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

Case SH2017-0042

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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
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:
Case Summary

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

Splenectomy
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
**SH2B3 is upregulated by STAT3/5**

SH2B3/LNK inhibits JAK2

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

Family History

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

- Younger Brother:
  - Unaffected

- Distant parental consanguinity

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Our patient’s *SH2B3* mutation

c.690_691insGGCCCCCG, p.D231fs*38

- Homozygous frameshift mutation in PH domain
- Deleterious mutation $\rightarrow$ non-functional protein

Our patient’s SH2B3 mutation

Our patient’s SH2B3 mutation

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
Essential thrombocythemia with germline *SH2B3* mutation