SCID – An Autopsy Report and Short Review

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Abstract: *Severe combined immunodeficiency (SCID) is a rare and fatal primary immunodeficiency disorder characterized by marked deficiency of both B and T lymphocytes. Hereby reporting a case of a six month old girl who presented with recurrent respiratory infections and not responding to antibiotics. Hematological investigations revealed pancytopenia and immature cells were not seen. The child had a progressive downhill course and died of septic shock with disseminated intravascular coagulation. Autopsy was requested and found to have severe lymphoid depletion with absence of both B and T cells in lymph nodes, spleen, and appendix. After detailed immunohistochemical study, a diagnosis of SCID was rendered. This autopsy workup highlights the importance of recognition and early diagnosis of this rare disorder, so that bone marrow transplantation may be offered early in life. Genetic analysis is necessary wherever possible, to detect the specific mutation in order to offer prenatal genetic counselling to the family.*

Keywords: SCID, primary immunodeficiency, ADA deficiency, autopsy

1. Case Discussion

A six-month-old girl presented to the AIIMS- new delhi hospital with a two-month history of recurrent fever and cough. The child was born to a primi-gravida, non-consanguineous full term by elective lower segment caesarean section, the indication being breech presentation, with a normal birth weight and family history. She attained all the milestones appropriate for her age. The child was well till the four months of age, when she was admitted in a private hospital for fever, cough and was treated with antibiotics. However the fever recurred soon after which was high grade and associated with productive cough as purulent sputum. Simultaneously, the mother had noticed reduced oral acceptance, loose stools and loss of weight of the child. There was no history of blood loss from any site.

General physical examination revealed pallor and mild hepatomegaly. There were bilateral bronchial respiratory sounds with occasional rhonchi and other systems were normal. Routine haematological investigations showed anemia (Hb-8gm %), leucopenia (2600/mm^3) and thrombocytopenia (80,000/mm^3). Peripheral blood film showed microcytic hypochromic red cells, leucopenia with relative monocytosis and monocytoid lymphocytes. No atypical or immature cells were noted. Biochemical investigations, including liver function tests and renal function tests were within normal limits. Blood culture, urine culture and stool cultures were negative for infective organisms. The child was initiated on broad-spectrum antibiotics therapy along with supportive care. However she deteriorated and developed generalized body swelling, oliguria, persistent high-grade fever with one episode of seizure-like activity and severe respiratory distress.

Despite all efforts, the child died and the suspected cause of death being septic shock.

At autopsy, there was consolidation in bilateral lungs accompanied by sub-pleural hemorrhage. There was hepatomegaly with congestion of liver. Colon showed multiple ulcerations measuring 1-1.5 cm in size. Thymus could not be identified. Other Organs, including spleen, kidneys, heart appeared grossly unremarkable.

Microscopic sections from ulcerated areas in colon showed submucosal infiltrate composed of histocytes admixed with eosinophils and occasional lymphocytes. Appendix showed marked depletion of lymphoid tissue as evidenced by the absence of immuno-staining for CD20, CD3 and S-100 for follicular dendritic cells (fig: 1TO 6). Similar depletion of lymphoid tissue was seen in spleen which showed histiocytic predominance and complete absence of CD20-positive cells with only scant positivity for CD3(fig:1TO 6). Lymph nodes from the various group (hilar, para-tracheal, mesenteric, para-aortic) were also examined. They showed depletion of all compartments, including lymphoid follicles, paracortical T-cell and medullary areas. Predominantly reticulin framework and stromal cells were identified. Immunohistochemistry revealed absence of a CD 20, CD3, CD4 and CD8 positive cells as well as the follicular dendritic cells (S-100 and CD21). Staining for CD34, CD117, Tdt and Pax5 did not reveal an obvious increase in immature cells in the lymph nodes (FIG:1TO 6).

The morphology and immunohistochemistry was consistent with a diagnosis of severe combined immunodeficiency (SCID). Correlating with the clinical picture, this appears to be a case of autosomal recessive SCID with severe B-cell depletion.
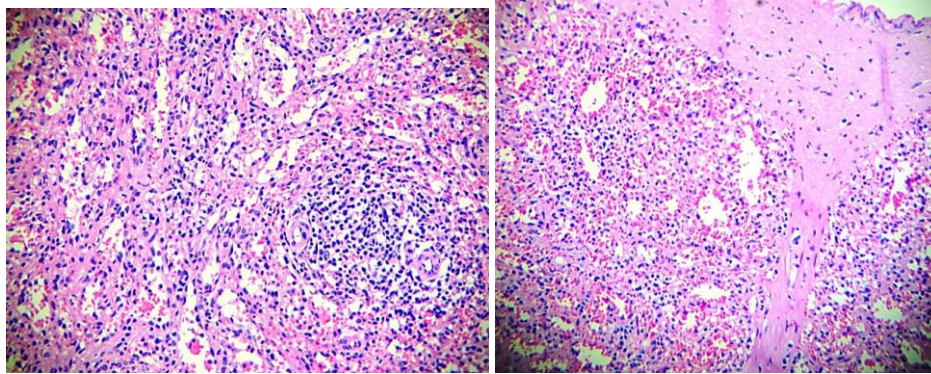
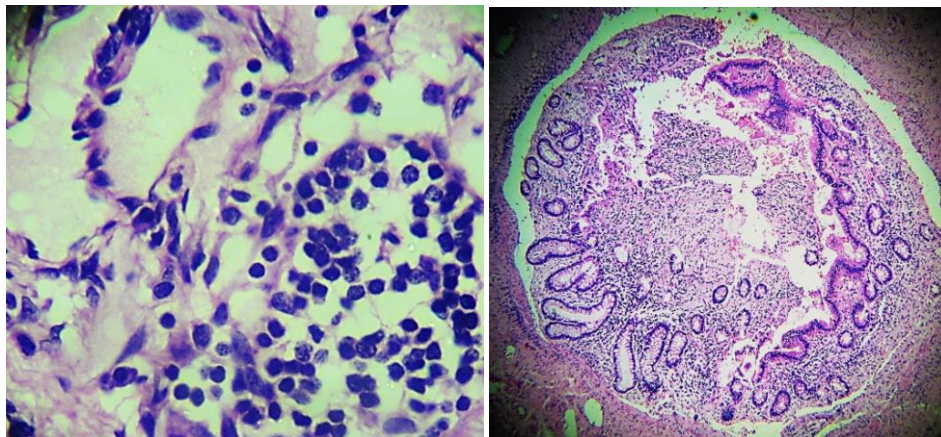**Figure 1 & 2:** Spleen with Scant Lymphoid Follicles and Expanded Red Pulp

Figure 3: Lymph Node with Occasional Follicle & Figure 4: Appendix with Scant Lymphoid Cells
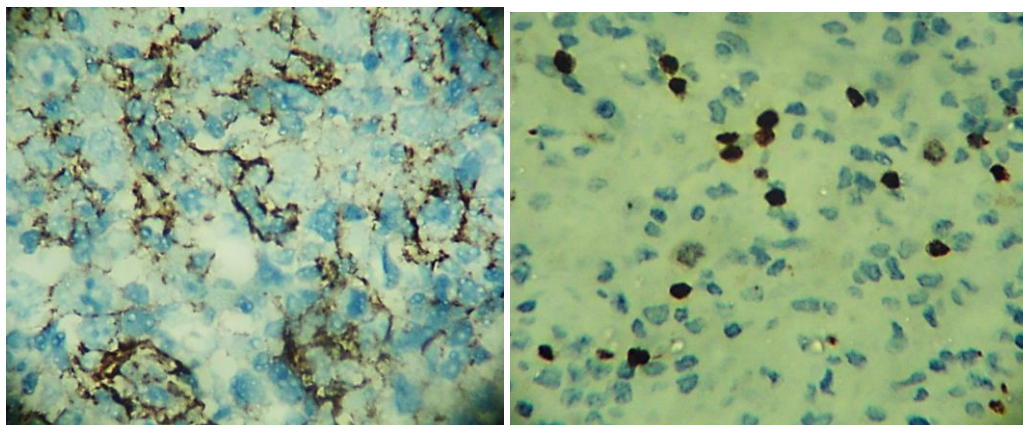

Figure 5: CD 21 Shows Follicular Dendritic Cells and Figure 6: Pax-5 Positive Few B

2. Lymphocytes

Short Review

Severe combined immunodeficiency (SCID) is a pediatric emergency caused by marked deficiencies of B and T-cell (sometimes accompanied by deficiency of NK-cell) functions[1]. SCID manifesting in infants usually as recurrent opportunistic infections and these infants are also at risk for graft-versus-host disease from transplacental exposure to maternal T cells while in-utero or from the use of non-irradiated blood/blood products contains a immunocompetent T lymphocytes[2,3].

Infants with SCID are usually lymphopenic (normal cord blood absolute lymphocyte count 2000-11,000/mm^3) and all the lymphopenic newborns should be investigated for their T-cell phenotypic and functional studies[2]. Patients with SCID have very small thymus, which contain no thymocytes and lacks cortico-medullary distinction and Hassall's corpuscle. However, thymic epithelium appears normal. Additionally, thymus-dependent areas of spleen are depleted, and lymph nodes, tonsils, adenoids , MALT/Peyer's patches are underdeveloped or absent[4]. The present case came with history of recurrent infections in infancy, not responding to antibiotics. At autopsy, the infant had absent thymus and depletion of lymphoid tissue in lymph nodes, spleen, ileal lymphoid tissue/Peyer's patches. This depletion was complete for B and T lymphocytes with remaining reticulin framework.

SCID demonstrates X-linked recessive inheritance in about half of the cases while the rest show autosomal recessive pattern of inheritance[1]. X-linked SCID (X-SCID)

showed uniformly profound lack of T or B-cell function, but a normal or elevated number of B cells which are however non-functional[2,3].The abnormal gene in X-SCID has been mapped to the Xq13 region, identified as the gene encoding a common gamma-chain receptor, which is shared by several cytokine receptors[5].

This explains the effect of mutation in a single gene on multiple cell types. Rare cases of an atypical X-SCID with few functional circulating mature T cells lacking the common gamma-chain gene mutation while B cells and NK cells revealed the mutation. This was presumed to occur due to a single reversion event in early T-cell precursors, which occurred after B-cell and NK-cell progenitors were committed[6].

Autosomal recessive SCID (AR-SCID) has been identified to occur due to six gene mutations[1], as seen in table 1. AR-SCID caused by mutations in adenosine deaminase gene (ADA) and it is also associated with multiple skeletal abnormalities as chondro-osseous dysplasia.

Table I: Molecular causes of SCID[1]

Mutations	Lymphocyte phenotype
X-linked SCID 1.Common Gamma chain mutations	T(-) B (+) NK (-)
Autosomal recessive SCID	
1.ADA gene mutation	T(-) B (-) NK (-)
2.Jak 3 gene mutations	T(-) B (+) NK (-)
3.ILTR □-chain gene mutations	T(-) B (+) NK (+)
4.RAG1 or RAG2 mutations	T(-) B (-) NK (+)
5.Artemis mutations	T(-) B (-) NK (+)
6.CD45 gene mutations	T(-) B(+)

Other mutations in AR-SCID include Jak 3 deficiency (signaling molecule associated with gamma-chain), IL-TR □ deficiency (leading to T-cell and B-cell defect and normal NK cell function), RAG1 or RAG2 deficiency (encode proteins necessary for somatic rearrangement of antigen receptor genes on T and B cells), Artemis gene product deficiency (novel factor which repairs DNA after double stranded cuts made by RAG1 or RAG2 gene products) and CD45 gene mutation (transmembrane protein tyrosine phosphatase which regulates Src kinases required for T and B-cell antigen receptor signal transduction)[7,8,9,10,11]. Our patient, a female child with normal family history and severe B, T-cell deficiency was diagnosed as AR-SCID. Further genetic analysis, however, could not be performed. This autopsy workup highlights the importance of recognition and early diagnosis of this rare disorder, so that the bone marrow transplantation would have been offered to save the life of this child.

SCID is fatal before second year of life if it is undiagnosed or not treated. Bone marrow transplantation from haplo-identical donors in the first four months of life offers 80 to 95% chance of survival[2]. Few patients with ADA deficiency have been given gene therapy using the retroviral gene transfer of normal gamma chain cDNA[12]. Hence, early or prenatal diagnosis is essential, which is possible by the evaluation of levels of B/T-cells and genetic analysis if the mutation in a family is already known[1].

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