

CASE REPORT

FAMILIAL CHRONIC GRANULOMATOUS DISEASE

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ABSTRACT

Chronic granulomatous disease (CGD) is a rare primary immunodeficiency disorder of phagocytes, characterized by repeated bacterial and fungal infections. We present a boy suffering from recurrent infections since infancy who was treated with various antibiotics and anti-tuberculosis medicines without any relief. All four of his brothers had recurrent respiratory tract infections and were treated empirically with anti-tuberculosis; all of them expired one after the other without any definitive diagnosis. He was diagnosed at ten years of age with pulmonary aspergillosis and CGD. This case highlights pitfalls of medical management of chronic cases in our society. Because of TB endemic area, it is a common practice among physicians to start anti-tuberculosis medicines without making a definite diagnosis.

We recommend thorough investigations including testing for CGD in every patient with recurrent or persistent infections especially if other siblings also have similar manifestations.

Keywords: Aspergillosis, Chronic granulomatous disease, Tuberculosis.

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INTRODUCTION

Chronic granulomatous disease (CGD) is a rare inherited primary immunodeficiency disorder. The underlying defect is functional impairment of the phagocyte NADPH-oxidase complex and is usually diagnosed by nitroblue-tetrazolium (NBT) negativity¹. CGD is characterized by repeated bacterial and fungal infections involving the lungs, skin, liver and lymph nodes. Pulmonary and cerebral aspergillosis is an important cause of morbidity and mortality in CGD². In low-income countries like ours with endemic tuberculosis (TB), physicians empirically treat patients without microbiological confirmation of TB. This not only leads to delay in the diagnosis but also result in mortality. We present this case to highlight the need of making a diagnosis of chronic and persistent infections in children.

CASE REPORT

Ten years old boy presented to our department with history of repeated episodes of

high-grade intermittent fever and chest infections since six months of age. His condition gradually worsened and was having persistent cough and lost about five kg weight in last six months. He had been to various hospitals and investigations including blood complete picture, blood culture and sensitivity, mantoux test and bone marrow aspiration and trephine biopsy were carried out. He was treated empirically for malaria, typhoid, and tuberculosis without any relief of his symptoms. At age of six years he developed cervical abscesses, which required incision and drainage and oral antibiotics.

He was 7th in the sibship of seven. All of his four brothers also suffered from repeated episodes of fever and cough. There was a significant history of abscesses in three of his brothers once in their lifetime. All of them received anti-tuberculosis (ATT) without any improvement. Unfortunately, all of them died at ages of 11, 7, 2 ½ years and 10 months without a definitive diagnosis.

Examination revealed a malnourished boy having weight 22kg, height 130 cm; below 5th and 10th centiles respectively. He was febrile with temperature of 101°F with associated tachycardia and tachypnoea. Systemic examination

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Received: 08 Jul 2018; revised received: 28 Jul 2018; accepted: 17 Sep 2018

was normal except a few crepitations on chest auscultation.

His investigations showed microcytic hypochromic anaemia with haemoglobin 8.1 g/dl, white blood cell count $12.8 \times 10^9/l$ (62% polymorphs, 34% lymphocytes), platelets $546 \times 10^9/l$, ESR 110 mm at the end of 1st hour, and C-reactive protein 33 mg/l. Blood smear for malarial parasite, typhidot, urine and stool routine examination and cultures, viral serology for hepatitis Band C were all negative. Liver function tests and renal function tests were also within normal limits. Ultrasound abdomen revealed splenomegaly. His CT scan chest done on 13 Oct 2016 was reported as; Soft tissue density nodules of varying sizes noted scattered in both lungs (fig-1). Flow cytometric analysis of neutrophil's oxidative burst using dihydrorhodamine (DHR) showed absence of

was made. He was managed with Intravenous amphotericin along with meropenam and amikacin. After 6 days his fever settled and his chest symptoms improved. Amphotericin B was

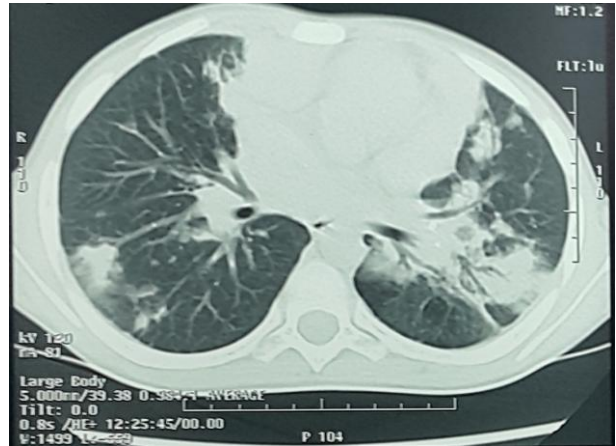


Figure-1: HRCT scan chest showing soft tissue density nodules of varying sizes noted scattered in both lungs.

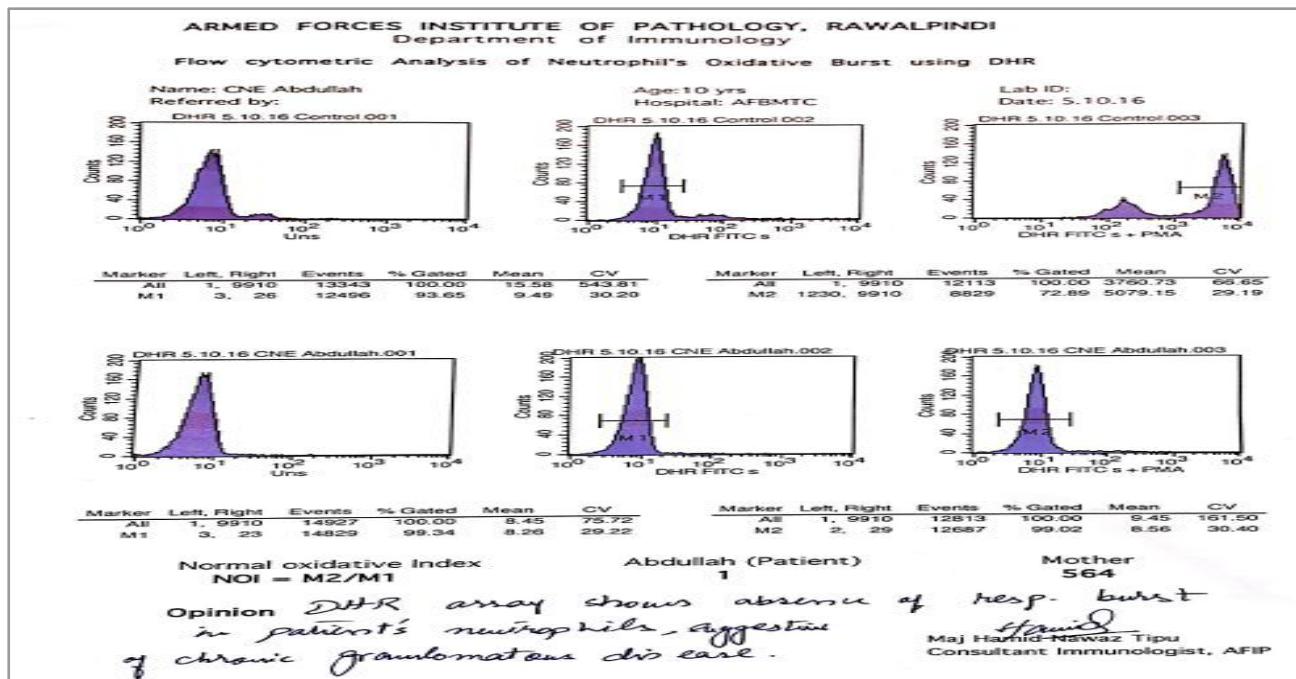


Figure-2: DHR assay

respiratory burst in his neutrophils suggestive of CGD (fig-2).

Considering the history, clinical picture and investigations, a diagnosis of Chronic Granulomatous Disease with pulmonary aspergillosis

given for 4 weeks followed by four weeks of oral voriconazole. Human leukocyte antigen (HLA) matching was carried out with his sisters but no HLA match was found for bone marrow transplant, which is the curative treatment for CGD. He is on prophylactic Voriconazole and

Co-trimoxazole. He was asymptomatic on his last visit on 1st Jul 2018.

DISCUSSION

Chronic granulomatous disease is an X-linked or auto somal recessive condition that affects approximately 1 in 200,000-250,000 live births. The actual incidence would be higher due to under diagnosis of patients presenting with milder disease phenotype³. In CGD, neutrophils have normal phagocytosis but defective killing of microorganisms because of markedly deficient or absent superoxide production due to inherited mutations of polypeptides of reduced NADPH oxidase (also known as respiratory burst oxidase). The patient is susceptible to recurrent bacterial and fungal infections usually in early infancy. Catalase producing organisms are often responsible for severe infections in these patients. Lungs are the most common site of infection followed by lymph nodes, skin, liver, and gastrointestinal tract^{2,3}.

Our patient presented with recurrent infections involving respiratory system since infancy. All four of his brothers had similar problems suggestive of an X-linked inheritance of this disorder. All of them were treated with antituberculosis without making a definitive diagnosis. This clearly reflects the empathy of our health care professionals whose empirical treatment led to death of four brothers.

The diagnosis of CGD is typically made by NBT test by identifying the neutrophil oxidative burst activity. The test is easy to perform and no special chemicals or equipment are needed. Only NBT and an ordinary microscope are sufficient. Normal neutrophils reduce nitroblue-tetrazolium to formazan, a dark blue pigment visible on microscopic inspection. Neutrophils of patients with CGD do not reduce nitroblue-tetrazolium⁴. Second method is the dihydrorhodamine (DHR) 123 test, utilises flow cytometry to detect the oxidation of dihydrorhodamine 123 in activated neutrophils. This test differentiates between X-linked and autosomal recessive forms as well⁵. Our patient was diagnosed by using DHR assay.

In the recent record of 268 CGD patients analysed by Marciano *et al*⁶, the most common site of infection in CGD is lung and the most frequent pathogens are *Aspergillus*, *Staphylococcus aureus*, *Serratiamarcescens*, *Burkholderiacepacia*, *Nocardia*, and *Salmonella spp*^{2,3,6}. History of repeated episodes of cough and fever and the findings of the HRCT scan of chest, associated with very good response to Amphotericin B and voriconazole, were highly suggestive of invasive pulmonary aspergillosis in our case.

The mainstay of management in CGD is lifelong prophylactic antibiotics and antifungals along with aggressive surgical and medical management^{1,3,6}. The use of IFN- γ as prophylactic medicine is still debatable. Though studies have demonstrated its capacity to reduce the number and severity of infections in CGD³. There is no evidence to justify long-term prophylactic use of IFN- γ in CGD⁷. Our patient is on prophylactic Co-trimoxazole and Voriconazole and is asymptomatic for last four months.

Allogeneic bone marrow transplant (BMT) is the only curative treatment for CGD and can reverse organ dysfunction as well^{8,9}. BMT was not offered to our patient because he has no HLA matched donor.

The CGD patients can survive to adulthood but are short statured with high rate of handicap. Regular Careful follow-up in centres of expertise is strongly recommended¹⁰.

Prenatal diagnosis of CGD can be performed by analysis of the NADPH oxidase activity of foetal blood neutrophils, but foetal blood sampling cannot be done before 16-18 weeks of gestation. Instead of that, analysis of DNA from amniotic fluid cells or chorionic villi provides an earlier and more reliable diagnosis for families at risk¹.

Our case highlights several issues of utmost importance. This is a common practice in a low resource country like ours, where prevalence of tuberculosis is very high; Patients are put on antituberculous drugs, if no other diagnosis is made. This child had several key features in

history especially family history of death of four brothers with similar clinical picture to suggest the possibility of an underlying immune disorder. A family history of males with severe or unusual infections can be a clue to the diagnosis of X-linked CGD, while consanguineous parents increase the risk for autosomal recessive disorders. Important hints were missed and that led to a significant delay in diagnosis.

CONCLUSION

Chronic granulomatous disease is a rare disorder that often goes undiagnosed. In any patient with history of prolong fever and recurrent infections, CGD should be considered so that a prompt diagnosis and early initiation of treatment can be done.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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