

RECURRENT RESPIRATORY TRACT INFECTION – AN UNUSUAL CAUSE

By

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CASE SCENARIO

- 2 yrs old boy 1st child 3rd degree consanguineous marriage
- Cold , cough and Fever – 2 weeks
- Breathing difficulty since 5 days
- H/o recurrent loose stools, recurrent respiratory infection – since birth, treated as OP with oral antibiotics.
- H/o poor feeding/ poor weight gain +

- H/o abscess of left axillary lymph nodes following BCG vaccination – I & D done.
- No h/o aspiration/ noisy breathing / reflux symptoms.
- No h/o previous sibling death
- No h/o contact with TB
- No significant antenatal and perinatal events.
- Immunization – up to age (UIP).

EXAMINATION

- Febrile.
- Oral thrush +
- Discharge + from right ear.
- Chest retractions + Crackles +
- Left axilla – I & D scar .
- No BCG scar.
- Weight, Height - below 3rd centile (WHO)
(Weight affected > Height)
- Other systems – Normal

DD'S

- Tuberculosis .
- Malnutrition .
- Immunodeficiency.
 - Primary immunodeficiency.
 - Secondary immunodeficiency .

INVESTIGATIONS

- Total counts – low. Absolute lymphocyte count – low
- High CRP, Blood & Urine C/S – sterile.
- Chest X ray – Increased BVM
- Mantoux and RGJ - negative.
- CT chest - right middle lobe pneumonia.
- Immunoglobulin profile - normal.
- HIV ELISA - negative
- ECHO - high normal PA pressure

DIAGNOSIS

Right Middle lobe pneumonia, Oral Candidiasis, ASOM, Failure to thrive, Chronic diarrhoea.

TREATMENT

- Child was treated with IV fluids, IV antibiotics
- Improved – fever, cough subsided, oral thrush healing
- Discharged with diet advice

FOLLOW UP

- Child brought back a month later with C/O
- Recurrence of respiratory tract infection and diarrhea.
- Recurrence of oral thrush ++
- ???????

FLOW CYTOMETRY

T cells, B cells, NK cell deficient SCID

INVESTIGATION	RESULT	REFERENCE RANGE
CD3+	53.2%	67-81
CD3+	210 cells/micL	877-1875
CD3+CD4+ (helper T cells)	32.6%	30-77
CD3+CD4+ (absolute count)	121cells/micL	328-2130
CD3+CD8+ (Cytotoxic cells)	18.7%	19-33
CD3+CD8+(Absolute count)	69 cells	200-616
CD3-/CD19+ (B cells)	5.2%	8-18
CD3-/CD19+ (Absolute count)	20cells/micL	116-396
CD3-/CD56+(NK cells)	11.1%	5-14
CD3-/CD56+(NK cells absolute count)	42 cells/micL	74-254
T4/T8 Ratio	1.75	>1.0

Revised diagnosis

T cell , B cell & NK cell-
Negative SCID

Severe Combined Immunodeficiency

- SCID - Severe combined immunodeficiency (SCID) is a primary immunodeficiency disorder with heterogeneous genetic etiologies, characterized by a profound defect in both T and B lymphocytes



EPIDEMIOLOGY

- 1 case per 50,000-75,000 births
- Age < than 3 months

ADA-deficient SCID less severe mutations – late presentation possible

- 50% of SCID cases are X-linked - only in males
- Autosomal recessive mutations - males : female – 1:1

X LINKED SCID

- Most common genetic mutation in SCID – mutation of **common γ chain of the interleukin (IL) receptors** shared by the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.
- γ chain function – increases the affinity of receptor for respective cytokine, enables receptor for intracellular signaling.
- This protein is encoded on the X chromosome – Xq13
-  T cells, NK cells  B cells

AR SCID / Swiss-type Agammaglobulinemia

- ADA deficiency
- Jak 3 deficiency
- IL – 7R alpha chain deficiency
- RAG1/RAG2 deficiency
- Artemis deficiency
- Ligase 4 deficiency
- DNA protein kinase catalytic subunit deficiency
- CD3delta , e or z chains.
- CD 45 deficiency

ADA DEFICIENCY

- 2nd most common mutation
- ADA - enzyme that breaks down purines.
- Deficiency – ↑ adenosine, 2'deoxyadenosine & 2'Omethyl adenosine



T cell apoptosis

- Point and deletion mutation in ADA gene on chr 20q13
- B-, T-, and NK-cell deficiency

LAB DIAGNOSIS

- **CBC** : lymphopenia - $< 2500/\text{mm}^3$ at birth – cord blood
Normal number of lymphocytes does not rule out SCID - lymphocytes may be nonfunctional.
- **Immunoglobulin** : low or absent, normal – transplacental
- **Flow cytometry** :
 - CD3+ CD4+ CD8+ - T cells**
 - CD19+ - B cells**
 - CD16 and CD56 – NK cells**
- **Leukocyte ADA enzyme activity** : sensitive and specific for the detection of ADA-deficient SCID.

- Chest radiographs

Classic SCID - small or absent thymus

early recognition of pneumonitis

ADA deficiency - bony abnormalities in the ribs and vertebrae.

- Prenatal diagnosis

CVS - 10 weeks gestation

amniocentesis

Fetal blood sampling - fluorocytometric testing, mitogen responses, enzyme levels if DNA analysis is not available

TREATMENT

- SCID IS A PEDIATRIC EMERGENCY
- Isolation , skin and mucosal hygienic care
- Parenteral nutrition - diarrhea and failure to thrive.
- Lymphocyte-depleted and irradiated blood product transfusions – prevents transfusion-associated GVHD.
- Sepsis & Pulmonary infection - Empiric broad-spectrum antibiotics administered parenterally
- Prophylactic nystatin - prevents mucocutaneous candidiasis.

DEFINITIVE Rx

- IVIg – to restore antibody levels until BMT
- BMT - treatment of choice.

Patients with SCID who are treated with BMT before age 3.5 months have better survival rates.

If B cells do not engraft, monthly IVIg replacement therapy


- Non irradiated blood products or live-virus vaccines

Can develop disease from attenuated viruses , may even die after exposure to these vaccines.

- PEG-ADA (polyethylene glycol modified bovine adenosine deaminase)

provides ADA activity in the bloodstream to eliminate the toxic effect of deoxyadenosine and adenosine which causes immune deficiency

Weekly IM injection of PEG-ADA.

- Gene therapy : Normal gene is inserted with a viral vector  replaces dysfunctional genes that give rise to SCID.
- Retrovirus is used as vector.

SE : Leukemia

WHY THIS CASE???

- Unusual age of presentation –
 - Usual age of Presentation < 3 months.
- Unusual way of presentation-
 - Without intervention - severe infection and death by 2 years.

How does this happen???

Phenomenon of Maternal T cell Engraftment

In healthy newborn –

- Transplacentally derived maternal T lymphocytes by maternal-fetal transfusion - rapidly eliminated by immune competent T cells.

Child with SCID

- failure to recognize & to reject foreign cells, allowing maternal T cells to persistently engraft.

- These cells usually exhaust overtime - so this provides prolonged period of immunity, but not persistent / permanent
- Hence some SCID patients present late and with less severity.
- Occur in more than 50% of patients with SCID.

Importance of Maternal T cell Engraftment

- Mediate immunologic functions
- GVHD
- Respond poorly to mitogens .
- Can cause allograft rejection
- Prevent engraftment of BM transplants from nonmaternal donors.
- Immune cytopenias.

FOLLOW UP PLAN FOR THIS CHILD

- Adenosine deaminase B level & Screening for other mutations.
- Antibody titers to vaccines.
- Tandem repeat analysis for maternal T lymphocytes & myeloid cells engraftment .
- HLA typing .
- HSCT
- Growth and nutrition monitoring.
- Avoid all live vaccines.

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