An Infant with Prolonged Fever

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We present an infant who presented with fever and generalized rash. She also had hepatosplenomegaly and persistent respiratory distress, and later developed multi-organ failure.

CLINICAL PROTOCOL

History: A seven-month-old, developmentally normal girl – born at term with birth weight of 2.5 kg to a non-consanguineously married couple – presented with fever and rash for 1½ months. The illness started with generalized erythematous, maculopapular rash involving the flexural areas, scalp and trunk, along with intermittent fever. The rash subsided over 15 days leaving behind a dry, scaly skin. During this period, she also developed cough and rapid breathing, and had received intravenous antimicrobials elsewhere with only partial response. The child was referred to our institute in view of reappearance of fever, rash and pedal edema. At admission, she had fever, cough, rapid breathing, poor feeding and irritability, along with dry scaly skin and fading rash. The child was first in birth order with no significant family history of prolonged illness, tuberculosis, or any unexplained death in family. She was immunized for age, and BCG site had a normal scar.

Clinical examination: She weighed 5.6 kg (<–2 SD); length was 62 cm (-2 SD). She was afebrile with pulse rate of 106/min, respiratory rate of 56/min and blood pressure of 94/60 mmHg. The skin was dry, scaly and eczematous with rash predominantly over the scalp and lower limbs with involvement of palms and soles. Bones and joints were normal as was examination of ears, nose and throat. Systemic examination revealed soft, distended abdomen with palpable liver (5 cm under costal margin with a span of 7 cm) and spleen (1.5 cm under left costal margin). The child also had tachypnea along with subcostal and substernal retractions; crepitations were auscultable over bilateral lung fields. Cardiovascular and neurological examinations were unremarkable.

Investigations **(*Tables* I** and **II**): Before presenting to our institute: C reactive protein (CRP) 1.2 mg/dL, lactate dehydrogenase (LDH) 246, procalcitonin 0.3 ng/mL, S. ferritin <10 ng/mL, ultrasonography abdomen normal, 2D-echocardiography (ECHO) and chest *X*-ray (CXR) normal, HIV serology non-reactive, hepatitis B surface antigen (HBsAg) negative. Dengue serology, malaria serology and widal tests were also negative. Blood culture grew *Pseudomonas stutzeri* and *Acinetobacter woffii*. Immunoglobulin levels were: IgA 87 mg/dL and IgG 1176 mg/dL.

Skin biopsy was done at our institute. Epidermis showed acanthosis with hyperkeratosis. The dermis showed mild perivascular infiltration with lympho-mononuclear cells and occasional histiocytes. Investigations at our institute : S. ferritin: 6.9 ng/mL, HIV non-reactive; anti-nuclear antibodies and anti-nuclear cytoplasmic antibodies were absent. Chest *X*-Ray and high resolution CT scan chest revealed small focal area of consolidation in right upper lobe. No evidence of bronchiectasis, pleural or pericardial effusion were seen. Ultrasonography of abdomen showed mild hepatomegaly with grade I fatty liver.

Bone marrow examination showed normocellular bone marrow with normal hematopoietic elements and mild prominence of histiocytes. CD1a staining was negative. Bronchoscopy was normal, broncho-alveolar lavage (BAL) did not show acid-fast bacilli (AFB) or fungus; BAL culture was sterile and BAL fluid did not have hemosiderin laden macrophages.

Microbiological investigations: Blood culture and sensitivity (thrice): sterile. Bone marrow culture: sterile, *Cytomegalovirus* (CMV) IgM antibody: negative, CMV polymerase chain reaction: negative, *Mycoplasma* serology: 1/64 (normal 1/32), *Toxoplasma* serology, *Brucella* serology: negative; Gastric lavage for AFB, fungus and *Pneumocystis jiroveci* were negative. Endotracheal (ET) aspirate culture revealed growth of

TABLE I HEMATOLOGICAL INVESTIGATIONS IN THE PRESENT CASE

Date	*4/08/14*	*27/08/14*	*17/09/14*	*30/09/14*	*7/10/14*
Hb (g/dl)	7.7	9.2	7.0	10.2	8.0
TLC/mm^3	23,900	24,900	23,600	14,700	50,300
DLC (%)	$P_{56}L_{37}$	$P_{50}L_{47}$	$P_{55}L_{39}M_3E_3$	$P_{39}L_{49}M_9E_3$	$P_{80}L_{10}M_3E_1$
ANC/mm^3	13,384	12,450	12,980	5,733	40,000
ALC/mm^3	8,843	11,703	9,204	7,203	5,030
Platelets/mm^3	5.20	7.49	7.87	6.98	4.26
ESR (westergreen, mm in 1st hr)		44	51	24	7

yeast; AFB stain was negative. Urine culture was sterile and Galactomannan assay was normal.

Immunological investigations: There was hypergammaglobulinemia with elevated serum IgG [1294 mg/dL (N 300-900)], IgM [201 mg/dL (N 40-160)] and IgE [248 IU/mL (N 0-6.6)]. Nitro blue tetrazolium test (NBT): Unstimulated 30%, stimulated 95%; Dihydrorhodamine (DHR): MFI unstimulated 1688 (control 869); MFI stimulated 8886 (control 8211); Oxidative Index: 5.2 (control 9.4), showed normal shift to right. Repeat DHR 12 days later: oxidation after stimulation of neutrophils showed minimal shift to right. MFI unstimulated 3180 (control 2622); MFI stimulated 5367 (control 11,806). Oxidative index: 1.68 (control4.5). P_{67}*phox*: reduced expression.

Course and management: The child received antibiotics, but her respiratory distress worsened during hospital stay. In view of persisting pneumonia, primary immunodeficiency was considered. Chronic granulo-matous disease (CGD) was considered as DHR was abnormal and P_{67}*phox* expression was low. Following bronchoscopy, respiratory distress worsened, mechanical ventilation was initiated on 15th day of hospital stay; vancomycin, piperacillin-tazobactam, amphotericin and cotrimoxazole was started empirically. She was ventilated in SIMV mode for 3 days followed by high frequency oscillatory ventilation for 8 days. She continued to worsen resulting in respiratory acidosis with persistent hypoxemia. She received two red cell transfusions for anemia during hospital stay, and later developed multi-organ dysfunction, renal failure. She died on day 30 of hospital stay.

TABLE II BIOCHEMICAL INVESTIGATIONS IN PRESENT CASE

Date	*24/09*	*04/10*	*13/10*
Sodium	137	138	141
Potassium	5.7	6.0	5.3
Ca/PO4	9.2/4.9	9.8/4.6	8.2/3.4
Urea	18	22	57
Creatinine	0.40.4	0.6	0.8
S.Bilirubin	0.7	0.7	
S.Protein/Albumin	5.5/NA	6.4/2.4	
SGOT/SGPT	28/NA	56/33	
Cholesterol		117	
Triglycerides		557	
CRP		28	

NA-Not available; Ca-serum calcium; Ph.-serum phosphorus; CRP-C-reactive protein.

Unit's final diagnosis: Chronic granulomatous disease with severe pneumonia, health care associated sepsis, and acute respiratory distress syndrome.

Discussion (Clinical discussant): This infant presented with prolonged fever, and infections with an underlying immune deficiency, inflammatory disorders or neoplastic disorders were considered. The neoplastic disorders which can present in infancy with prolonged fever are leukemia, lymphoma, Langerhans cell histiocytosis (LCH), neuroblastoma, and Castleman's disease. A normal bone marrow examination excluded these diagnosis, except for LCH. Though skin biopsy revealing a CD1a would have been more helpful, still in the absence of bone disease, bone marrow showing CD1a negativity, and chest *X*-ray not suggestive, LCH did not appear to be a clinical possibility. Among the auto-inflammatory or autoimmune disorders, systemic lupus erythematosus (SLE) could be ruled out as ANA was negative; absence of gastrointestinal disease rules out the inflammatory bowel disease (IBD) and absence of oral ulcers nearly rules out Behcet's disease. Child did not have features of Kawasaki disease, and normal cell counts and ferritin levels made possibility of hemophagocytic-lympho-histiocytosis unlikely. Systemic onset juvenile idiopathic arthritis (sJIA) may or may not have arthritis as a prominent feature but presents classically as fever, rash,

hepatosplenomegaly and serositis. These patients have polymorphonuclear leucocytosis and thrombocytosis which were seen in this child. However, the rash is classically evanescent in sJIA, not like fixed flexural rash as in this baby. The initial CRP and ESR were normal, and a normal ferritin nearly rules out any inflammatory disorder like sJIA.

Many infectious causes can lead to prolonged fever in infancy. In this child, the focus was lung, and the organisms isolated were *Pseudomonas*, *Acinetobacter and Candida*. With HIV being ruled out, primary immune deficiencies should be considered. The conditions which are likely to present at this age are; severe combined immune deficiency (SCID), a hyper-IgM disorder, CGD and Wiskott Aldrich syndrome (WAS). WAS is an X-linked disorder and is very unlikely in a girl child. Hyper-IgM can have autosomal recessive or X-linked transmission. Patients can have recurrent respiratory infections, including *Pneumocystis jiroveci* pneumonia. They can also have immune dysregulation and malignancies. Neutropenia may be seen and they classically have low IgG, IgA and a high or normal IgM. The index child had raised IgG along with IgM. CD40, which is usually low in autosomal recessive hyper-IgM, was normal in this child, rendering the diagnosis of hyper-IgM unlikely. SCID presents as severe fatal infections in infancy and classically, these children have lymphopenia, hypogammaglobulinemia and absent thymus. Therefore, SCID looks unlikely, but European society for immunodeficiency (ESID) criteria for diagnosis of SCID suggest laboratory criteria of low CD3 cells, and reduced naïve CD4 and CD8 T cells. The index child having low CD3 and reduced naïve T cells, SCID cannot be completely ruled out. These patients, because of the autologous circulating T cells, frequently have skin rash, enlarged lymph nodes and even normally sized thymus. They can present atypically even beyond infancy with granulomas and lymphoid malignancies [1].Thus, the index child could have had SCID without lymphopenia because of autologous T cells or it could be a leaky SCID with hypomorphic mutations which are not very lethal. The immunoglobulins in SCID can be very variable because of transplacentally transferred IgG; in an event of infection, the IgM can also rise [2]. SCID with maternal engraftment can have T cells with no lymphopenia; they have a graft versus host disease (GVHD) like illness, presenting with rash, hepatosplenomegaly and raised IgE. These features were seen in this child; however, other two important features of diarrhea and eosinophilia were not seen.

Chronic granulomatous disease is a result of phagocyte dysfunction and patients present with recurrent bacterial deep seated infections. Classical features of excessive inflammation(polymorphonuclear leucocytosis, hypergammaglobulinemia) and an abnormal DHR were present in this child. The P_{67}*phox* expression was low, supporting the diagnosis of CGD. A child with CGD usually has an abnormal NBT and an abnormal respiratory burst in activated lymphocytes which is usually less than 5% of the control. In this case, DHR was low but the difference from the control was not more than 5%; and an NBT was normal. Situations in which one can have a falsely abnormal DHR with normal NBTare: myeloperoxidase deficiency, the SAPHO syndrome and G6PD deficiency. These are unlikely in the index child, because these are reasonably milder immune deficiencies. Therefore, autosomal recessive CGD (AR-CGD) appears to be a strong possibility. AR-CGDs are milder diseases than *X*-linked CGD. They have slow smouldering disease, leucocytosis, hypergammaglobulinemia, abnormal DHR and can have low P_{67}phox expression. The low number of T cells and the naïve T cells can be explained because of sepsis that can cause increase in apoptosis in both the subsets of CD3 T cells, and can result in a falsely low CD3 T cells [3].

The final diagnosis of the unit was pneumonia with disseminated fungal disease, underlying primary immune deficiency, AR CGD with severe sepsis and with low naïve T cells, a possibility of SCID with maternal T cell engraftment.

Senior Resident of treating unit: The diagnosis was difficult because initial NBT report was normal. However, with a strong possibility of CGD, DHR was done which was abnormal following which P_{67}*phox* was assayed which helped clinch the diagnosis. Autosomal recessive CGD is rare but in the presence of mutations in P_{67}*phox* genes, the diagnosis can be made. These children present with recurrent infections and granulomatous inflammation.

Pediatrician 1: The crucial investigation here is DHR. If the DHR is abnormal, diagnosis is almost certain. Though the DHR shift is not as marked as one would see in X-linked CGD, which is the commoner variant. However, with this DHR report, there really is no differential diagnosis.

Chairman: It seems that this child was born with some kind of immune deficiency and most likely CGD. Can other defects of innate immune system like complement deficiencies present at this age with bacterial infections, and do we need to rule them out in such situations?

Clinical discussant: Yes, complement deficiencies can also lead to recurrent infections but usually the children

with complement deficiencies present with recurrent *Neisseria* infections and slow smouldering course not usually fatal in infancy.

PATHOLOGY PROTOCOL

A partial autopsy was performed, and the peritoneal cavity revealed ascites with 300 mL of straw-colored fluid. The pleural cavities and pericardial cavity were normal. The lungs were heavy (150 g), and the overlying pleura was dull. Inspissated secretions were identified within airways. Both lungs revealed lower lobe consolidation with a firm texture and loss of crepitancy of lung parenchyma (***Fig* 1*a***). An infarct (1.5 cm), was identified in left lower lobe. No areas of breaking-down abscesses or caseous necrotic foci were detected. On histology, most of the respiratory and terminal bronchioles revealed ulcerated epithelium and the lumen were filled with Periodic acid-Schiff (PAS) positive inspissated secretions. The alveoli were filled with pigmented macrophages (***Fig* 1*b***). The pigment was PAS positive consistent with lipofuscin-like material. CD 68 immunostain highlighted these macrophages (***Fig* 1*d***). Many multinucleated giant cells with ill-formed epithelioid granulomas were noted within interstitium (***Fig* 1*c***). The rest of the lung showed features of bronchopneumonia, diffuse alveolar hemorrhage and occasional fibrin thrombi within pulmonary vein. Additionally, the infarct microscopically revealed presence of Aspergillus hyphae with early invasion into the lung parenchyma (***Fig* 1*e***). Gram's stain, and stain for AFB and Nocardia were negative. Polymerase chain reaction (PCR) for respiratory syncytial virus, metapneumo virus, influenza virus and parainfluenza virus were negative.

Heart weighed 60 g; the anterior and posterior pericardial surfaces were normal. Right ventricular dilatation was noted. There was discoloration of the left ventricular wall along inflow and outflow tract (***Fig.* 2*a***). On histology, pericarditis was identified which featured similar macrophages, and few giant cells. The inflammation was extending to underlying myocardium which revealed myocyte loss, necrosis and interstitial edema. Many well-formed granulomas associated with giant cells were identified in the myocardium of both ventricles including papillary muscles and atrium (***Fig.* 2*b*** and **2*c***). The infiltrate was chiefly composed of macrophages (highlighted by CD68) and few lymphocytes (CD3+). PCR done on heart tissue for Coxsackie was negative.

Liver weighed 250 g with pale appearance suggestive of fatty change. Microscopically, macrovesicular steatosis and canalicular cholestasis was noted. Many granulomas were identified within the portal tracts (***Fig* 2*d***), and lobule composed of similar cellular infiltrate. Spleen weighed 21 gram was within normal limits both on gross and microscopic examination. The lymphoid population was preserved. Kidneys weighed 105 gms with pale and blotchy cortical surface. Similar granulomas were identified in the interstitium wherein the

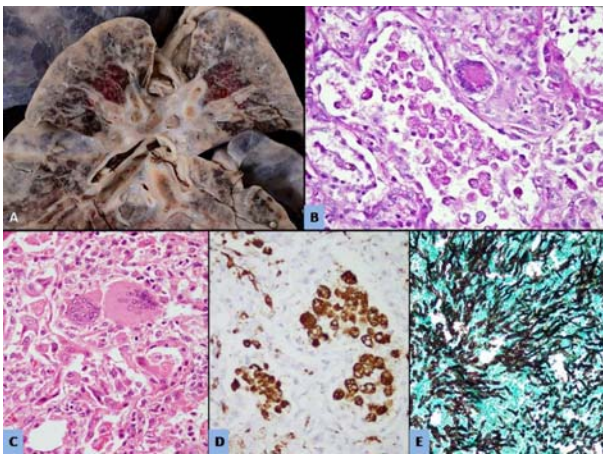

FIG. 1 *(a) Cut surface of lungs with diffuse consolidation and inspissated secretions within the airways; (b): The alveoli demonstrating periodic acid-Schiff (PAS) positive pigmented macrophages within its lumen (PAS x400, original magnification); (c): Many multinucleated giant cells with ill-formed epithelioid granulomas noted within interstitium of the lung (H&E × 400); (d): CD 68 immunostain highlighting the macrophages (immunoperoxidase × 400); (e): Methamine silver stain highlighting the septate, slender Aspegillus hyphae. (Methamine silver × 200).*

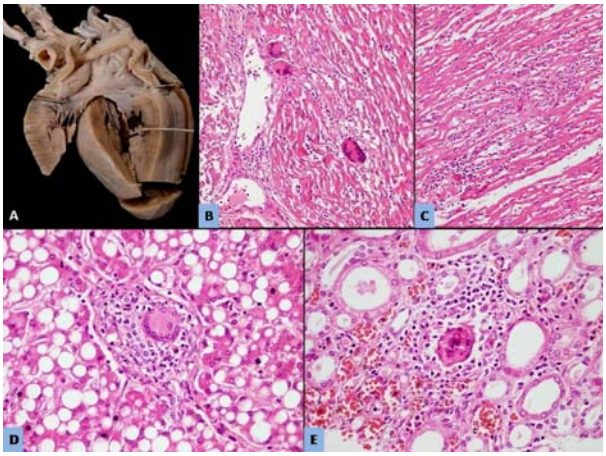

FIG. 2 *(a): Gross photograph of heart depicting discoloration of the left ventricular wall; (b and c): Well-formed granulomas associated with giant cells identified in the myocardium of both ventricles (H&E × 200); (d): Well-formed granulomas with giant cells within the portal tracts (H&E × 400); (e): Similar granulomas within the interstitium of kidneys (H&E × 400).*

macrophages were filled with similar material (***Fig* 2*e***). Additionally glomerular immaturity (70-80% immature glomeruli) with pigment cast nephropathy was noted with proximal tubules in the cortex filled with pigmented casts. Occasional thrombi were identified in one of the tributaries of renal veins. Sections from the entire gastrointestinal tract, including stomach, esophagus, small and large intestine were normal. No pigmented macrophages were noted within the lamina propria. Granulomas were also identified in random sections taken from skeletal muscle, connective tissue around cartilage, and subcutaneous fat in section from the abdominal wall (***Fig* 3*a-c***). Bone marrow, thymus and mesenteric and hilar lymph nodes showed preserved T and B cell population highlighted by CD3 and CD20 immunostains (***Fig* 3 *d-f***). Hemophagocytosis was noted in lymph nodes and spleen.

Overall autopsy diagnosis

- Granulomatous inflammation admixed with pigmented macrophages involving lungs, heart, liver, kidneys, Cartilage, skin and skeletal muscle — consistent with Chronic Granulomatous disease
- Invasive Aspergillosis in lungs
- Hemophagocytosis (Lymph node and spleen)
- Ascites

Severe combined immunodeficiency (SCID) was unlikely due to normal thymus and preserved lymphoid population within the lymphoid organs.

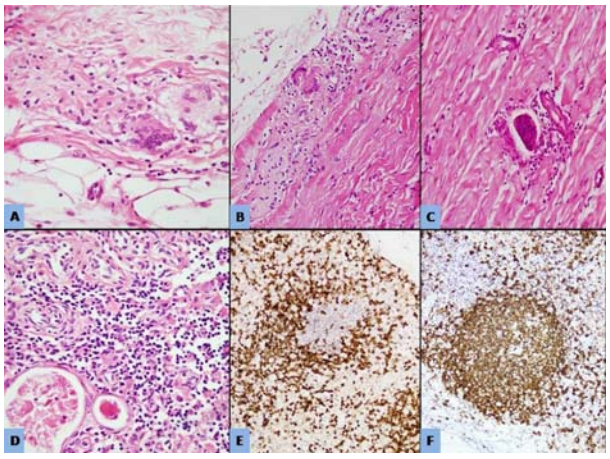

FIG. 3 *Granulomas with giant cells within the subcutaneous fat (A); Skeletal muscle(b); connective tissue (c) (H&E x400). Thymus depicting preserved T and B cell population (d: H&E x400);CD3 immunostain highlighting the preserved T cell population (e: immunoperoxidase x200); CD20 immunostain highlighting the preserved B cell (f: immunoperoxidase x200).*

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Pediatrician 1: The fact that the child remained well for initial 5 months of life virtually rules out usual kinds of severe combined immunodeficiency. The deterioration started in second half of infancy. Humoral immunodeficiencies are the commonest group to appear at this age. Humoral immunodeficiency was ruled out by doing immunoglobulin levels which were elevated. CGD can have two kinds of presentation. Usual presentation is what was seen in this child, a slow, smouldering course. It typically presents with a consolidation in the lungs which does not resolve. Fine needle aspiration of the lung lesion reveals fungus. Children with X-linked CGD can have very rapid, fulminant course. This case fits with CGD, and because the child had autosomal recessive form of CGD, the dissease course was not rapid. The complement deficiencies present as a catastrophe with rapid downhill course and these children usually do not survive the episodes of infections. The pathological findings in this child were consistent with those for CGD, but we cannot label this child as having CGD till we have a molecular and genetic diagnosis.

Pediatrician 2: What is the mechanism for presence of these pigmented macrophages which have been shown so prominently in this case?

Pathology discussant: When Pphox assays and genetic analysis was not being widely done, the presence of these pigmented macrophages was considered to be a very important marker for the diagnosis of CGD. The mechanisms proposed are that the pigment is some uncharacterized pigment from the microbes to which the phagocytes of these children are constantly exposed to. Due to inherent defect in phagocytosis, this pigment gets collected within the cells. It is believed to be lipofuscin or lipofuscin-like pigment which is PAS positive.

Pathologist 1: In my opinion, the granulomas found in the myocardium were not because of the infection but were due to the disease (CGD) itself.

Chairman: Because CGD is a phagocytic defect, intracellular killing of the organisms is impaired. Consequently, the macrophages have persistence of the organisms and their particles. Persistence of this infectious material incites granuloma formation. Therefore, in the end it is infection only causes formation of granulomas.

DISCUSSION

Chronic Granulomatous disease (CGD) is an inherited disorder of phagocytic cells [4] caused by mutations in any of the five genes encoding the various sub-units of

NADPH-oxidase system [5-8]. The resultant defect causes an inability of phagocytes to generate the bactericidal superoxide anions and hence an inability to contain certain infectious pathogens. Any one of five genes encoding the structural or regulatory subunits of phagocyte NADPH oxidase complex might be affected, of which most common is the X-linked-gp91^{phox}, other four are inherited as autosomal recessive [5-8]. The disease is relatively uncommon, affecting 1in 2,00,000 and 1 in 2,50,000 live births [9]. It manifests in infancy or childhood with repeated, severe bacterial and fungal infections which are difficult to treat. Infections by catalase positive organisms are most common, particularly *Staphylococcus aureus, Bukholderia cepacia , Serratia marcescens, Nocardia and Aspergillus* [9].

CGD is heterogenous in its manifestations, related to the subtypes, and severity of associated macrophage defect. In majority of patients, the superoxide production is undetectable resulting in early manifestations. Rarely, there are low levels of respiratory burst activity which may delay the manifestations into early adulthood [10]. Histological features in various organs are: active chronic inflammation, with or without abscess or granuloma formation, and presence of pigmented macrophages [4, 11-13]. Pigmented macrophages in various organs, especially hepatic sinusoids and colonic mucosa, have been described as a characteristic feature [11]. The pigment within the macrophages is PAS-positive and proposed to be lipofuscin-like pigment, the wear-and-tear pigment of the body. in the present case, granulomas were identified in all the organs, including lung, liver, kidneys, skin, connective tissue and heart. Involvement of the heart by the granulomatous inflammation in the present case has not been described commonly. CGD has been listed as one of the extremely rare causes of granulomatous inflammation of the heart [14]. The nature of the cellular infiltrate helps to differentiate this from viral myocarditis, where the infiltrate is chiefly composed of lymphocytes in contrast to CGD where pigmented macrophages are the predominant cells. Similar granulomatous involvement of the connective tissue of the body, including the deeper dermis and subcutaneous fat was another remarkable feature noted in the present case.

REFERENCES

1. Shearer WT, Dunn E, Notarangelo LD, Dvorak CC, Puck JM, Logan BR, *et al*. Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: The Primary Immune Deficiency Treatment Consortium experience. J Allergy Clin Immunol. 2014;133:1092-8.
2. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, *et al*. Human severe combined immunodeficiency: Genetic, phenotypic and functional diversity in one hundred eight infants. J Pediatr. 1997;130:378-87.
3. Hotchkiss RS, Osmon SB, Chang KC, Wagner TH, Coopersmith CM, Karl IE. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. J Immunol. 2005;174:5110-8.
4. O'Shea PA. Chronic granulomatous disease of childhood. Perspect Pediatr Pathol. 1982;7: 237-58.
5. Segal AW. Absence of both cytochrome b-245 subunits from neutrophils in X-linked chronic granulomatous disease. Nature. 1987;326:88-91.
6. Baehner RL. Chronic granulomatous disease of childhood: Clinical, pathological, biochemical, molecular, and genetic aspects of the disease. Pediatr Pathol. 1990;10:143-53.
7. Umei T, Takeshige K, Minakami S. NADPH-binding component of the superoxide-generating oxidase in unstimulated neutrophils and the neutrophils from the patients with chronic granulomatous disease. Biochem J. 1987;243:467-72.
8. Curnutte JT, Kuver R, Scott PJ. Activation of neutrophil NADPH oxidase in a cell-free system. Partial purification of components and characterization of the activation process. J Biol Chem. 1987;262:5563-9.
9. Winkelstein JA, Marino MC, Johnston Jr RB, Boyle J, Curnutte J, Gallin JI, *et al*. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore). 2000;7:155-69.
10. Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G. Chronic granulomatous disease: A review of the infectious and inflammatory complications. Clin Mol Allergy. 2011;9:10.
11. Levine S, Smith VV, Malone M, Sebire NJ. Histopathological features of chronic granulomatous disease (CGD) in childhood. Histopathology. 2005;47:508-16.
12. Schappi MG, Smith VV, Goldblatt D, Lindley KJ, Milla PJ. Colitis in chronic granulomatous disease. Arch Dis Child. 2001;84;147-51.
13. Schappi MG, Klein NJ, Lindley KJ, Rampling D, Smith VV, Goldblatt D, *et al*. The nature of colitis in chronic granulomatous disease. J Pediatr Gastroenterol Nutr. 2003;36;623-31.
14. Ferrans VJ, Rodríguez ER, McAllister HA Jr. Granulomatous inflammation of the heart. Heart Vessels Suppl. 1985;1:262-70.