Severe Combined Immunodeficiency (SCID) caused by thymic aplasia due to a mutation in *TBX1*

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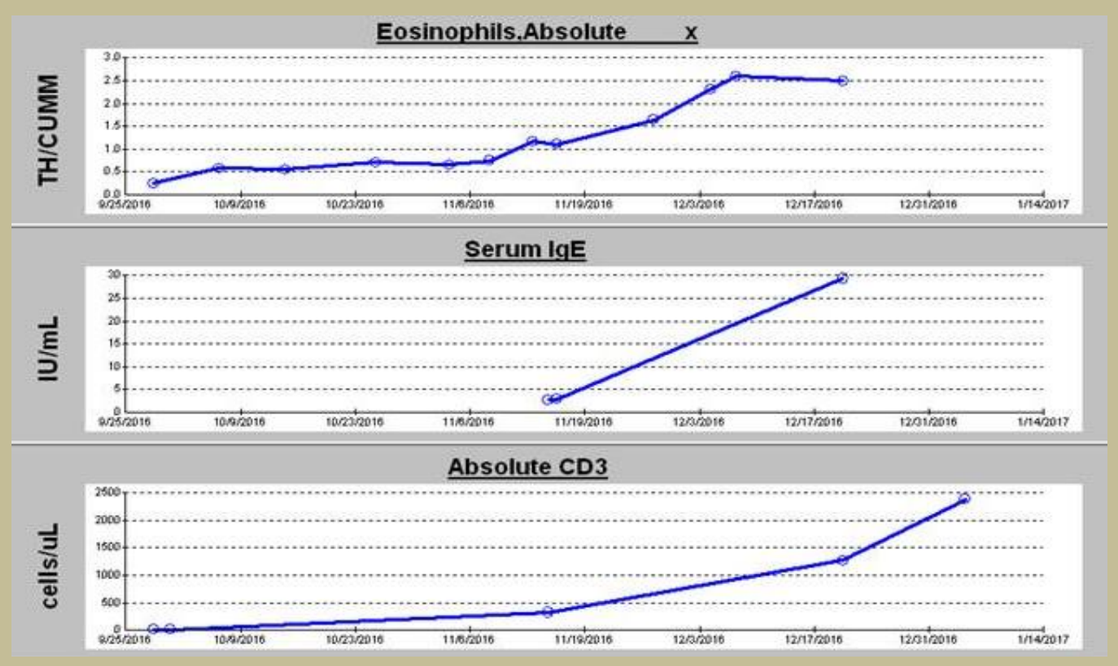
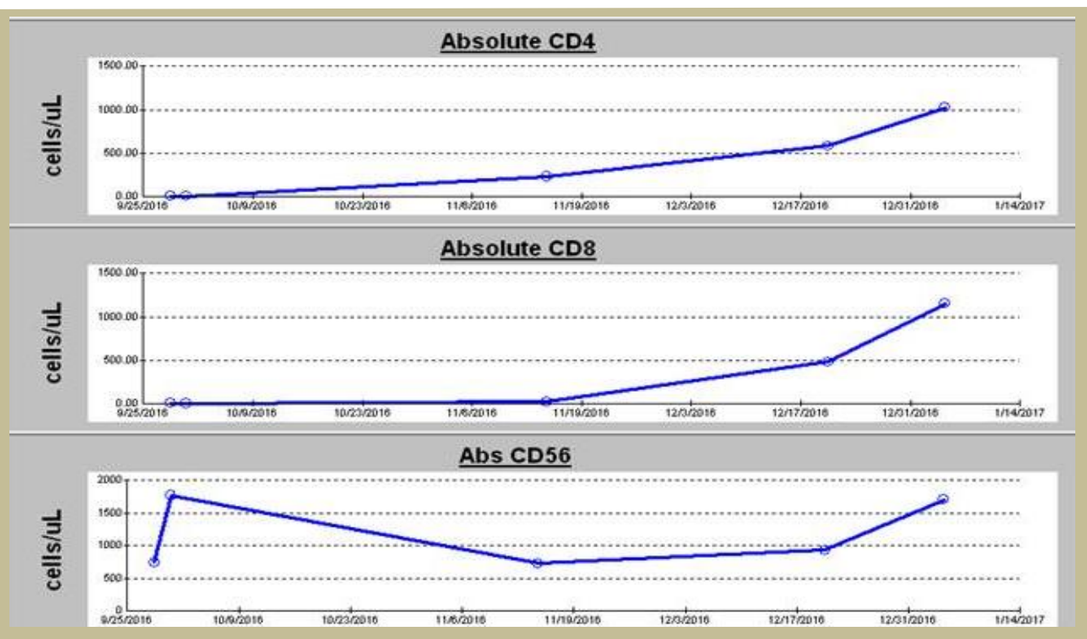
Background

Severe combined immune deficiency is a rare, life threatening disease characterized by defective T lymphocyte development or function. The various underlying defects lead to a "combined" immune deficiency characterized by disturbance in the function of both T and B cells. Patients with this disease are highly susceptible to life threatening infections by viruses, bacteria, and fungi. Untreated, most patients with this disease will die from overwhelming infection within the first year of life. Complete thymic aplasia is a rare cause of SCID but increasingly recognized with SCID newborn screening. Tbox transcription factor 1 (TBX1) is important in thympoiesis; heterozygous mutation in TBX1 are a rare cause of velocardiofacial syndrome but not a common cause of complete thymic aplasia in humans.

Case Presentation

- 10 day term female with 0 TRECS on newborn screening.
- T-B+NK+ SCID phenotype found with very low CD3 T cells and absent T cell function with normal quantities of B and NK cells.
- Absent thymic shadow on CXR.
- Complete sensorineural deafness was present in the patient's mother, maternal grandfather, and maternal great grandmother.
- A 20 base pair heterozygous duplication was found in TBX1 c.1176_1195dup20.
- HSCT, the common treatment for SCID, was abandoned and thymic transplantation was instead pursued.
- While awaiting an appropriate donor thymus, the child developed an atypical whole body skin eruption. This was accompanied by increases in total IgE, absolute eosinophil count, and T lymphocyte counts (CD4 and CD8) all consistent with Omenn Syndrome.
- Omenn syndrome was treated with corticosteroids and cyclosporine.





Discussion

We report one of the first cases of TBX1 haploinsufficiency causing complete thymic aplasia and SCID. The mutation identified,c.1176_1195dup20, which leads to a frameshift mutation in the TBX1 gene and predicted loss of protein function through protein truncation or nonsense-mediated mRNA decay. This variant has not been previously published as a pathogenic mutation in the TBX1 gene. TBX1 is located on the long arm of chromosome 22 at position 11.21 and appears to play a critical role in embryonic development of the pharyngeal arches. Mutations in this can lead to thymic aplasia or DiGeorge Syndrome phenotype.

In the case of thymic aplasia associated with complete DiGeorge Syndrome, patients typically have low CD3 cells and absent proliferation to mitogens. Our patient was similar to this phenotype, except for she did not have any of the other typical clinical findings of DGS. However, these patients may develop some mature T lymphocytes either through maternal engraftment or oligoclonal expansion of memory T cells who have not undergone thymic processing. These naïve T lymphocytes typically have abnormal T-cell receptor spectratyping. This can lead to autoreactive T lymphocytes which contribute to Omenn syndrome. The pathogenesis of this phenomenon is incompletely understood, but there is likely a loss of central tolerance secondary to athymia, which leads to autoreactivity.

Unlike many other variants of SCID, bone marrow transplantation is not likely to be curative in this patient. Patients with athymia who undergo HCST have a lower rate of long term survival than patients with SCID. Allograft thymic transplantation has shown promise with similar long term outcomes to HSCT. After successful transplantation, patients develop host derived naïve T cells with a normal T-cell receptor repertoire.

References

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