Case Report

Recurrent episodes of pneumonia in a toddler: Don't forget chronic granulomatous disease

Alkesh Kumar Khurana[1], Abhishek Goyal[1], Ujjawal Khurana[2], Bhavna Dhingra[3]

Departments of [1]Pulmonary Medicine, [2]Pathology and Lab Medicine and [3]Pediatrics, AIIMS Bhopal, Bhopal, Madhya Pradesh, India

Abstract

A 4-year-old boy presented with community acquired pneumonia, hepatosplenomegaly and bilateral cervical lymphadenopathy. The peripheral blood film showed significant monocytosis and bone marrow examination revealed multiple histiocytic granulomas. Presence of CD 68 positive granulomas supported by cytological findings enabled us to make a diagnosis of chronic granulomatous disease.

Keywords: Chronic granulomatous disease, granulomas, pneumonia

Introduction

Chronic granulomatous disease (CGD) is a rare congenital immunodefeciency disorder characterized by impaired phagocytosis.[1] Pathogenic mutations cause dysfunctional NADPH oxidase. This results in inability to produce superoxide anion necessary for killing of bacterial and fungal microorganisms. Consequently these patients develop recurrent infections by *Staphylococcus aureus*, *Serratia marcecens*, *Burkholderia cepacia*, *Nocardia* and *Aspergillus* species. The widespread non-caseating granulomas may be seen in lungs, liver, spleen, skin, and gastrointestinal tract. Immunohistochemical markers aid to make the diagnosis.[2] This case is presented to make the physicians keep a high index of suspicion in cases of non-resolving or recurrent episodes of pneumonia.

Case Report

A 4-year-old boy presented to our hospital with complaints of dyspnea and cough for the last one month. He was diagnosed with pneumonia previously and had received cephalosporins for more than a week without any improvement. A chest radiograph, a week before had shown consolidation in right upper zone. There was a history of recurrent respiratory infections since infancy for which he had received anti tuberculous therapy (ATT) twice, although there was no documentation of isolation of acid fast bacilli (AFB). There was no family history of similar illness in the siblings or parents.

On examination, he was febrile, had clubbing, hepatosplenomegaly and significant bilateral cervical lymphadenopathy, however, no skin lesions were there. He weighed 13.6 kg, below 95% percentile for his age and hence was malnourished. Chest radiograph at current admission showed consolidation in posterior segment of right upper lobe, similar to the one done a week before admission to our hospital [Figure 1].

Hemoglobin was 8.6 gm%, Total Leucocyte Count ($7.35 \times 10^3/\mu l$) and platelet count ($359 \times 10^3/\mu l$). However, differential cell count (DLC) revealed only 9% neutrophils (Absolute neutrophil count $720/\mu l$), 40% lymphocytes, 30% monocytes (Absolute monocyte count

Address for correspondence: Dr. Alkesh Kumar Khurana, Department of Pulmonary Medicine, AIIMS Bhopal, Bhopal, Madhya Pradesh, India.
E-mail: lungcancer@rediffmail.com

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_29_19

How to cite this article: Khurana AK, Goyal A, Khurana U, Dhingra B. Recurrent episodes of pneumonia in a toddler: Don't forget chronic granulomatous disease. J Family Med Prim Care 2019;8:1260-2.

2180/μl), 15% eosinophils (Absolute eosinophil count 1080/μl), 1% Basophils, 2% metamyelocytes, and 1% myelocyte. The peripheral blood smear showed intense rouleax formation and absolute monocytosis and eosinophilia with neutropenia [Figure 2]. The erythrocyte sedimentation rate (ESR) was 48 mm at the end of first hour. Liver function tests, renal function tests and blood sugar levels were normal. Mantoux testing showed equivocal induration after 48 hours. Urine culture grew both E. coli and Klebsiella (10^4 cfu/ml). Serum IgG levels, serum IgA levels and serum IgM levels were 5296 mg/dL (elevated), 1062 mg/dL (elevated), and 117 mg/dL (normal) respectively. Serum albumin levels were 2.24 mg/dL and serum globulin levels were 7.68 mg/dL (Reversed A/G ratio of 0.29). Since the child could not cough out optimal sputum sample, flexible bronchoscopy was done. Broncho alveolar lavage (BAL) showed mixed cellular pattern with a differential cell count of 35% neutrophils, 16% lymphocytes, 48% monocytosis/macrophages and 1% eosinophils [Figure 3]. The presence of significant neutrophils in BAL fluid ruled out absolute neutropenia and suggested only migration of neutrophils to the site of infection. The BAL fluid culture grew *Pseudomonas aeroginosa* and acid fast bacillus (AFB) stain was negative. Fine Needle Aspiration (FNA) was done from cervical lymph node which showed reactive lymphoid hyperplasia, lymphohistiocytic clusters along with pigment laden macrophages. AFB stain was negative. Bone marrow examination revealed Myeloid/Erythroid ratio as 5.2:1. The presence of CD 68 positive granulomas in the trephine biopsy along with suggestive cytological findings was sufficient to make the diagnosis of chronic granulomaous disease [Figure 4]. The child was managed with injectable piperacillin-tazobactam as per culture sensitivity alongwith supportive management measures and discharged in a stable condition after two weeks of hospitalization. The child came for follow up after 4 months, the weight at follow up was 14.5 Kg, a Dihydrorhodamine test and prophylactic antibiotics were advised but the parents refused.

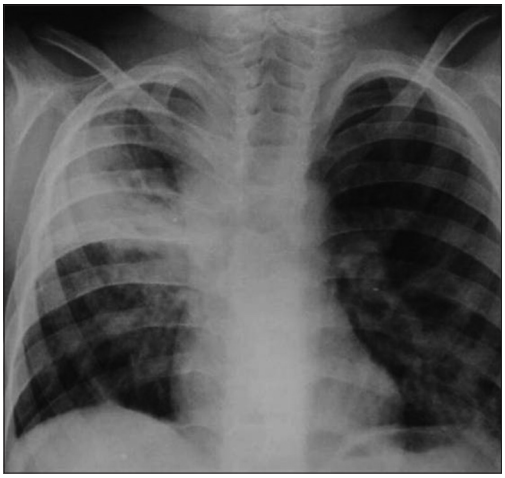

Figure 1: Chest radiograph at admission showed consolidation in posterior segment of right upper lobe

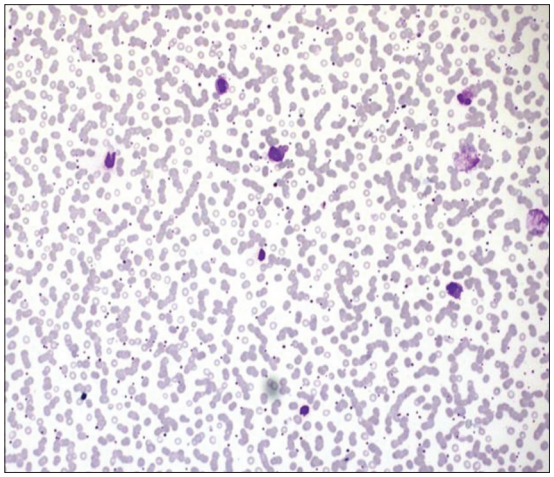

Figure 2: Peripheral blood smear showed absolute monocytosis and eosinophilia with neutropenia; the background shows intense rouleaux formation. (Leishman; ×100)

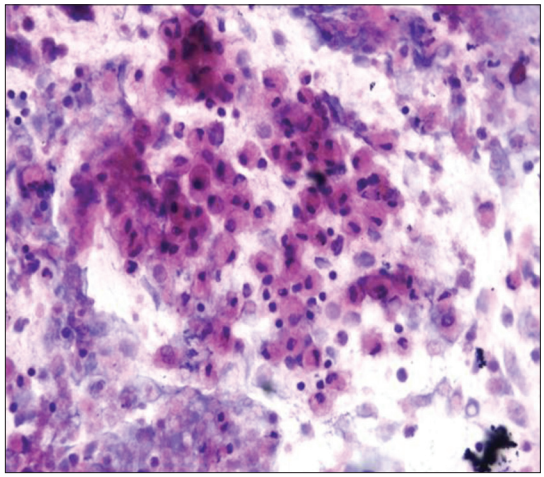

Figure 3: Broncho alveolar lavage (BAL) showed mixed cellular pattern (48% monocytosis/macrophages, 16% lymphocytes, 35% neutrophils, and 1% eosinophils)

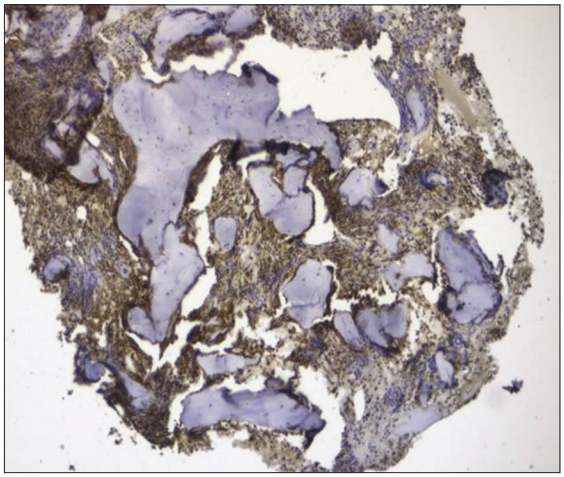

Figure 4: Bone marrow showed monocytosis and formation of histiocytic granulomas which were highlighted on immunohistochemistry. (CD 68; ×40)

Discussion

CGD is caused by a defect in the NADPH oxidase enzyme of phagocytic cells. This causes inability to produce the superoxide anion required to kill bacterial and fungal microorganisms.[3] At least five different mutations have been reported leading to inactivation of NADPH oxidase. X linked mutations involving the *gp91phox* are more common but associated with a lower life expectancy. Autosomal recessive mutations involving the *p22phox*, *p47phox* and or *p40phox* are less common, they all have a relatively better prognosis and are more prevalent in consanguineous marriages. The incidence of CGD is around 1 in 2,00,000 in United States to 1 in 70,000 in Israeli Arab population.[4] The age of presentation as well as the spectrum of clinical manifestations is variable. Mostly, the patients suffer from recurrent severe bacterial and fungal infections with non caseating histiocytic granulomas formed all over multiple organs like skin, lungs, lymph nodes, and gastro intestinal tract. The most common bacterial infections are *Staphylococcus aureus, Burkholderia Cepacia, Serratia marccescens* and *Nocardia*. The most common fungus isolated is *Aspergillus* in these patients.[2,5]

The pulmonary manifestations are most common which may be infectious (pneumonia, abcess, pleural effusion, atelectasis), or inflammatory (granuloma formation, fibrosis in chronic cases). Radiological findings may include consolidation, tree in bud appearance, nodules in early stages and bronchiectasis/fibrosis in later stages.[1,2] The index case discussed here presented with segmental consolidation and yielded *Pseudomonas aeroginosa* on BAL sample. Mycobacterial infections should always be ruled out in CGD patients, especially in high endemic TB countries. In addition to lungs, brain, liver, spleen and gastrointestinal tract may also be involved. Some patients may also have concomitant autoimmune problems because of dysregulated inflammatory response.[1] The younger age at presentation, high immunoglobulin levels and presence of plasma cells on bone marrow aspirate were against common variable immunodeficiency.[6] The absence of albinism, neurological symptoms and no characteristic granules helped in ruling out Chediak-Higashi syndrome (CHS).[7] The absence of neutrophilia ruled out Leukocyte adhesion defect.[8]

Treatment is usually aimed at the organism isolated from the involved organ. Long term prophylaxis with cotrimoxazole and itraconazole has been shown to decrease infection rate in CGD patients.[1] The immunosuppressive therapy in the form of corticosteroids may be required in acute granulomatous exacerbations of lung, bowel or urinary tract. Allogeneic hematopoietic stem cell transplantation is considered as the definitive curative option but lack of appropriate expertise and donors are the limiting factors. Gene therapy trials have been performed in over 100 patients with clinical benefits.[9]

The authors have obtained appropriate written consent from the parents to publish this case in a scientific journal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Mahdaviani SA, Mohajerani SA, Rezaein N, Casanova JL, Mansouri SD, Velayati AA, *et al.* Pulmonary manifestations of chronic granulomatous disease. Expert Rev Clin Immunol 2013;2:153-60.
2. Song E, Jaishankar GB, Saleh H, Jithpratuck W, Sahni R, Krishnaswamy G, *et al.* Chronic granulomatous disease: A review of the infectious and inflammatory complications. Clin Mol Allergy 2011;9:10.
3. Chiriaco M, Salfa I, Di Matteo G, Rossi P, Finocchi A. Chronic granulomatous disease: Clinical, molecular and therapeutic aspects. Pediatr Allergy Immunol 2016;27:242-53.
4. Arnold DE, Heimall JR. A review of chronic granulomatous disease. Adv Ther 2017;34:2543-57.
5. Goldblatt D. Recent advances in chronic granulomatous disease. J Infect 2014;69:S32-5.
6. Alkan G, Keles S, Reisli R. Evaluation of clinical and immunological characteristics of children with common variable immunodefeciency. Int J Pediatr 2018;23:3527480.
7. Ghaffari J, Rezaee SA, Gharagozlou M. Chediak higashi syndrome. J Pediatr Rev 2013;1:80-7.
8. Rosenzweig SD, Holland SM. Phagocyte immunodefeciencies and their infections. J Allergy Clin Immunol 2004;113:620-6.
9. Kawai T. A therapeutic approach towards chronic granulomatous disease. Nihon Rinsho Meneki Gakkai Kaishi 2014;37:437-46.