Large Granular Lymphocytic Expansion in X-linked Agammaglobulinemia (X-LA)

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History

• Male patient diagnosed with X-LA at the age of 2 years
• L295P mutation identified in the Btk gene
• Treated with 3 weekly IVIG therapy
• At age 15, he developed polyarthritis and was diagnosed with JRA
• Trial of etanercept had to stopped due to thrombocytopenia and osteomyelitis
• Developed significant patchy myositis (CPK > 1000)
• No evidence of infection on tissue biopsy
Work Up

- Large granular lymphocytosis was noted on the peripheral blood
- CBC: 1.76/9.7/29.7/59    ALC: 920    ANC: 400
- LGL Screen:

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<thead>
<tr>
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<th>Peripheral Blood</th>
<th>Bone Marrow Aspirate</th>
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<tbody>
<tr>
<td>CD3+CD57+</td>
<td>55%</td>
<td>36.9%</td>
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<tr>
<td>CD3+CD8+</td>
<td>71%</td>
<td>74.6%</td>
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<tr>
<td>CD3+CD4+</td>
<td>25.5%</td>
<td>18.1%</td>
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- CD3/αβ : 96.5% on peripheral blood
- A clonal T cell rearrangement pattern was detected in the peripheral blood and the bone marrow
- Spleen enlarged to 20 cm; splenic aspiration showed oligoclonal T cells
Disease Course

- Diagnosed with Large Granular Lymphocytic Leukemia
  - Clonal proliferation of either CD3+ CTLs or CD3- NK cells\(^1\)
  - Lymphocytic infiltration of various organs including liver, spleen and bone marrow\(^1\)
  - Associated with autoimmune disease and immune mediated cytopenias\(^2\)
- Liver biopsy showed nodular regenerative hyperplasia (NRH) with development of portal HTN
  - NRH is micronodular transformation of the hepatic parenchyma without fibrous septa\(^3\)
  - Responsible for majority of liver involvement in primary hypogammaglobulinemia\(^4\)
- PET scan did not show lymphadenopathy outside the spleen
- Treated with methotrexate, cyclosporine, \(\alpha\)-interferon, sirolimus and anakinra
- Continued to have intense myositis
- Developed subdural hematoma following a fall in the setting of thrombocytopenia
Disease Course

- At age 23, he developed meningeal symptoms
- CSF showed lymphocytosis and hemophagocytic macrophages
- No evidence of hemophagocytosis elsewhere
- Treatment initiated with low-dose daily oral cyclophosphamide and steroids
- Developed shingles and CNS varicella → treated with IV acyclovir
- Continued to deteriorate, eventually leading to death
Discussion

- Does T-cell LGL in XLA suggest a regulatory role for Btk in the control of T cell expansion?

