

Case Report

Chromobacterium violaceum sepsis in an infant with chronic granulomatous disease

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Introduction

Chronic granulomatous disease (CGD), a primary immune deficiency with impaired phagocytosis, has an incidence of 4-5 per million [1]. *Chromobacterium violaceum* is a Gram negative, motile, facultative anaerobic, oxidase and catalase positive bacillus which is thermo sensitive and widely found in the water and soil of tropical climates [2]. In 1927, Malaysia reported the first human case of *C. violaceum* sepsis [3]. Although *C. violaceum* is a rare cause of septicemia in immunocompetent individuals, it is seen more frequently in immune deficient patients. *C. violaceum* infection carries a significant mortality in CGD patients. Further, due to its rarity, the optimal antibacterial regime is not well established.

Case Presentation

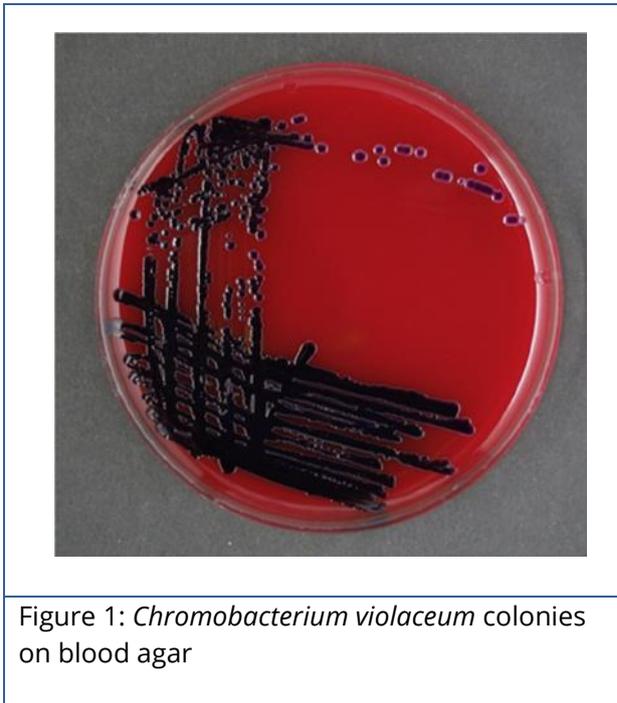
A 10-month-old girl presented with high fever and watery stools of 5 days duration. She had no vomiting, urinary symptoms, cough or difficulty in breathing. Feeding and activity were poor. She had been given oral cephalexin and symptomatic treatment for diarrhoea at a local hospital with no clinical improvement. A week prior to this illness she had been treated for bronchopneumonia and completed a ten-day course of intravenous co-amoxiclav and oral clarithromycin at the local hospital during which blood and sputum cultures had revealed no growth.

She was the second child of second-degree consanguineous parents. She had undergone incision and drainage for cervical lymphadenitis and abscess formation twice, at 2 and 6 months of age. At six months of age, she was diagnosed to have CGD based on a nitroblue-tetrazolium (NBT) test with < 5% of neutrophils showing normal activity. Mutation studies for the most frequent form of CGD involving the P47 subunit of NADPH oxidase were negative and further genetic testing was pending. Her elder brother had died at 11 months of age from unexplained sepsis after one month of inward treatment with broad spectrum antibacterial agents as per the medical records.

She was on long term prophylaxis with cotrimoxazole and itraconazole. Cotrimoxazole 450mg/m²/day in two divided doses and itraconazole 5mg/kg/day single dose were given each day, with good compliance.

Examination revealed a febrile, irritable child with no significant abnormalities. The haematological parameters were, white cell count of 3.6×10⁹/L (73% neutrophils), haemoglobin 9.8 g/dL and a platelet count of 112×10⁹/L. C-reactive protein was 105mg/L and ESR 70mm/1st hour. Her renal and liver function tests and coagulation profile were normal. Bacterial sepsis was suspected and marginal pancytopenia was attributed to it. She was started on intravenous cefotaxime and metronidazole after taking blood for culture.

Blood culture revealed the distinctive purple colonies of *C. violaceum*. Bacterial colonies on blood agar were convex, smooth and circular and the presence of the violacein pigment gave them the characteristic violet colour (Figure 1). The antibiotic sensitivity test (ABST) showed sensitivity to imipenem, gentamicin, ciprofloxacin and cotrimoxazole and intermediate sensitivity to ticarcillin and resistance to ampicillin and ceftazidime. Treatment was changed to intravenous gentamicin and meropenem, based on the antibiotic sensitivity pattern. The child showed a rapid clinical improvement, with complete resolution of fever within 24 hours of commencement of the new antibacterial regimen which was continued for three weeks, and recovered uneventfully.



Discussion

CGD is a rare immunodeficiency with defective phagocytic function, resulting in recurrent intracellular bacterial and fungal infections and the formation of granulomas [4]. Affected individuals are predisposed to infection with catalase-positive organisms due to an impaired respiratory burst in the neutrophil [5]. CGD is a heterogeneous genetic disease

affecting phagocyte NADPH oxidase, leading to deficient production of reactive oxygen metabolites. The enzyme NADPH oxidase is composed of several subunits. Defects may occur in the cytosolic components (p47phox, p67phox and p40phox) that translocate to the membrane upon activation or in the components of the membrane-bound cytochrome b558, (gp91phox and p22phox). The Gp91phox locus is located on the X-chromosome and the p22phox, p47phox and p67phox loci are on different autosomes. CGD can be caused by a defect in any one of these components leading to different modes of inheritance [6]. In our patient, the mutation studies for the cytosolic component p47phox, which is the cause of the most frequent autosomal recessive CGD, were negative. It is likely that she has another form of autosomal CGD based on the fact that the patient is a girl and with the history of the death of a male sibling following a similar clinical course.

C. violaceum is an uncommon human pathogen. It is a motile, facultative anaerobic, Gram-negative bacillus, found in the water and soil of the tropics. It is not a fastidious organism and grows easily in routine culture media. There are pigmented and non-pigmented strains with similar pathogenic potential [7]. Non-pigmented strains are frequently confused with *Pseudomonas* spp. or *Vibrionaceae* spp. because of the similarity in their biochemical properties. The organism is usually resistant to penicillins and cephalosporins [8].

The usual mode of entry of the bacterium is thought to be via exposure of non-intact skin to contaminated soil or water [9]. Playing in muddy water can predispose children to this infection and the majority are community acquired. However, hospital acquired infections do occur, especially in children with immune deficiency with a suitable entry site [10,11]. The mode of acquisition of the infection in this case was not clear but she had multiple cannula insertion sites in both feet during the hospitalization one week prior to this admission, including an infected site where water contamination would have been possible.

Cotrimoxazole is the antibiotic of choice for prophylaxis in patients with CGD. It decreases the incidence of bacterial infections due to its broad-spectrum antimicrobial activity and selective concentration in phagocytes and has minimum action on gastrointestinal flora [12]. Immune-deficiency, differences in in-vivo sensitivity and poor compliance can lead to acquisition of virulent organisms despite being on antibacterial prophylaxis.

In CGD, cotrimoxazole prophylaxis is shown to increase the interval between life-threatening episodes of infection but it does not prevent them completely [10]. CGD usually manifests at an early age with frequent infections by virulent catalase-positive pathogens. *C. violaceum* infection frequently presents as septicaemia, pneumonia, abscess formation and diarrhoea [13,14]. Orbital cellulitis, osteomyelitis, conjunctivitis and meningitis are rare presentations. It causes severe infections including bacteraemia especially in the background of immunodeficiency [15]. Diarrhoea without other evidence of a gastroenteritis can be explained as a systemic manifestation of septicaemia in our patient. Systemic infection caused by *C. violaceum* is rare but can be severe and is associated with significant mortality (>60% case fatality rate). Diagnosis of *C. violaceum*

infection is based on culture from clinical specimens as there is no specific serological test available [16]. Evidence of bacterial sepsis by an elevated C reactive protein and white cell count support the diagnosis. The pancytopenia revealed in the initial full blood count of this patient can be explained by the transient bone marrow suppression seen in severe sepsis.

Many studies have demonstrated sensitivity of *C. violaceum* to fluoroquinolones, carbapenems and aminoglycosides [17]. However, due to rarity of infections, there are no clinical trials evaluating different treatment regimes. Inadequate duration of treatment can lead to relapse of infection. Therefore, the general recommendation is to treat with antibiotics for 4 to 6 weeks [18].

Our patient was started on a combination of carbapenem and aminoglycoside as soon as *C. violaceum* was isolated and even before the ABST was available as carbapenems have been found to be the best antibiotic to start empirically in children with CGD [19,20]. The above antibiotics were continued, as the subsequent ABST showed sensitivity and the patient showed a good clinical response. Renal functions were monitored once in 3 days as assessing gentamicin levels in blood was not possible.

This infant with CGD and *C. violaceum* sepsis responded well to aminoglycoside and carbapenem therapy and made an uneventful recovery despite underlying immunodeficiency.

There are many cases in the literature where the diagnosis of *C. violaceum* infection has led to the suspicion and subsequent diagnosis of CGD. This case illustrates the importance of looking for *C. violaceum* infection in patients with CGD who live in tropical regions of the world [13]. High degree of suspicion on unusual pathogens and early appropriate treatment is vital in reducing the infection related morbidity and mortality.

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