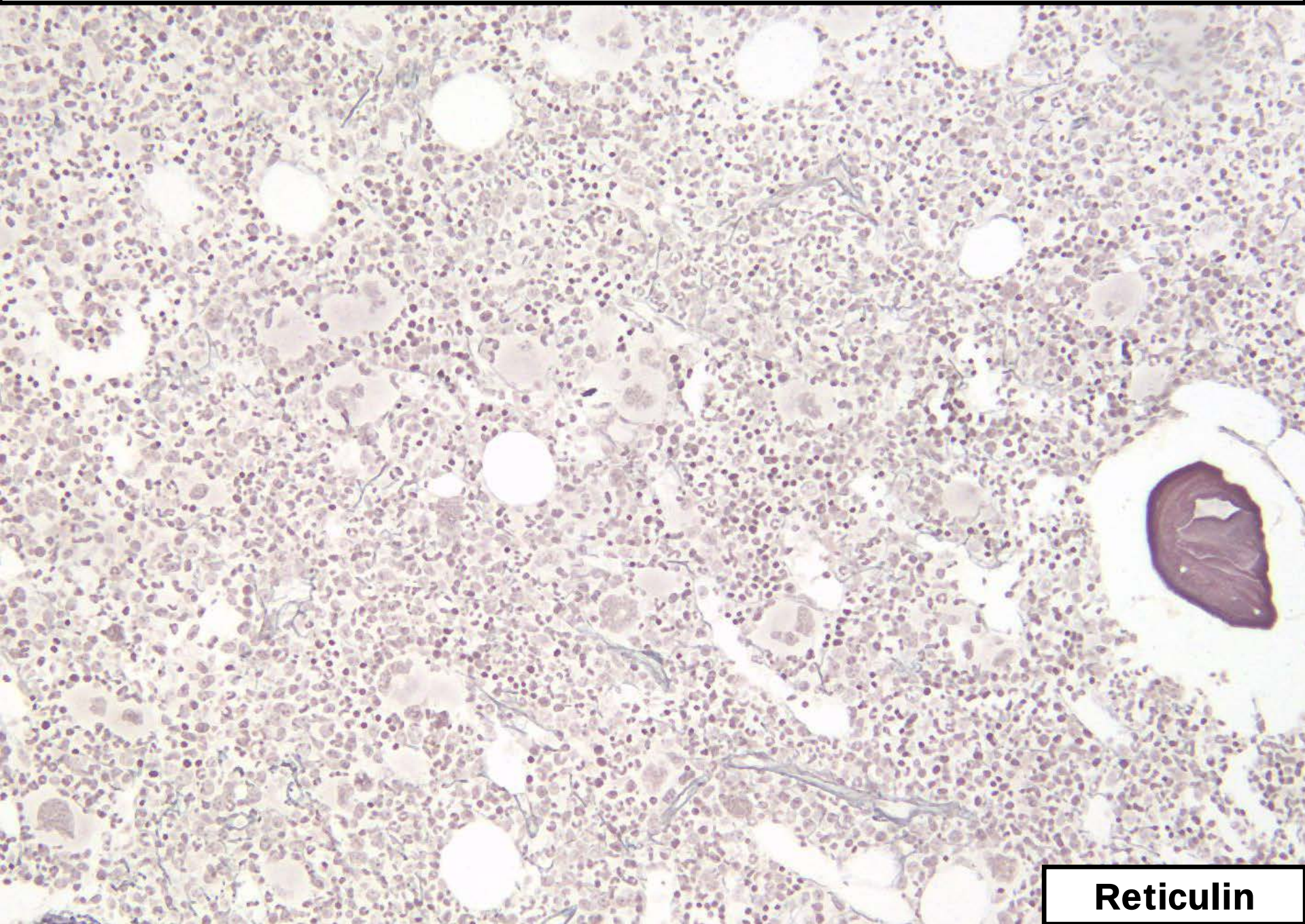


Bone marrow biopsy



Reticulin

Case Summary

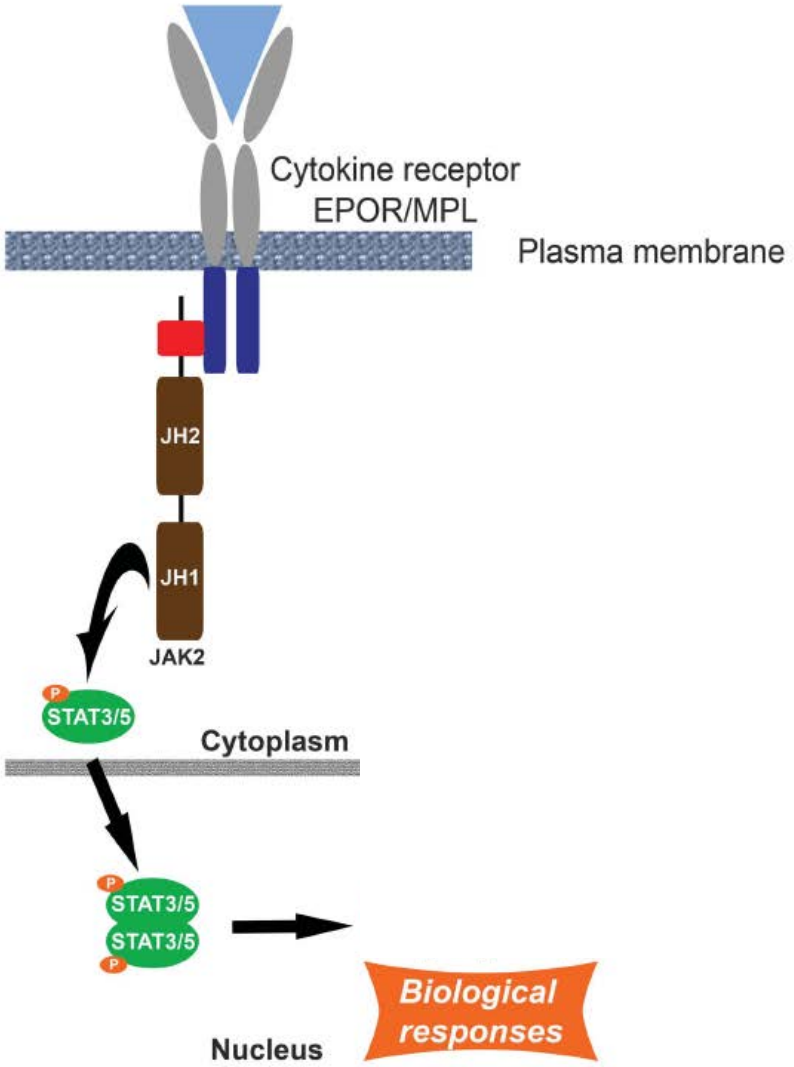
- Flow cytometry: No increase in blasts
- Cytogenetics: 46,XX
- FISH: negative for *CDKN2A* deletion
- NGS (467 cancer-associated genes):
  - No **somatically** acquired mutations
    - (including *JAK2, MPL, CALR*)
  - VUS: *AXIN2*, *FANCE*, and *EPHB1*
  - **Germline homozygous mutation in *SH2B3***

SH2B3/LNK structure and function

- *SH2B3* encodes an adaptor protein (LNK):
  - 3 functional domains
    - Dimerization domain (DD)
    - Pleckstrin homology domain (PH)
    - Src homology 2 domain (SH2)

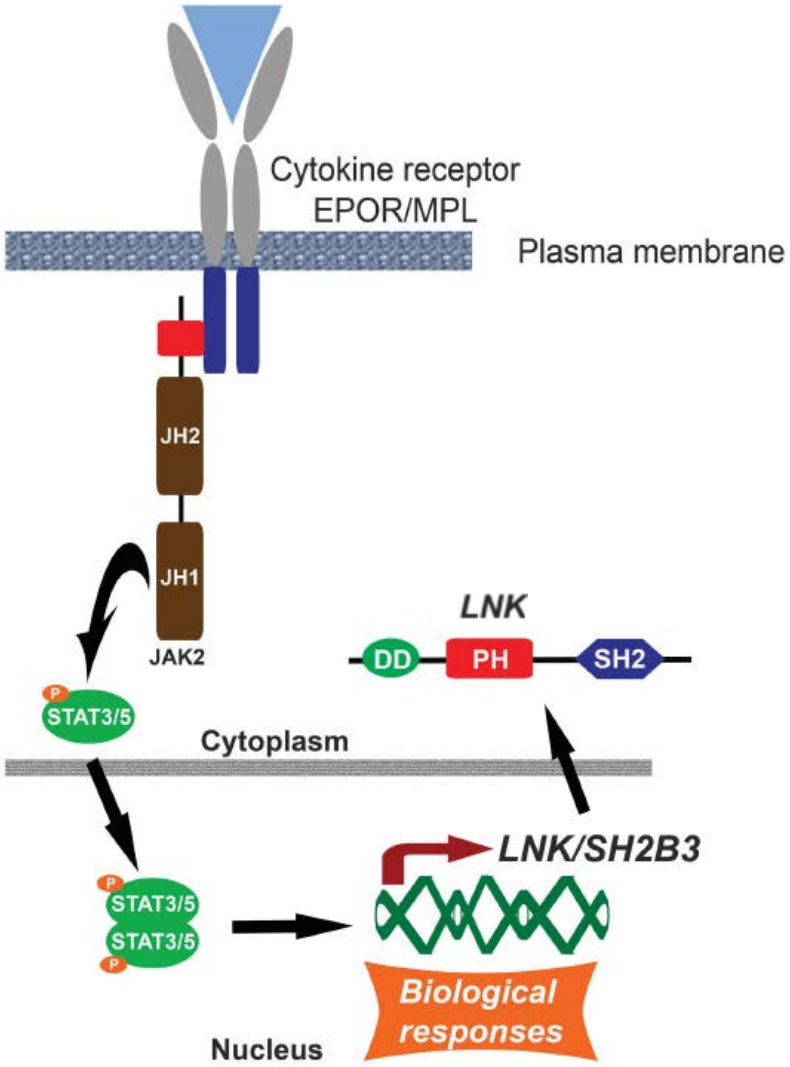
  - Inhibits the JAK/STAT pathway
  - Negatively modulates signaling of several cytokine receptors

JAK-STAT pathway



Maslah, N., et al. "The role of LNK/SH2B3 genetic alterations in myeloproliferative neoplasms and other hematological disorders." *Leukemia* (2017)

SH2B3 is upregulated by *STAT3/5*



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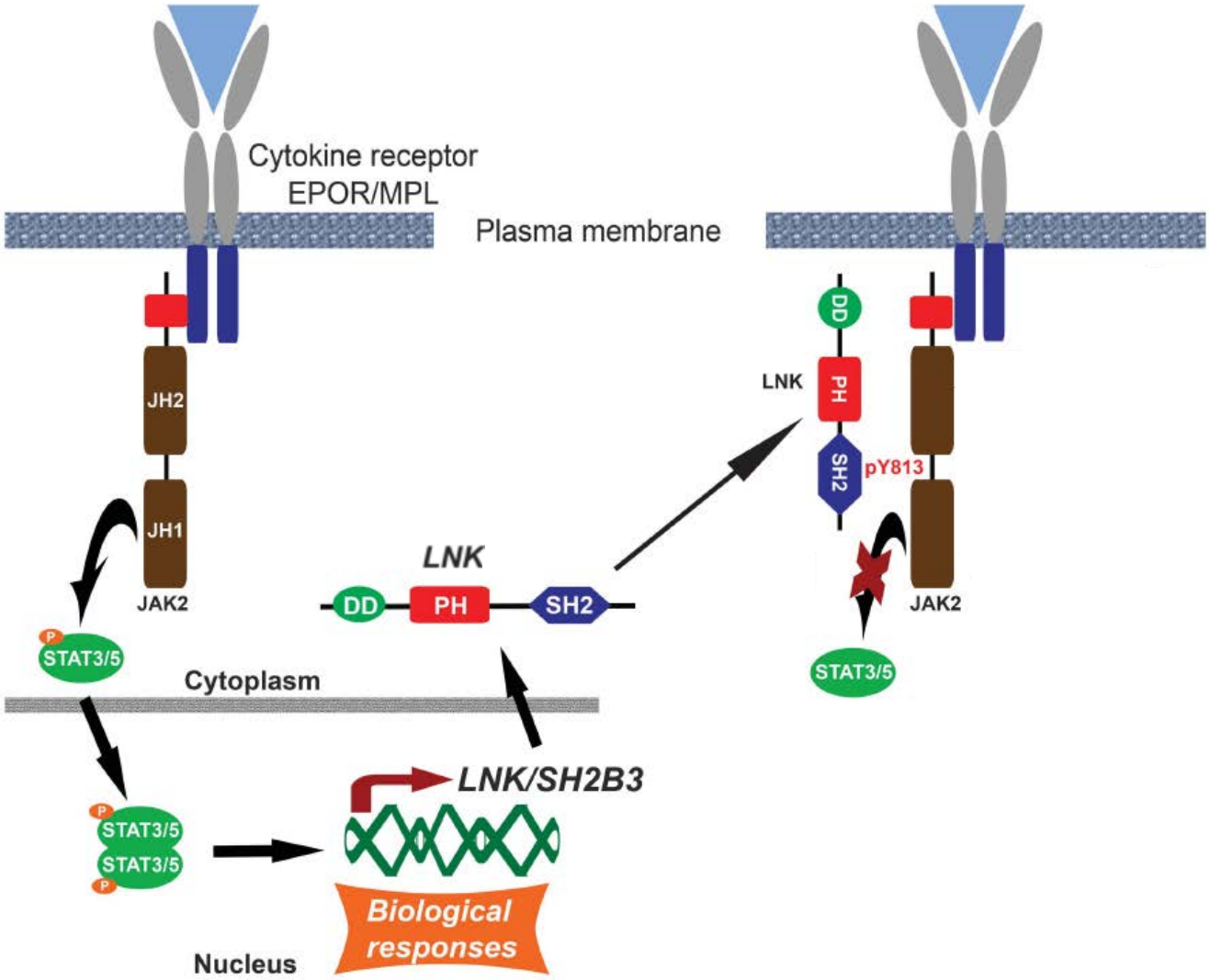
SH2B3/LNK inhibits JAK2



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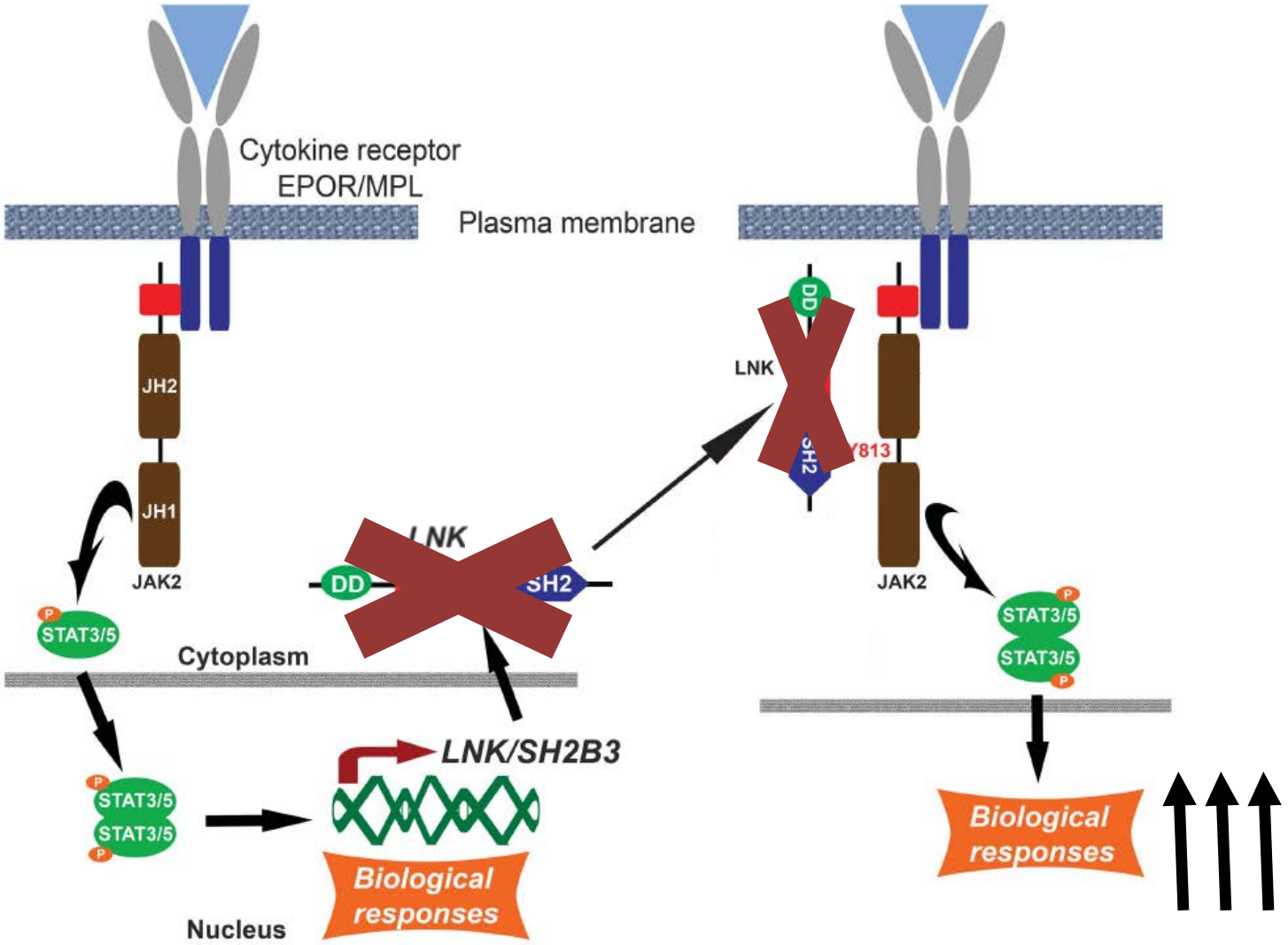
Loss of LNK → unchecked signaling



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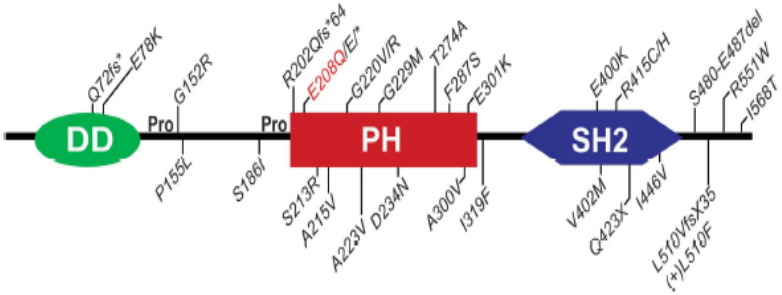
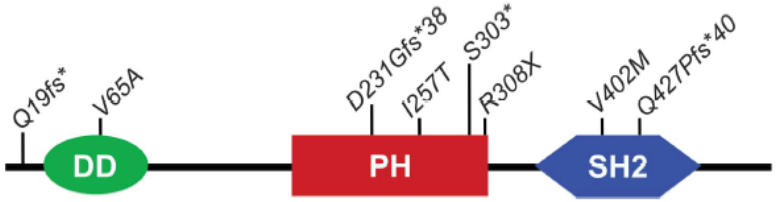
Somatic *SH2B3* mutations in heme neoplasms

- MPN:
  - Occur in 5-7% of MPN (all subtypes)
  - **Missense** mutations are most common
  - Increased frequency in transformed MPN (13%)



- ALL:
  - Occur in 1-2% of ALL
  - **Frameshift** mutations/deletions are most common
  - Potentially associated with relapse



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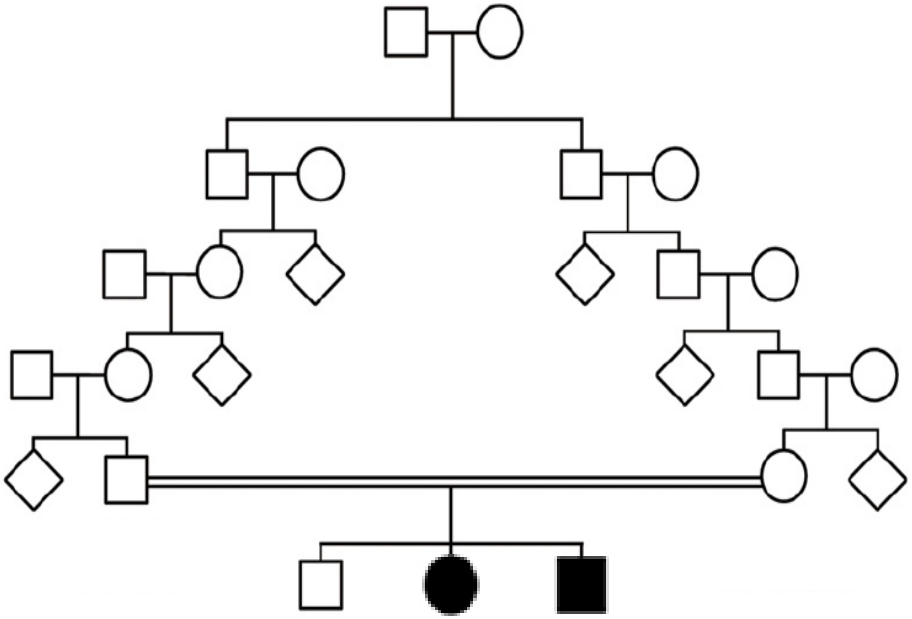
Family History

- Older Brother:
  - Hepatitis (autoimmune)*
  - Hashimoto thyroiditis
  - Glycogen storage disease
  - Growth retardation*
  - Developmental delay*
  - **B-ALL***
- Younger Brother:
  - Unaffected
- Distant parental consanguinity



Perez-Garcia, Arianne, et al. "Genetic loss of SH2B3 in acute lymphoblastic leukemia." Blood 122.14 (2013): 2425-2432.

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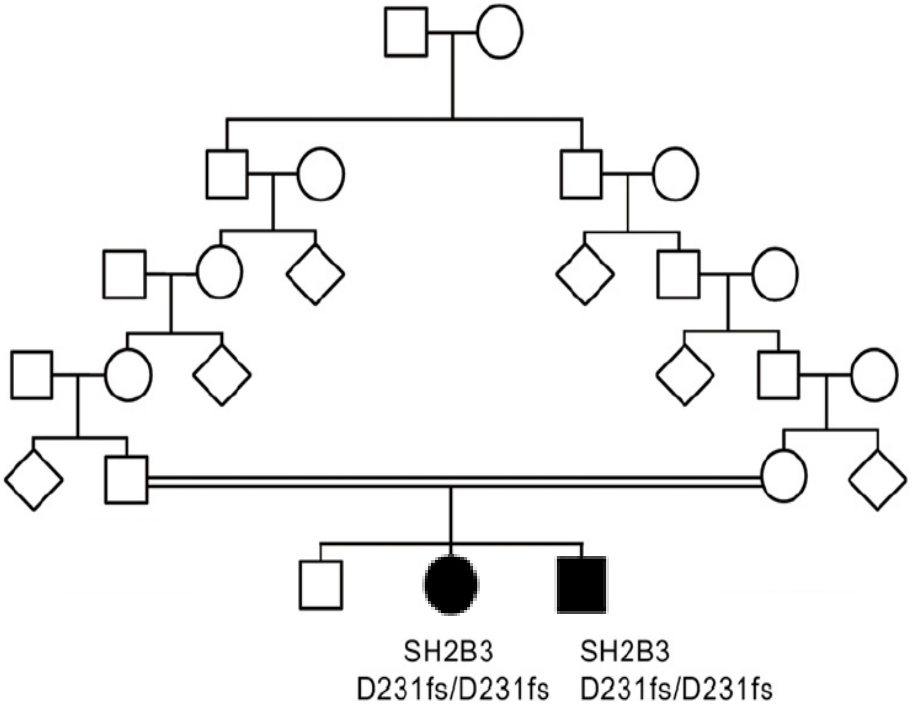

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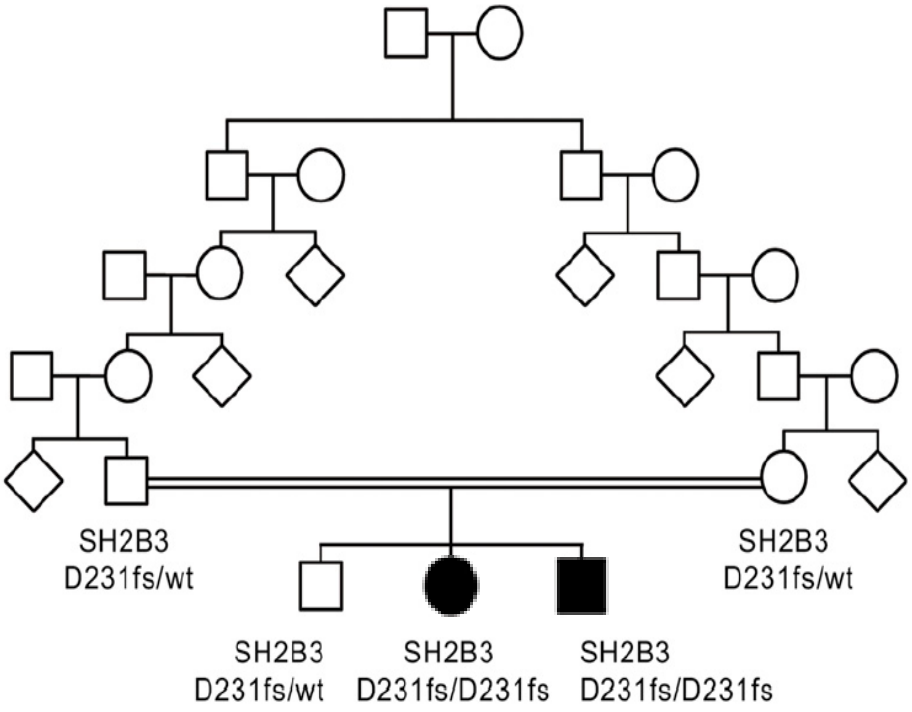

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Our patient's *SH2B3* mutation

c.690_691insGGCCCCG, p.D231fs*38

- Homozygous frameshift mutation in PH domain
- Deleterious mutation → non-functional protein

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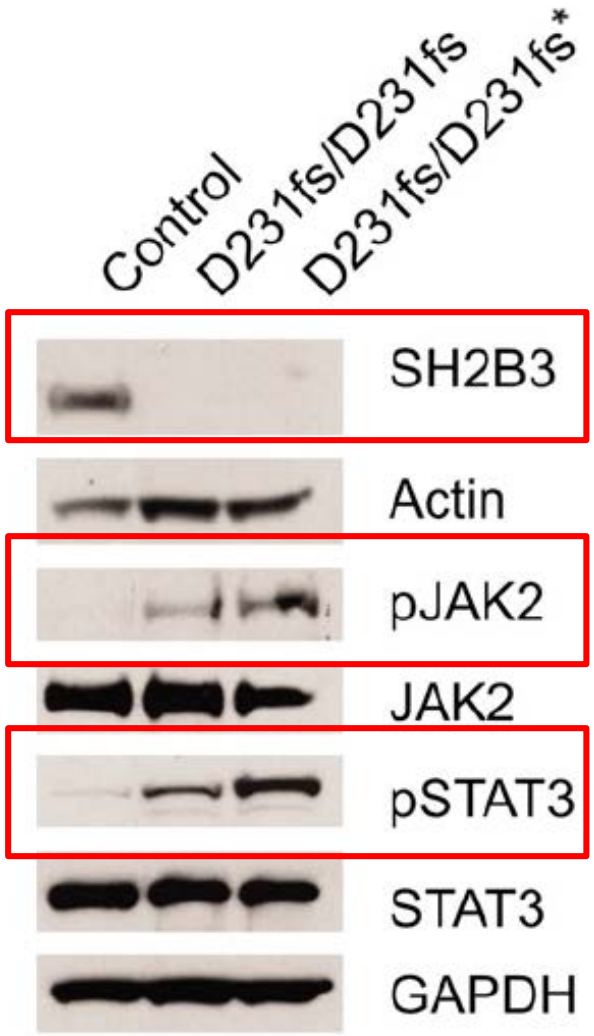

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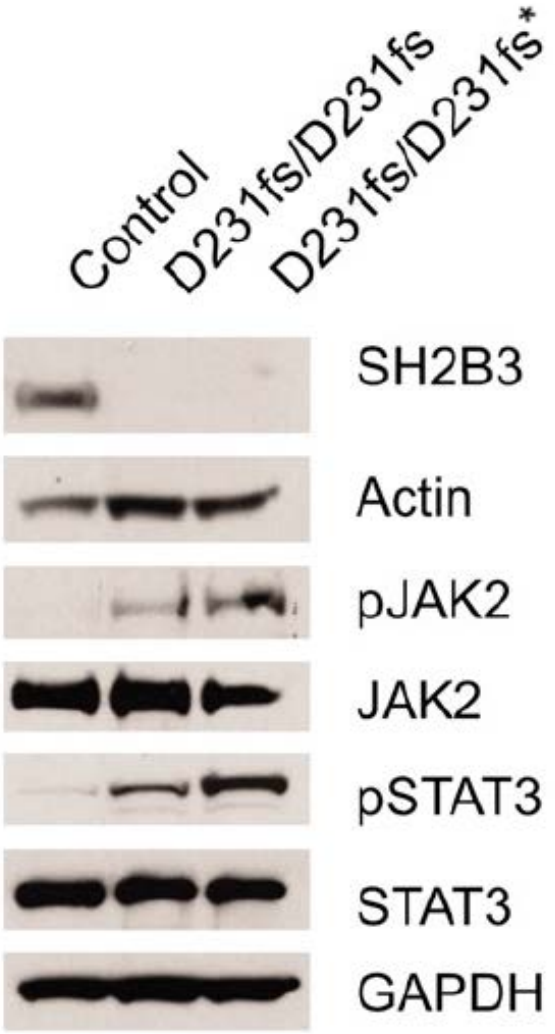

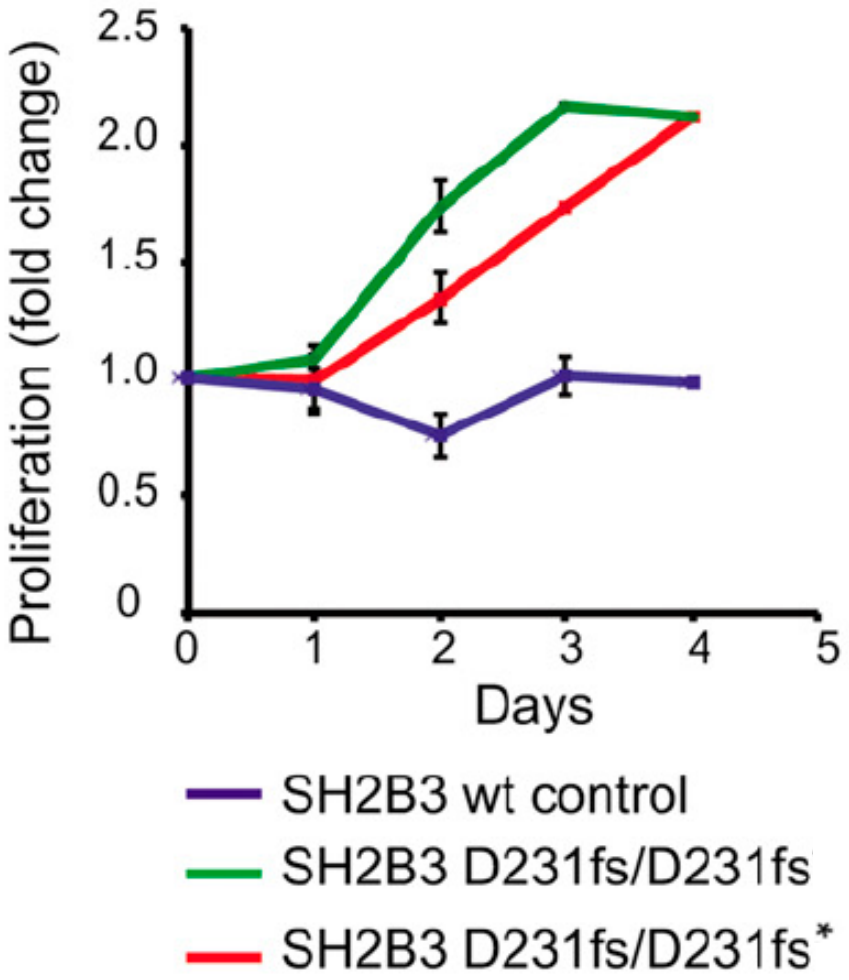

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Interesting features of case

Do germline *SH2B3* mutations/variants predispose to hematopoietic disorders?

- In this family, there appears to be evidence for predisposition to B-ALL
- Evidence for predisposition to ET-like phenotype?

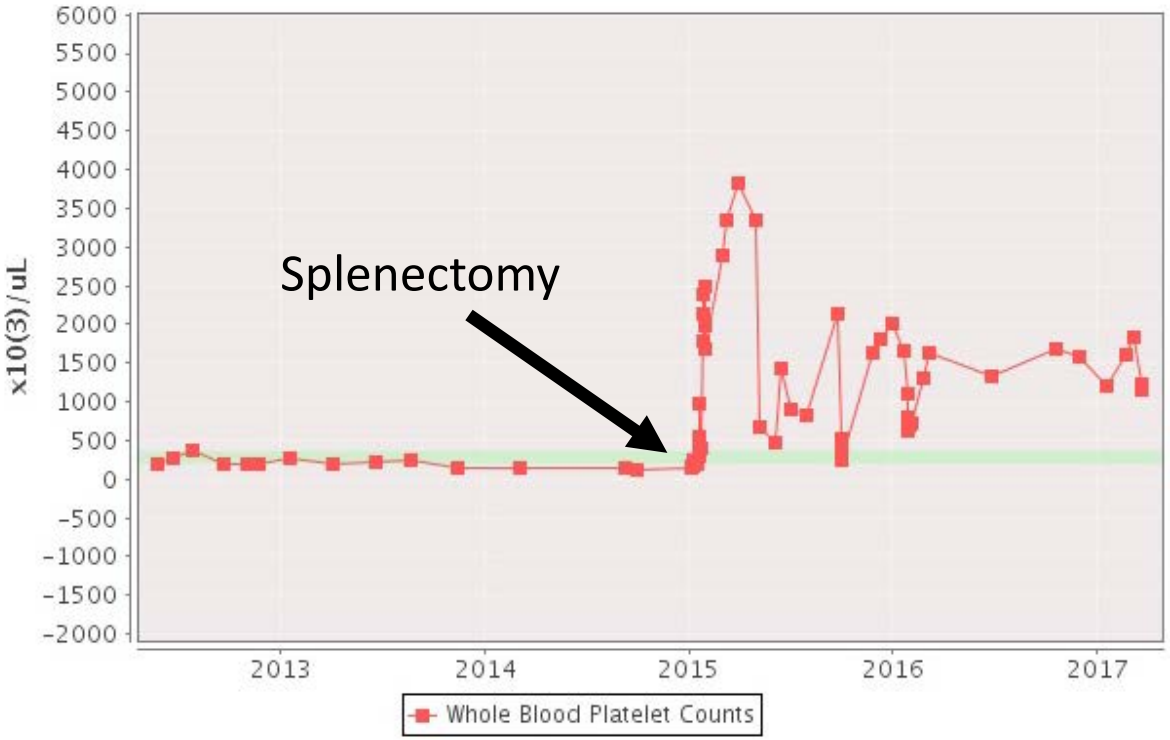
Interesting features of case

How do we classify this "ET-like" disorder?

- Is hereditary/congenital thrombocytosis a reasonable consideration?
  - Germline mutation/variant
  - Mendelian pattern of inheritance
  - Polyclonal
    - In this case, we have no evidence of a clonality
    - Whole exome/genome studies would be more definitive

Follow-up

- Platelet counts have remained elevated
- Treatment:
  - **Hydroxyurea** (30mg/kg/day) for 1 year, no improvement in platelet count
  - **Ruxolitinib** (up to 10 mg BID) for 2 months, developed neutropenia
  - Currently being treated **ASA** only
- Has not had any thrombotic complications



Final Panel Diagnosis

Essential thrombocythemia with germline *SH2B3* mutation