An Infant with Repeated Respiratory Infections and Failure to Thrive

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We describe the clinical and autopsy findings of a 7-month-old baby with complaints of repeated respiratory infections and failure to thrive.

CLINICAL PROTOCOL

History: A seven-month-old boy presented with complaints of fever and cough for four months and tachypnea for 1 week prior to admission. He was born to a third gravida by normal vaginal delivery with birthweight of 3 kg and an uneventful perinatal period. He was immunized for age. He had been symptomatic from four months of life and was hospitalized thrice for pneumonia and treated with intravenous antimicrobials prior to admission in PGI. He was not thriving well, with history of oral ulcers for past four months. One unit of un-irradiated blood was transfused 10 days prior to admission in PGI.

Family history revealed death of his father at 45 years of age due to electrocution. He had two elder male siblings who were alive and well. There was a history of death of two maternal uncles at age 6 and 11 months due to repeated infections. There was no history of contact with pulmonary tuberculosis.

Clinical examination: His weight was 3.5 kg (<-3Z score); length; 63 cms (at -3Z score); and head circumference: 38 cms (<-3Z score). He was afebrile with a pulse rate of 142/min which was regular and good volume. Respiratory rate was 68/min; blood pressure; 80/50 mm Hg; capillary filling time, 2 sec; and SaO2 on pulse oximetry : 76%. He looked emaciated with severe pallor and dry skin. There was no icterus, clubbing or rash. BCG scar was absent. Oral cavity examination revealed thrush.

Both lung fields revealed bilateral crepitations. No organomegaly or lymphadenopathy was detected. The cardiovascular system examination was unremarkable. On central nervous system examination, he was noted to be irritable but there were no focal neurological deficit, or signs of meningeal irritation.

Provisional diagnosis: Failure to thrive, and Repeated chest infections. A possibility of cystic fibrosis (CF) or immunodeficiency was considered.

Laboratory Investigations: His hematological, biochemical, coagulation and blood gas analyses during hospital stay are detailed in ***Tables* I and II**.

Microbiology work up showed:

Blood cultures (Day 2 and Day 4): sterile
Fungal blood culture (Day 3): sterile
Endotracheal (ET) tube aspirate (Day 3): *Klebsiella pneumoniae*
Gastric lavage for acid-fast bacilli (AFB) (Day 2 and Day 3): negative
Mantoux test: non-reactive
Urine: routine examination was normal; Urine fungal smear: negative
HIV ELISA: Non-reactive; Cytomegalovirus (CMV) IgM: positive

Primary immunodeficiency work up: Immunoglobulin profile (sent after blood transfusion): IgM < 11 mg/dL (normal 40-160 mg/dL); IgG 786 mg/dL (normal 300-900 mg/dL); IgA 61 mg/dL (normal 15-70 mg/dL).

Lymphocyte subset analysis by flowcytometry: CD3 - 45.7%; CD19 - 1.6%; CD16 - 21.7%. Impression: Both T and B lymphocyte numbers are significantly decreased; consistent with T-B-NK+ SCID (severe combined immunodeficiency).

Radiology: The initial *X*-rays done outside showed hyperinflated lungs with definite opacities in parahilar location. Subsequently, there was an increase in the homogenous opacities. Based on the *X*-rays, presence or absence and size of thymus were difficult to comment upon but it was definitely not enlarged. Subsequent *X*-rays done in our hospital showed consolidation with air

TABLE I BLOOD AND COAGULATION PARAMETERS DURING THE STAY

Dates	*Hb (g/dL)*	*TLC (per cmm)*	*DLC (%) P/L/M/E*	*Absolute lymphocyte count (per mm^3)*	*Others*
1 month before presentation*	8.5	10,600	–	–	Plat Ct. 1,67,800/mm^3
15 day before presentation*	7.8	11,200	62/28/6/4	3136	–
Day 3*	5.7	7,000	23/67/7/3	4690	–
Day 1*	8.4	7,900	32/58/7/3	4582	–
Day 1	7	5,300	–	–	Plate Ct. 73,000/mm^3
Day 2	7.8	3,200	82/3/13/2	96	Plat Ct. 81,000 /mm^3
Day 3	7.2	4,300	76/3/20/1	129	Plat Ct. 1,32,000/mm^3
Day 4					PT 18s; PTI 72%; APTT 31s; d-dimer positive
Day 5	6.3	5,200	90/3/6/1	156	Plat Ct. 74,000/mm^3

**hemograms done outside before admission in our hospital; PT-Prothrombin time; APTT: activated partial thromboplastin timb; PTI: prothrombin index; P- polymorphs; L- lymphocytes; M- monocyles; E- eosinophils.*

TABLE II BIOCHEMICAL PARAMETERS OF THE PATIENT

Parameters	*Day 1*	*Day 2*	*Day 4*	*Day 6*
Na/K (mEq/L)	123/3.7	146/3.5	145/4.6	146/5.5
Urea/creatinine (mg/dL)	30/0.2	23/0.3	76/0.6	166/1.1
S. protein (g/dL); A/G	-	5.1; 2.4/2.7	5.1; 2.6/3.5	-
S. bilirubin (mg/dL)	-	0.7	0.7	-
CRP (mg/L)	-	32	47	-
pH	7.33	-	7.4	7.05*
PaO_2 (mmHg)	102	-	63	55*
$PaCO_2$ (mmHg)	44	-	40	49*
HCO_3 (mmol/L)	23	-	25	13*

*S: Serum; A: albumin; G: globulin; *on day 7.*

bronchogram in bilateral lung fields. There was evidence of right middle lobe collapse and consolidation. Repeat *X*-rays showed evidence of pneumomediastinum. Another *X*-ray, done 2 days before death, showed bilateral diffuse homogenous opacification of both lung fields with extensive air bronchograms.

Course in hospital: The baby presented with respiratory failure for which he was intubated and put on manual IPPR. He was maintained on manual IPPR throughout the hospital stay. Though his initial SaO2 was maintained around 92%, from day three onward of hospital stay it was persistently below 80%. He was started on broad spectrum antimicrobials (ceftriaxone, amikacin, cloxacillin), which were subsequently changed to imipenem (ET aspirate report – *Klebsiella* spp). In view of the possibility of fungal infection (as evident from oral thrush) amphotericin was also started. He was transfused with packed red cell 10 mL/kg to correct anemia. With worsening sepsis and hypoxemia, he developed shock on day five of hospital stay that was managed with fluid boluses and inotropes. However, the shock was refractory and he developed oliguric renal failure and suffered a cardiac arrest from which he could not be revived.

Unit's final diagnosis: Persistent pneumonia with sepsis, oral candidiasis. A possibility of cystic fibrosis and primary immunodeficiency–SCID is considered.

Discussion on clinical protocol: We have a baby who is not thriving well since 3 months of age. So, the illness starts well in the first 6 months of age. He had repeated episodes of pneumonia with oral thrush. In fact, none of the chest *X*-rays done outside were normal. So, with this combination of symptoms immunodeficiency is very likely. Virtually there is no differential diagnosis for an

infant who presents with this combination of symptoms. If there is immunodeficiency, this can be primary or secondary. HIV infection, which is the commonest cause of secondary immunodeficiency disease, was ruled out by the treating unit. There were no other obvious causes of secondary immunodeficiency like a malignancy or exposure to glucocorticoids. So, most likely what we are dealing with is primary immunodeficiency (PID) in this child which has started in the first few months of life.

How do you suspect PID?

The Jeffrey Modell foundation has suggested 10 warning signs of a PID and this is the most well accepted guideline available to clinicians to suspect an immunodeficiency (***Box* I**).

If a child has two or more of these signs then PID is more likely. In our patient six of these signs were present. So it is more than likely that this child had PID manifesting in the first 6 months of life.

What is the likely type of PID here?

We have a 7-month-old baby with failure to thrive and repeated hospitalizations for pneumonia requiring several courses of intravenous antimicrobials. These clinical manifestations would be common to any immunodeficiency presenting in infancy, but the giveaway is the fact that he became symptomatic at 3-4 months of age and children who become symptomatic so early in life usually have a cell-mediated immunodeficiency. SCID is the syndrome of cell-mediated immunodeficiency which presents so early.

In addition, there is a family history of an X-linked recessive disorder- two maternal uncles dying in infancy with repeated infections. This is consistent with a type of SCID, the X-linked SCID – which affects only boys and the mother is usually the carrier.

Box I WARNING SIGNS FOR PID

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more episodes of pneumonia within 1 year.
5. Failure to gain weight or grow normally.
6. Recurrent deep skin or organ abscesses.
7. Persistent oral thrush or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PID.

On physical examination, the baby had severely impaired anthropometric parameters because of the illnesses he had suffered for last several months. There was no lymphadenopathy. Absence of lymphadenopathy can occur in 3 types of PID – X-linked agammaglobulinemia, SCID and hyper IgM syndrome. There is perhaps no other condition where you can get absent lymph nodes in a baby. We cannot comment on the tonsils. But again if tonsils were also absent, it is these three conditions where tonsillar tissue is not seen. He had oral thrush, which is indicative of a cell-mediated immunodeficiency, i.e. SCID.

There are significant pointers in the history and physical examination supporting the diagnosis of PID. On investigations there was significant lymphopenia. The lower limit of normal lymphocyte count from birth to 6 months is 2000/cmm; 12 months it is 4000/cmm. An absolute lymphocyte count as low as 2000/cmm during infancy is highly suggestive of SCID. Our patient had decreased T cell numbers. The serum immunoglobulin showed an IgM which was undetectable and lymphocyte subset analysis showed T-B-NK+ phenotype. So overall the investigations are supportive of a diagnosis of SCID. However, we must realise the limitations to these available investigations. We have not performed a lymphocyte proliferation response to mitogens, like phytohemaglutinin, which would have confirmed the diagnosis of SCID as lymphocytes in SCID do not proliferate to mitogen response. Similarly, we do not have an antibody response after immunization because the baby was so sick this could not be done, and most importantly, mutation analysis is not available.

SCID is one of the most difficult of all PIDs to diagnose clinically and is perhaps the only immunodeficiency where definition incorporates mutation analysis as part of the enumeration. Here, we only have clinical features and laboratory investigations consistent with the diagnosis of X-linked SCID.

What other PIDs need to be excluded?

Agammaglobulinemia is unlikely as the baby presented very early. Children with agammaglobulinemia become symptomatic after 6 months of life. In hyper IgM-syndrome, the IgM levels should be elevated. Here the IgM was absent, so this is unlikely. For chronic granulomatous disease (CGD) we do not have the reports of NBT dye-reduction or the DHR-shift on flowcytometry. These children have leucocytosis and hypergammaglobulinemia and the clinical picture is very different. Wiskott-Aldrich syndrome (WAS) could be considered because this was a male and had persistent thrombocytopenia. However, in the absence of

microthrombocytes in the peripheral smear and WAS protein in flowcytometry, this could be a clinical possibility, though less likely.

SCID is a syndrome and not a disease. There are at least 13 different types of SCID and it is impossible to differentiate one from the other without mutation analysis.

What are the common infections that are expected in SCID?

You could have many bacterial infections of both gram positive and gram negative organisms. This child had received BCG, so disseminated BCG infection can occur in this baby. *Pneumocystis jirovecii* infection can again be very prominent feature of SCID. Among the viral infections (this baby had received at least 2 un-irradiated blood transfusions), CMV could be expected as CMV IgM was positive.

The final diagnosis would be SCID with superadded infections- disseminated BCG, CMV, fungal and bacterial infections. But I must say that, the morphological correlates of SCID on autopsy are very few. SCID is not a diagnosis which you make on autopsy. The only morphological correlate would be an absent thymus or a thymus which is below 1g and this thymus would show an absence of Hassall's corpuscles and absent corticomedullary differentiation. There may be absent lymph nodes and absence of lymphocytes in Peyer's patches.

DR. MEENU SINGH: Whenever a patient with recurrent or persistent pneumonia like this comes to our unit we give slightly wider range of diagnosis to be ruled out especially after the nutritional and the chronic infection parts are taken care off. Cystic fibrosis (CF) is unlikley because of the presence of persistent pneumonia and hyperinflation in this particular child. As the investigations have revealed, it is prudent to think of PID at the outset and with the history of two maternal uncles' death in infancy, possibility of SCID was thought of and investigations were carried out. As far as the superadded infections are concerned, disseminated BCG infection is a common finding in children with SCID. However, in the beginning, one should certainly rule out CF by doing sweat chloride test. This was probably not followed in this child as the main working diagnosis was an immunodeficiency.

DR. SUNIT C SINGHI: I am not going to dispute the diagnosis that has been forwarded. I think in patient who comes at 4 months with episodes of repeated infections, the diagnosis of CF is not out especially with the chest *X*-rays showing hyperinflation. The first and second chest *X*-rays showing a shadow of the shape of thymus. But if it has completely involuted, one does not know now. On the top of that, we have counts from outside which showed lymphocytes to be normal which are difficult to explain. Is it because of the overwhelming infections that had exhausted the lymphoid tissue? It could be disseminated tuberculosis which could do all of it and it could be even any overwhelming infection. I think normal lymphocyte counts needs an explanation and to begin with at least there should be no reason not to consider other differential diagnosis causing recurrent pneumonias and CF

DR. SANJAY JAIN: With the simultaneous presence of hepatitis, pneumonitis, pancytopenia with diarrhea, diagnosis of disseminated cytomegalovirus infection (CMV) is straight-forward.

Dr. Joseph L Mathew: in our unit we arranged a date for sweat chloride test. Because he was on ventilator, we could not get it done. Secondly, the ten criteria put forth by Jeffrey Modell foundation to suspect PID, is a very sensitive definition. In other words, all children with PID will have a score of >2. Then it loses specificity in the sense that, there are infants with two episodes of pneumonia in a year who get treated with two rounds of antibiotics, they too land up in getting screened for PID with that criteria. The third point is on one side the infant is not producing IgM because his total IgM is only 11mg/dl. So, to say that he had CMV infection and he produced CMV IgM positivity would be very hard. Perhaps it is the blood transfusion which is related to this.

DR. VARUN DHIR: The strong family history just points to an X-linked disorder and with the lymphocyte count being so low the diagnosis virtually stands as SCID. Only query is why the immunophenotype demonstrating T-B-NK+ type. In fact, with absolute lymphocyte count of 150 or 100/cmm, any percentage of NK cells come as a T-B-NK. This would lead to a diagnosis of ADA deficiency type of SCID. But that is not consistent with the family history of the patient. In X-linked SCID there would be a common gamma chain. One way, we could have done it by doing common gamma chain expression by flowcytometry, which is available.

DR. SURJIT SINGH: The lymphocyte subsets in a patient with SCID is very difficult to interpret. Here, there was absolute lymphocytopenia. So, in this setting, even though some lymphocytes stained for CD3, the number was so low that we interpreted this as T-B-NK+. This is not the phenotype of X-linked SCID. X-linked SCID is T-B+NK-. I really cannot explain why this baby did not show some B cells. But SCID is a very difficult condition to enumerate without mutation analysis. If the

lymphocyte counts are as low as these, possibly there is no differential diagnosis. However, in a patient with SCID, the lymphocyte count can go up under certain situations and the most common situation is, when there is maternal engraftment of T-cells. As this was a male, if there were maternal engraftment of T-cells, the lymphocyte counts can be high. There are ways to differentiate whether these lymphocytes are the baby's lymphocytes or they belong to the mother. Normally, a SCID child does not mount an antibody response provided it is an absolute SCID, which happens in ADA deficiency (T-B-NK). These children usually would not have an antibody response to any infection. Here CMV IgM was positive. We do not know the titre whether-low titres or high titres. Several SCIDs have leaky syndrome that means they have some lymphocytes which can manifest with either an antibody response or some immunoglobulin. The immunoglobulins in this patient were never zero. Some studies have shown that some children with SCID have relatively higher immunoglobulins.

PATHOLOGY PROTOCOL

A partial autopsy was performed on this 7-month-old male child. The peritoneal and pleural cavities revealed presence of ascites and pleural effusion with 250ml of straw-colored and 150ml of hemorrhagic fluid, respectively.

The thymus weighed 2 g (normal for this age-12 g), and was small and atrophic (***Fig.* 1A**). The lobular configuration was lost and cortico-medullary distinction was not discernible on histology. The epithelial cells were present in diffuse sheets with scant Hassall's corpuscles (***Fig.* 1B**). There was marked depletion of lymphocytes with focal areas showing abundance of mast cells (***Fig.* 1C**). All these features are indicative of thymic dysplasia which is noted in patients of SCID.

All the lymphoid rests of the body, including the lymph nodes, revealed depletion of lymphoid population. A small lymph node identified in the peri-pancreatic region showed almost complete absence of lymphoid follicles and germinal centre with prominence of sinuses (***Fig.* 1D**). The T cell zones i.e. the paracortical areas revealed scant population of T lymphocytes which were highlighted by immunoreactivity with CD3 (***Fig.* 1E**). CD20 immunoreactivity highlighted the markedly depleted B lymphocytes (***Fig.* 1F**). The spleen weighed 18 g (normal for this age-25 g). On histology, there was capillarization of sinuses. The peri-arteriolar sheath, which are the T cell zones, were depleted. The submucosal lymphoid aggregates in appendix and Peyer's patches were represented by small clusters. The Peyer's patches were hard to identify on gross examination. Lymphoid depletion was also identified in the section taken from the bone marrow.

The lungs were heavy weighing 180 g (normal for age-110 g). The mucosa over the tracheo-bronchial tree was congested; all the airways were filled with inspissated secretions. Both lungs revealed diffuse consolidation with a firm texture and loss of crepitancy of lung parenchyma (***Fig.* 2A**). No areas of breaking-down abscesses or caseous necrotic foci were detected. On histology, most of the alveolar spaces were packed with granular eosinophilic secretions which were periodic acid-Schiff (PAS) positive. In other areas, instead of the granular material, the alveolar spaces were packed with foamy macrophages with finely vacuolated cytoplasm which were positive with Oil Red 'O' (***Fig.* 2B**). The features are indicative of endogenous lipoid pneumonia developing secondary to obstruction. Interstitial fibrosis and inflammation was minimal. At places, the inspissated secretions had tracked down to the respiratory bronchioles and alveolar spaces with surrounding parenchyma showing features of bronchopneumonia and collections of Gram negative cocci. In addition, many multinucleated giant cells were identified within the alveolar spaces (***Fig.* 2C**). Occasional CMV inclusions were noted within the alveolar lining cells (***Fig.* 2D**). Squamous metaplasia within the bronchiolar lining was noted at places. Furthermore, features of diffuse alveolar damage with formation of hyaline membrane were identified. Polymerase chain reaction (PCR) done for detection of Respiratory Syncytial Virus (RSV) was performed.

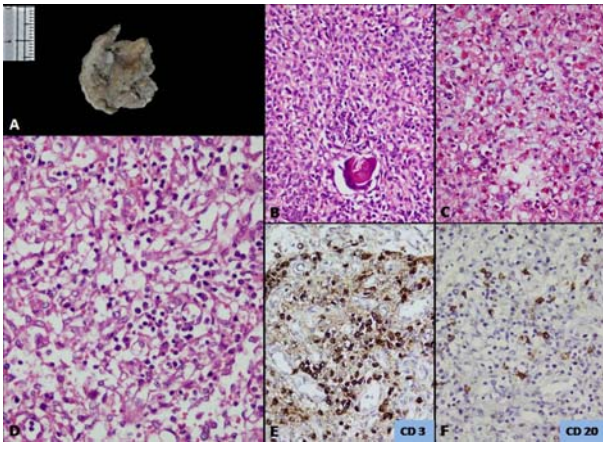

FIG. 1 *(a) Small and atrophic thymus with loss of lobular configuration, (b) Epithelial cells in diffuse sheets and scant Hassall's population and depleted lymphoid cells (H&E x400); (c) Increased number of mast cell within the thymic parenchyma (H&E x400); (d) Lymph node with absent of lymphoid follicles and germinal centre and marked depletion of lymphocytes (H&E x400); and (e & f) CD3 and CD20 immunostaining reveals scant population of T- and B-cells, respectively (immunoperoxidase ×400); color images at www.indianpediatrics.net*

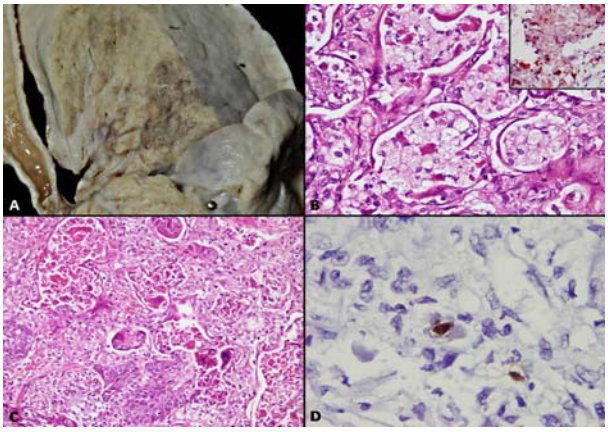

FIG. 2 *(a) Gross pictures of cut surface of right lung showing diffuse consolidation; (b) Alveolar spaces packed with finely vacuolated macrophages (H&E x400); inset – Positivity with oil-Red-'O' (H&E x400); (c) Multinucleated giant cells lining the alveolar spaces (H&E x400); and (d) Occasional Cytomegalovirus inclusion detected with immunostain for CMV antigen. (immunoperoxidase ×400); color images at www.indianpediatrics.net*

In the lung, no granulomas were identified and Ziehl-Neelsen stain for AFB was negative. The liver weighed 158gms (normal for this age-280gms) and did not reveal any significant pathology. No features to suggest cystic fibrosis were identified in liver and pancreas microscopically. Similarly, vas deferens and testes were normal. Large and small intestine did not reveal any inspissated secretions. Kidneys were fused at the lower pole with isthmus present posterior to the aorta. Adrenals weighed 1.5 g (normal for this age-5.5 g), on microscopic examination revealed cytomegalovirus inclusions within the adrenal cortical cells. Heart including other organs was within normal limits on gross and microscopic examination.

DR MINI P SINGH: The lung tissue which we received was subjected to RNA extraction using the trizol method, and subjected it to RT-PCR for both the human RSV and human metapneumovirus (MPV). The sample was positive for RSV with a band corresponding to 680 base pair length of DNA and negative for MPV.

Autopsy diagnosis

A case of severe combined immunodeficiency with

- Thymic dysplasia with marked lymphoid depletion in lymph nodes, spleen, appendix, Peyer's patches, and bone marrow
- Bronchopneumonia and diffuse alveolar damage (due to RSV)
- Endogenous lipoid pneumonia
- Cytomegalovirus (CMV) inclusion in lungs and adrenals
- Horse-shoe kidney
- Ascites and pleural effusion

OPEN FORUM

DR SUNIT C SINGHI: I have several queries. Regarding the diagnosis as it was put forward was not in doubt. But, it does not explain how the BCG did not cause a disease here, which could not happen with SCID as far as I know. The lymphocyte counts done outside in the first 2 months were normal. Is it because they don't do it or is there any explanation for these normal counts? In this age group, the CMV infection usually involves the lungs. If it is not there, there would be an explanation for this.

DR SK JINDAL: How long after the BCG vaccination there can be recrudescence? Normally, after BCG inoculation the bacilli disappear after few weeks and subsequently the immune reaction which is there and which is the purpose of BCG vaccination. In this case, the vaccination was given at birth and the child developed infection after several months. So, disseminated BCG infection could not be considered as a clinical diagnosis.

DR MEENU SINGH: Regarding the endogenous lipoid pneumonia as it was presented, it was following an obstruction. Is it the mucous causing bronchiolar obstruction or is it because of RSV infection which can lead to obstruction and lipoid pneumonia? Mostly lipoid pneumonias are because of milk aspiration as milk contains fat globules.

DR PRATIBHA D SINGHI: No significant infection other than RSV and CMV were present. The presence of gross ascites with straw colour fluid and pleural effusion are not usual features of RSV infection alone. Do we have any explanation for this?

DR KIRTI GUPTA: Detection of CMV inclusion in the lungs was very difficult and these were picked up on immunohistochemistry. Regarding lipoid pneumonias, it includes 2 types – the endogenous and exogenous. The exogenous one is due to milk aspiration whereas; the endogenous one occurs due to obstruction of the major airways. So, there was excess production of mucous because of infections and this mucous got reabsorbed and collected in macrophages. And this is not CF as in CF the impaction of thick viscid secretions occurs in the bronchial glands not in the major airways like in this case.

DR S PRABHAKAR: Is there any explanation for the three reports of lymphocyte counts done outside which mentioned lymphocyte counts of 28-58%?

DR SURJIT SINGH: SCID is associated with low lymphocyte counts and the more severe the

immunodeficiency the lower would be the lymphocyte counts. The absolute lymphocyte count in fact can be used for the screening for SCID. Any baby in the first 12 months of life, who has an absolute lymphocyte count below 3000 is very likely to have SCID, and any baby who has less than 2000 has to have SCID. Absolute lymphocyte counts are frequently missed as paediatricians mostly focus on neutrophils. Newborn screening for SCID is now a reality, because this is a true medical emergency and if transplantation is done in these babies within a few months of life, chances of survival are 80-90%. Why this baby did not have disseminated BCG infection even when the BCG vaccine had been given? There could be many reasons for this. SCID is not a disease, it is a syndrome and it depends on how severe is the immune deficiency. There are all kinds of phenotypes which can manifest as SCID. Depending on the T-cell response one may or may not have infection with one or more of the organisms. So, it is not surprising that BCG has not disseminated.

DR RK RATHO: Regarding CMV IgM positivity, in contrast to the cut-off value of 0.3 this patient had 1 OD. It is definitely quite high. Patient with SCID with CMV IgM positivity, having CMV inclusions imply that it was an active response to infection rather than due to transfusions. Also, suppose the patient was diagnosed with RSV infection during life, what would be the way of treatment? Do you have ribavarin treatment or other prophylactic measures?

DR MEENU SINGH: Probably we have to educate the public regarding immune deficiency. In presence of a suspicious family history, one should definitely go for screening procedures. Common infections encountered in immune deficient patients are RSV. It is more severe in patients who have underlying lung disease, immune deficiency, CF, heart disease etc. In these patients ribavarin is recommended. Especially in patients who are to be put on ventilator, a special circuit is connected for administering ribavarin. Our patient was on ambu bag ventilation and not on a mechanical ventilator.

DR S PRABHAKAR: Pediatricians see these cases more frequently; for others, it is not such a common disease and this case was instructive.

DISCUSSION

Primary immunodeficiency disorders (PIDs) comprise more than 150 different disorders that affect the development, function, or both of the immune system [1]. All forms of PIDs are rare and have an overall prevalence of approximately 1:10,000 live births with the exception of IgA deficiency. PIDs are classified into eight major categories (***Box* 2**) according to the component of the immune system primarily involved [1].

SCID disorders involve both B- and T- cells and includes about 22 different groups of diseases within its category [1,2]. Most of the B-cell abnormalities appear secondary to the lack of T-cell help, which underscores the role of T-cell in B-cell development. Inheritance of this congenital syndrome may show X-linked or autosomal recessive pattern. Affected infants are highly susceptible to recurring infections of viruses, fungi and bacteria and invariably die within 2 years of birth. The patients usually present within first six months of life with failure to thrive, chronic diarrhea, persistent oral thrush, skin rash, pneumonia, and sepsis. Disseminated BCG infection is commonly seen in patients with SCID. Similarly, prolonged interstitial pneumonia of viral etiology such as parainfluenza virus or cytomegalovirus or *Pneumocystis jerovicii* is also common in patients with combined immunodeficiency [3,4].

The autopsy findings in the index case highlight the morphological changes encountered in patients with SCID–thymic dysplasia, hypoplasia of spleen, lymph nodes and marked depletion of lymphocytes in all the lymphoid reservoirs of the body. Mast cell hyperplasia within the thymus is an interesting morphologic feature reported in SCID patients early in the literature [5]. The patients are prone to repeated respiratory infections secondary to immunodeficiency. RSV has been earlier reported in autopsy series in SCID infections [6]. It usually manifests with presence of multinucleated giant cells lining the alveolar spaces. Infection with CMV in SCID has also been well-documented in the literature [7]. Rare examples of endogenous lipoid pneumonia, developing secondary to obstruction have been documented in autopsy cases of SCID [8]. In endogenous lipoid pneumonia fat-filled finely vacuolated macrophages fill the alveoli as seen in the index case. CF was excluded based on absence of characteristic

Box 2 CLASSIFICATION OF PRIMARY IMMUNO-DEFICIENCY DISORDERS

1. Combined T-cell and B-cell immunodeficiencies
2. Predominantly antibody deficiencies
3. Other well defined immunodeficiency syndromes
4. Diseases of immune dysregulation
5. Congenital defects of phagocyte number and function
6. Defects in innate immunity
7. Autoinflammatory disorders
8. Complement deficiencies

morphologic findings at autopsy for instance- secondary biliary cirrhosis, small atrophic gall bladder, inspissated secretions within pancreatic ducts, meconium ileus and absence of vas deferens.

Endogenous lipoid pneumonia in autopsy series of SCID patients has seldom been documented in the literature and the index case in addition to the other features, adds observational data to the examples of SCID autopsy patients reported in the literature.

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