CASE REPORT

Salt Losing Crisis, Deep-seated Abscess and BCG Lymphadenitis in an Infant with Chronic Granulomatous Disease

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ABSTRACT

Chronic Granulomatous Disease (CGD) is an inherited disease affecting the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex causing defective formation of superoxide in phagocytes. Patients usually manifested with recurrent bacterial and fungal infections and maybe fatal. They may also present with inflammatory manifestation due to the dysregulated inflammatory in CGD. We are reporting a case of a 5-month-old boy with salt losing crisis, deep seated infection of splenic abscesses and osteomyelitis of right foot, and later developed BCGitis. Genetic studies confirmed the diagnosis of autosomal recessive chronic granulomatous disease in this patient.

Keywords: Chronic Granulomatous Disease, BCG Lymphadenitis, Inborn Error of Immunity, Malaysia, Primary Immunodeficiency Diseases

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INTRODUCTION

Chronic granulomatous disease (CGD) is an inherited primary immunodeficiency disease (PID), characterized by recurrent infections and inflammatory complications due to defective nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex function leading to absence of superoxide and hydrogen peroxide production in phagocytes (1). The presentation in CGD patients varies from recurrent symptomatic cutaneous and bone infections as well as abscess formation and lymphadenitis (2). Here, we describe a case of an infant with autosomal recessive CGD which presented initially with salt losing crisis followed by sepsis, deep seated infection of splenic abscesses and osteomyelitis in the right foot, and later developed regional BCGitis four months after routine vaccination.

CASE REPORT

A baby boy was delivered normally with the birth weight of 2.5kg and required a brief admission to the neonatal unit for right unilateral cleft lip and palate. There was no consanguinity in the parent but there was a positive history of early neonatal death in the family member (Figure 1). However, he presented at one month old with salt losing crisis with severe hyponatraemia (serum sodium 105 mmol/L, urinary fractional excretion of sodium FeNA 3.3%), poor weight gain with other evidence of hypocortisolism (serum potassium 4.2 mmol/L, serum cortisol 280 nmol/L, serum testosterone 4.78 nmol/L). He was treated as clinical sepsis with negative blood culture. He responded well to supportive therapy of fluid resuscitation, broad spectrum antibiotics and cortisol replacement therapy. A week later, he showed signs of new infection without obvious source. Extensive investigation for the possible bacterial, fungal or mycobacterium cause was negative. Screening by echocardiogram did not show any evidence of vegetation but ultrasound of the abdomen revealed multiple splenic abscesses and the kidneys were normal.

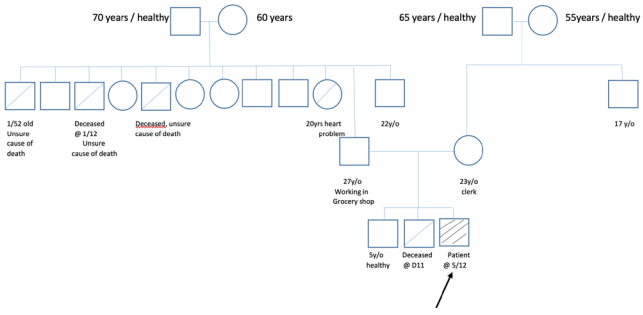

Figure 1: Patient's family tree

Hence, he was treated conservatively with combination of vancomycin, piperacillin/tazobactam, metronidazole and fluconazole via intravenous route for 5 weeks. A repeated ultrasound of the spleen after 2 weeks of treatment did not show resolution and the treatment was continued for another 2 weeks. Baseline serum immunoglobulin and complement levels were within normal ranges and HIV screening was negative. He subsequently developed methicillin-resistant coagulase negative Staphylococcus epidermidis (MRCONs) sepsis and started to develop multiple skin abscesses at venipuncture sites. At this point, a presumptive diagnosis of CGD was entertained and was referred to Paediatric Immunology Consultant for further investigation. He also developed right foot abscess at the site of peripherally inserted central catheter (PICC) with Serratia marcescens and Enterobacter species isolated which progressed to osteomyelitis of the right foot. He was treated with piperacillin/tazobactam and gentamicin for six weeks duration (combination of antibiotics was chosen based on the organism sensitivity pattern). Interestingly, at this point of time, his adrenal function fully recovered and adrenal replacement therapy was tapered off. His weight also improved remarkably.

At the age of 4 months, he started to have gradual swelling of the left axillary which was not associated with fever. A firm, non-tender mass, measuring 3cm x 3cm was palpable at the left axilla (Figure 2). No other palpable lymph nodes were observed. Auscultation of the lungs was clear with equal breath sound. There was a hepatomegaly measuring 4cm below the right costal margin. Other systemic examinations were unremarkable.

Several investigations including laboratory tests and imaging studies were performed. The initial laboratory findings were as follows: white blood cell count 15,600/mm^3 (neutrophils: 50.7% and lymphocytes: 23.9%), haemoglobin concentration 9.5 g/dL, platelet count 747,000/mm^3, and erythrocyte sedimentation rate (ESR) 85 mm/h. He had a positive C-reactive protein (CRP) of 110 mg/L. Gastric lavage for acid fast bacilli (AFB) and tuberculosis (TB) PCR were negative. Chest X-ray revealed persistent perihilar haziness, without any new changes. The X-ray of right foot showed chronic osteomyelitic changes. Abdomen ultrasonography showed multiple splenic abscesses.

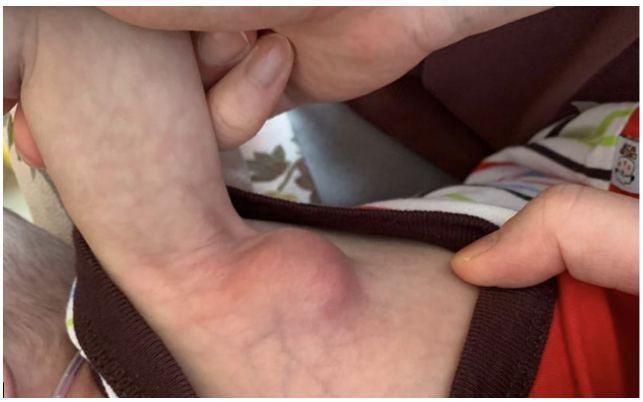

Figure 2: Left axilla swelling before needle aspiration measuring 3cm x3cm, firm in consistency, non-tender on palpation, with overlying erythematous skin.

The immunological investigations were listed in Table I. There was a reduced T cell with normal B cell and NK cell absolute counts but no hypogammaglobulinemia. The patient had a decreased neutrophil oxidative burst (0.19%) with reduced stimulation index (S.I.) (0.93, compared to control S.I.= 37.46). The patient's mother had normal neutrophil oxidative burst (98.3%) and S.I. (35.40) (Figure 3). In view of this information, a diagnosis of autosomal recessive CGD was made and his blood was sent for targeted PID panel next-generation sequencing genetic test. The patient was homozygous for a variant identified in the CYBA gene, c.385G>T (p.Glu129*).

Table I: Immunological investigation results of the patient

Immunoglobulin Level	5/4/21	4/5/21
IgG	7.39 (1.64 – 5.88 g /L)	10.9 (1.64 -5.88 g /L)
IgA	0.32 (0.16 – 0.5 g /L)	0.78 (0.16 – 0.5 g /L)
IgM	0.5 (0.32 – 1.32 g /L)	0.72 (0.32 – 1.32 g /L)
TBNK	Absolute (cells/uL)	Percentage (%)
T cell	1939 (2500-5500)	66.9 (53-84)
T helper	1309 (1600-4000)	45.1 (35-64)
T cytotoxic	644 (560- 1700)	22.2 (12-28)
B cell	528 (300-2000)	18.2 (6-32)
NK cell	366 (170-1100)	12.6 (4-18)

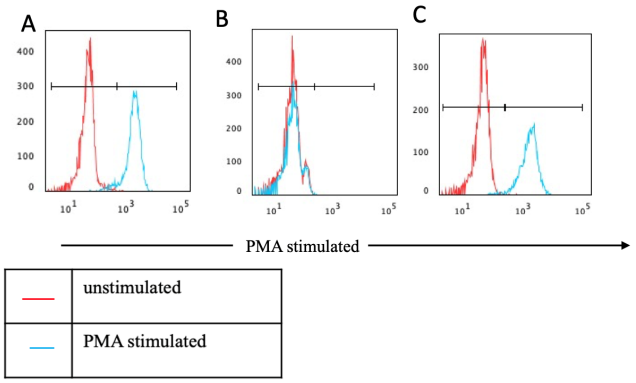

Figure 3: Histograms from flow cytometry based oxidative burst assay for CGD. A) Control sample with normal shift of the activated neutrophils (blue) B) DHR of a CGD patient with a defect in CYBA showing absent shift of the stimulated neutrophils (blue) C) Patient's mother with granulocyte function. The red line reflects the unstimulated sample, while the PMA-stimulated sample is represented in the blue line histogram.

A needle aspiration of the left axilla swelling was performed, and the specimen was sent for acid fast staining, which revealed 1-6 AFB/ 1 field. Mycobacterium bovis was isolated from the culture. In view of his primary immunodeficiency status, he was started on anti-tuberculosis treatment which consisted of pyrazinamide, rifampicin, ethambutol and isoniazide

as per local protocol (minimum 6 months duration of therapy). The mass became smaller, and the patient was discharged in good clinical condition with a preparation plan for bone marrow transplant.

DISCUSSION

We describe a case of a child with autosomal recessive CGD presented with atypical symptoms, salt losing crisis in the neonatal period. His serum testosterone was within normal range at presentation and he did not have virilisation of external genitalia or skin hyperpigmentation, which were not suggestive of adrenal causes of salt losing crisis. We postulated that the salt losing crisis event that occurred in this patient was most likely due to inadequate adrenal response to severe sepsis, as the condition resolved after the initial infection was treated. However, we could not identify any positive isolates in the blood and urine during that episode. There was no published case report describing salt losing crisis in patients with CGD, however there have been multiple case series on salt losing crisis caused by transient pseudohypoaldosteronism related to urinary tract infections in immune-competent populations (2).

CGD is the third commonest type of PID reported from Malaysia and X-linked CGD was the commonest type reported (3). Mutations in the *CYBB* gene lead to X-linked CGD (commonest), whereas mutations in the *CYBA, NCF1, NCF2* and *NCF4* genes cause autosomal recessive CGD. Previous reports showed CGD patients have higher preponderance to regional lymphadenopathy after BCG vaccination (1,4). Other PIDs have been identified to be associated with adverse events following BCG vaccination such as severe combined immunodeficiency disease (SCID), mendelian susceptibility to mycobacterial disease (MSMD) and hyper-IgM syndrome.

All patients with regional BCGitis may be evaluated for the possibility of primary or secondary immunodeficiency, as infections caused by weakly virulent mycobacterial species such as *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) vaccine strains are suggestive of an immunocompromised state (1,4). Other reported organisms frequently isolated in patient with CGD are *Aspergillus, Burkholderia species, Nocardia, Staphylococcus species, Serratia species*, and *Scedosporium species* (4).

Administration of BCG vaccine is contraindicated in those known to have CGD (5). However, in this case the diagnosis was only made later after he developed a series of severe infections. Thus, high index of suspicious for PID screening is warranted early especially in those presented with severe infections such as deep-seated abscess or sequalae from BCG vaccination. The dihydrorhodamine (DHR) flow cytometry test is a gold standard test that is used to quantify NADPH oxidase activity in neutrophils. The test is useful to distinguish X-linked CGD cases, autosomal recessive as well as in evaluating for carrier status in female relatives of patients with X-linked CGD. Moreover, the DHR is proportionately fast, cheap and is considered a powerful diagnosing test especially in settings where limited access to genetic testing prevails.

Regional lymphadenopathy after BCG vaccination in immunocompetent person usually undergoes spontaneous resolution but may occasionally progress slowly to become suppurative in 15% - 30% of cases (5). Despite his underlying condition, the onset of regional BCGitis occurred later at four months of age as it usually arises within two weeks to six months after BCG vaccination. The clinical management of suppurative BCG lymphadenitis remains debatable even in immunocompetent populations (4,5). In most cases, one needle aspiration is effective, but repeated aspirations may be needed for some patients in combination with anti-tuberculous medications and/or intranodal injection of isoniazid aspiration after needle aspiration (5).

CONCLUSION

This case highlights the importance of CGD to be considered as one of the differential diagnoses in children presented with salt losing crisis, deep-seated abscess or sequalae from BCG vaccination and CGD patients have been showed to be highly vulnerable to tuberculosis, especially for those living in tuberculosis endemic countries.

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