Lipopolysaccharide Responsive Beige-Like Anchor (LRBA) Protein Deficiency in a 12-year-old Female with Failure to Thrive

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Background

- LRBA protein upregulates the function of CTLA4.
- CTLA4 is an immune system checkpoint which regulates T cell activation.
- LRBA deficiency leads to failure of the immune system checkpoint, leading to aberrant lymphoproliferation, autoimmunity, immunodeficiency, and recurrent infections.

Case Report

- The patient is a 12-year-old previously healthy female with weight loss, growth deceleration, and cytopenia over a one-year period.
- Two months prior to diagnosis, she developed an upper respiratory infection manifested by cough, chest pain, night sweats, and intermittent fevers.
- She was found to have splenomegaly on exam.
- CT scan showed multiple nodular lesions (Figure 1).
- Lung biopsy was consistent with granulomatous and lymphocytic interstitial lung disease (GLILD). Laboratory work up revealed hypogammaglobulinemia and low absolute CD3+, CD4+, CD8+, CD16+/56+ and CD19+ cells (Table 1).
- WBC count was 3.5, NK cell function and lymphocyte mitogen stimulation tests were within normal limits. LDH was 456 (ref range 100-325 units/L).
- Pulmonary function tests (PFTs) showed restrictive lung disease with decreased diffusion capacity.
- Gene sequencing revealed two variants of unknown significance in the LRBA gene not inherited maternally (Figure 2).
- LRBA expression was decreased (Figure 3).
- She has a 17-year old sister with failure to thrive at age 13 which resolved spontaneously, who has asymptomatic leukopenia and shares the same genetic variants.
- A 15-year old sister without the genetic variants is healthy.

Imaging

Figure 1: HRCT showing reticulonodular interstitial infiltrates with multiple superimposed pulmonary nodules

Table 1: Immune Evaluation

<table>
<thead>
<tr>
<th>Immunoglobulin</th>
<th>Result</th>
<th>Reference Range</th>
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</thead>
<tbody>
<tr>
<td>IgG</td>
<td>136</td>
<td>647-1496 mg/dL</td>
</tr>
<tr>
<td>IgA</td>
<td>&lt;8</td>
<td>53-237 mg/dL</td>
</tr>
<tr>
<td>IgM</td>
<td>&lt;6</td>
<td>47-175 mg/dL</td>
</tr>
<tr>
<td>IgE</td>
<td>&lt;4</td>
<td>&lt;200 IU/mL</td>
</tr>
<tr>
<td>CD3</td>
<td>628</td>
<td>850-3200 cells/µL</td>
</tr>
<tr>
<td>CD4</td>
<td>427</td>
<td>400-2100 cells/µL</td>
</tr>
<tr>
<td>CD8</td>
<td>175</td>
<td>300-1300 cells/µL</td>
</tr>
<tr>
<td>CD19</td>
<td>77</td>
<td>120-740 cells/µL</td>
</tr>
<tr>
<td>NK</td>
<td>52</td>
<td>92-1200 cells/µL</td>
</tr>
</tbody>
</table>

B cell panel

- Decreased absolute B cell number and % of isotype switched memory B cells

Tetanus IgG Ab | <0.10 | Protective > 0.15 IU/mL
Diphtheria IgG Ab | <0.01 | Protective = or > 0.01 IU/mL
Varicella Zoster IgG Ab | <10 | Protective > 135
Rubella IgG Ab | 25 | Protective > 10 IU/mL
S. pneumoniae 23 serotypes IgG Ab | <0.3 | Protective = or > 1.3 mcg/mL

Genetic Evaluation

Figure 2: Variant of Uncertain Significance detected in the LRBA gene by Invitae PIDD panel, confirmed by Exome Sequencing

Discussion and Conclusion

- This newly identified variant in LRBA is likely pathogenic, leading to low expression of LRBA protein.
- The patient was treated with IVIG and Rituximab.
- GLILD resolved completely, with almost complete normalization of DCO.
- She experienced catch up growth and is free of infections while on monthly IVIG replacement.
- It is possible that this variant may lead to varying phenotypes depending on the level of deficiency.
- A CTLA-4 trans-endocytosis assay can further assess the functionality of LRBA.

References