Multifocal abscess in a neonate: Neonatal chronic Granulomatous disease- Case report

Amir-Mohammad Armanian[1], Parisa Iravani[2], Majid Mohammadizadeh[3], Hamid Rahimi [4]

ABSTRACT

Chronic Granulomatous Disease (CGD) is a genetically heterogeneous condition characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation. CGD is the most common of the inherited disorders of phagocytic function and is characterized by susceptibility to recurrent severe infection. Although this disease is rarely seen in neonates. **Case Report:** We have encountered a baby with unusual multiple abscesses in various parts of the body. Because the hallmark of the clinical presentation of CGD is recurrent infections at epithelial surfaces in direct contact with the environment such as the skin, lungs and gut, we took steps to diagnose this disease, too. **Conclusion:** Ultimately it is true that this disease is rarely seen in neonates but in any case, that the neonate has multiple abscesses must be thought to have this condition and it should be treated.

Key words: Chronic granulomatous disease, multifocal abscess, Neonate

[1,3]Assistant Professor of neonatology, [2]Resident in Pediatric, [4]Assistant professor of Pediatric infectious disease

Isfahan University of Medical Sciences, Isfahan, Iran

Corresponding author mail: armanian@med.mui.ac.ir

INTRODUCTION

Chronic granulomatous disease (CGD) is a genetically heterogeneous condition characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation .CGD is the most common of the inherited disorders of phagocytic function and is characterized by susceptibility to recurrent severe infection associated with dysfunctional nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.

The frequency of CGD in the United States is approximately 1:200,000 live births [1]. The disease primarily affects males, as most mutations are X-linked. The autosomal recessive forms of CGD are more common and overall incidence rates may be higher in

cultures in which consanguineous marriage is common [2]. CGD may present at any time from infancy to late adulthood, but the majority of patients are diagnosed as toddlers and children before the age of five [3-5].

Patients with CGD typically experience recurrent infections caused by bacterial and fungal pathogens. Response to viral infections is normal in patients with CGD. Bacterial infections in CGD tend to be symptomatic and are associated with fever and mildly elevated leukocyte counts [6]. Fungal infections are often detected either at asymptomatic stages on routine screening for infections [7]

The most common sites of infection are lung, skin, lymph nodes, and liver [8].

The types of infections most often seen (in descending order of frequency) include:

1. Pneumonia
2. Abscesses (skin, tissue, organs)
3. Suppurative lymphadenitis
4. Osteomyelitis
5. Bacteremia/fungemia
6. Superficial skin infections (cellulitis/impetigo)
7. The most common sites for abscesses are perianal/perirectal and the liver [1, 9, 3-5].

In general, the organisms that infect patients with CGD are catalase-producing and include Staphylococcus aureus and aspergillus species. Other organisms isolated less frequently include Streptococcus species, Neisseria meningitidis, Acinetobacter junii, Candida species, Klebsiella pneumoniae, Mycobacterium tuberculosis, nontuberculous mycobacteria, Proteus species, and Leishmania species [3-5]. Infection with catalase-negative organisms is uncommon, but severe chronic recurrent actinomycosis has been reported [10]. Liver abscesses encountered in CGD are usually staphylococcal, consist of a dense and caseous material, and often require excisional surgery [25].

Diagnostic tests for CGD rely on various measures of neutrophil superoxide production. These include direct measurement of superoxide production, cytochrome c reduction assay, chemiluminescence, nitroblue tetrazolium (NBT) reduction test, and dihydrorhodamine 123 (DHR) oxidation test (11, 12).The

oldest and best-known laboratory test for CGD is the nitroblue tetrazolium (NBT) test. This provides a simple and rapid (but largely qualitative) determination of phagocyte NADPH oxidase activity.

Antimicrobial prophylaxis in CGD patients relies on a triad of therapies:

- Antibacterial: TRIMETHOPRIM-SULFAMETHOXAZOLE (TMP-SMX or CO-TRIMAXAZOLE)
- Antifungal: ITRACONAZOLE
- Immunomodulatory: INTERFERON-GAMMA (IFN-GAMMA)

This combination therapy dramatically reduces the rate of severe infections from 1 per patient year to almost 1 every 10 patient-years [13-17].

There are several retrospective series that suggest that TMP-SMX is effective in preventing bacterial infections [13, 18-20]. Several observational series and a single randomized trial demonstrated that ITRACONAZOLE is highly effective as antifungal prophylaxis in CGD [14, 21-24]. An international multicenter randomized trial examined prophylactic Immunomodulatory therapy with IFN-gamma [15].

Successful hematopoietic cell transplantation (HCT) is a definitive cure for CGD [26, 27].When the first 92 patients with "fatal granulomatosis of childhood" were reported, 45 had already died, 34 of them before the age of 7 years. Survival has dramatically improved, and CGD is now a disease that is eminently survivable into adulthood [28-30, 31-33].

CASE PRESENTATION

A 15-day-old baby girl with 37 weeks gestational age, due to fever and poor feeding referred to the hospital around the city. She was sepsis work-up and was treated with intravenous antibiotics. Due to the treatment failure and continued fever, lethargy and poor feeding she was referred to our hospital. The neonate (Birth weight = 2800 gr. & GA = 37 week) who is the only child in the family was born by caesarean due to her maternal request. The parents were relatives but there was no particular disease in them. Upon arrival examination, there was low-grade fever with a temperature of 38.5 ° C axillary. Despite the treatment with antibiotics, she has a perianal abscess (about 2 x 2.5 cm) with tenderness and a painful erythematous mass about 1 x 1

cm in the lumbosacral area (Figure 2) and cellulite in the middle section of the fifth finger of the left hand (Figure 1).

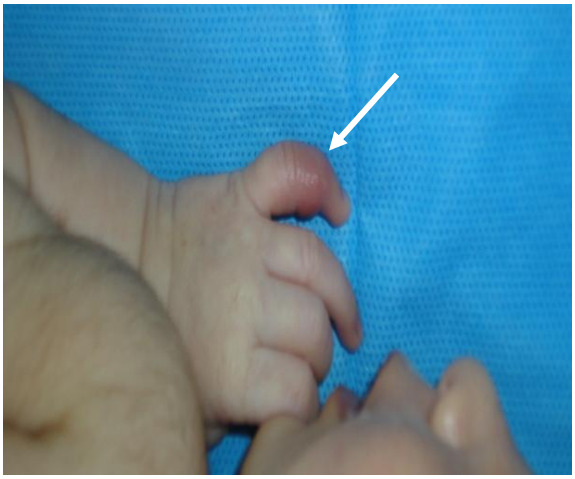

Figure 1: Cellulite in the middle section of the fifth finger of the left hand

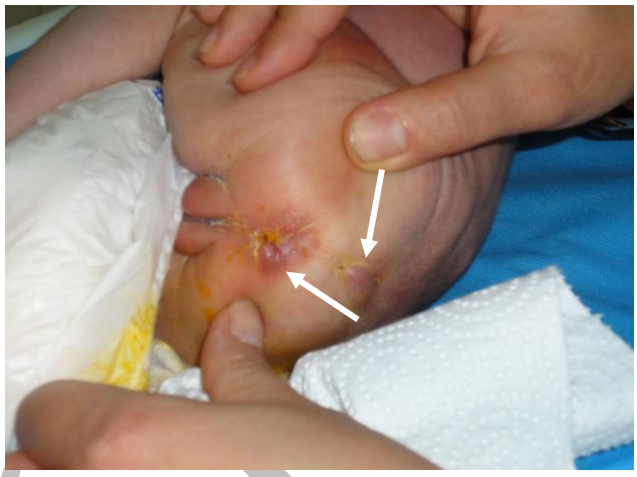

Figure 2: Perianal abscess

The results of the laboratory data were as follows: WBC = 22600, with Neutrophil = 62%, Lymphocyte = 26%, Platelets = 156000, Hb=11.5, CRP = 3+ (48) and ESR = 114. Leukocytosis was seen in the PBS, with Neuter preference. The child had no history of trauma and prenatal problems. After hospitalization, protective measures were taken and the treatment was started with intravenous antibiotics. B / C, U / C and CSF / C of the patient were negative. On the second day of admission to our center the fever was cut and perianal abscess was drained. In the course of hospitalization, lumbosacral mass also was converted to a fluctuated abscess (Figure 3). In the smears and cultures from the abscess drainage, it was seen 8 to 10 numbers of WBC, gram-negative bacilli and enterobacter grew that was sensitive to ciprofloxacin and meropenem. According to this report, meropenem added to previous vancomycin.

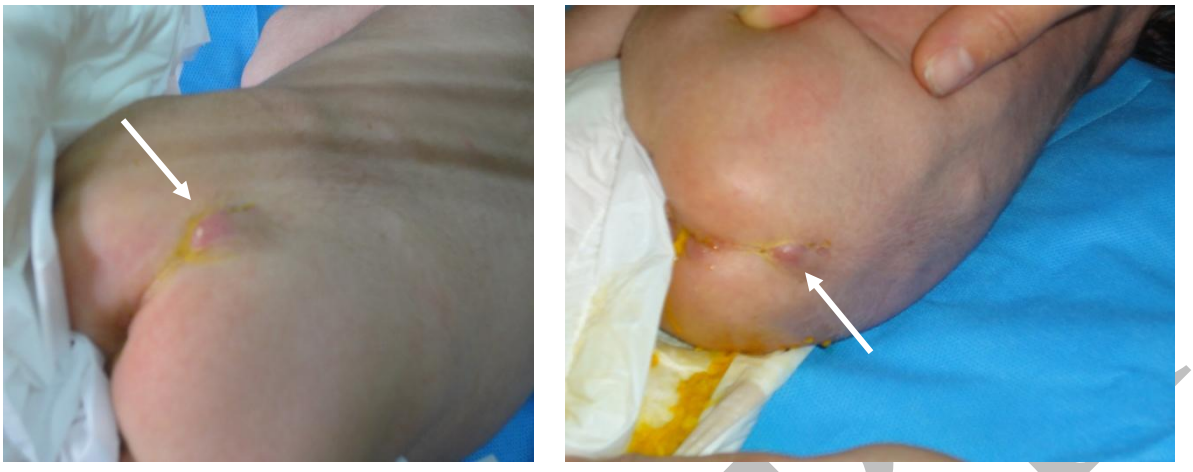

Figure 3: Lumbosacral mass was converted to a fluctuated abscess.

For rule out of internal organ involvement, the infant was echoed. The echo was normal. In the abdominal ultrasound, it was found numerous masses suspected to liver abscess in the infant (Figure 4).

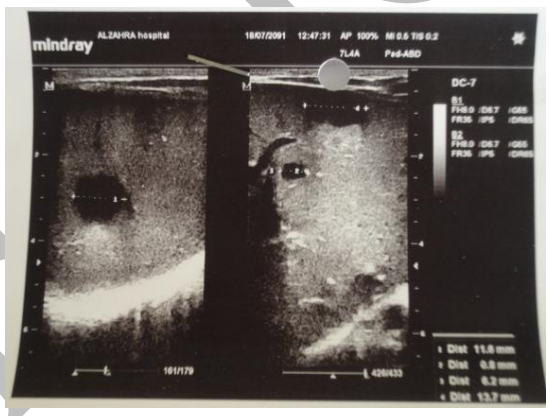

Figure 4: In the abdomen ultrasound, it was found numerous masses suspected to liver abscess

Due to suspected immunodeficiency of the patient including CGD, tests of CD markers, NBT and serum IgA were sent, which NBT have been 100% disrupted. Normal C3, C4 and CH50 68 (NL range: 76-225) were reported. IgA serum levels were also normal. CXR showed no evidence in favor of pneumonia. Normal LFT was reported. ADA was 15 and at the upper limit of normal. On the fourth day after admission,

there was created an abscess in the right hand thenar area (Figure 5), which found enough fluctuation after a few days and it was drained during the treatment. From the fifth day after admission, the infant's condition had improved and cellulite of the fifth finger of the left hand was laid down in size. Perianal abscess and thenar area abscess after drainage were constantly improved.

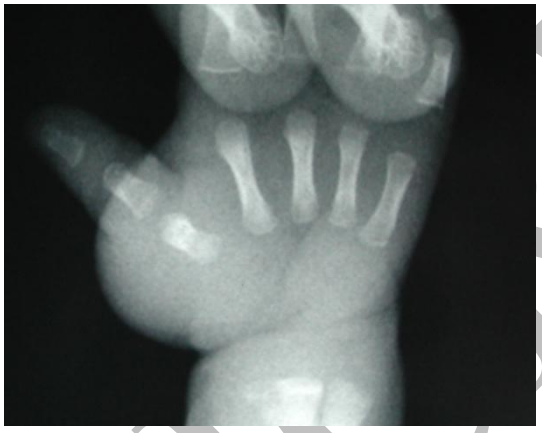

Figure 5: an abscess in the right hand thenar area

However, unfortunately in the ninth day of admission to this center, in the obtained radiograph of the infant's hand, there were evidences of osteomyelitis in the middle section of the fifth finger of the left hand finger and distal radius (Figure 6).Due to lack of excisional drainage of the infant liver multi-abscesses, there was ultrasound weekly for F / U with observing small changes in the ultrasound report.

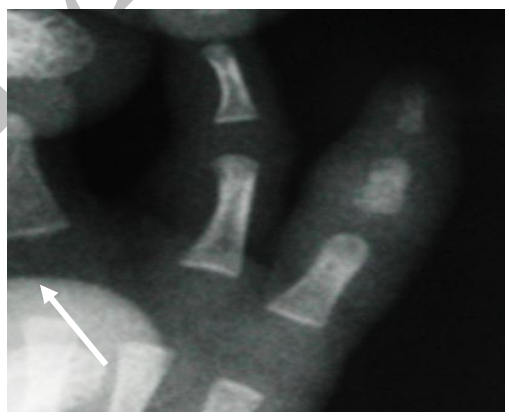

Figure 6: Osteomyelitis in the middle section of the fifth finger of the left hand finger

Due to the possibility of creating disseminated BCG, it was initiated the rifampin - isoniazid syrup as prophylaxis.

The infant ESR and CRP were serial controlled as follows:

CRP: 48 → 20 → 18 →9

ESR: 115 →125 → 125 →43

NBT of the infant's parents was also controlled, which was normal. Due to the lack of DHR testing in Iran, it was decided to redo the NBT test after the discharge of the infant. Based on the recommendation of pediatric immunology service, the administration of prophylactic cotrimoxazole syrup and itraconazole was started. After the initiation of IFN, fortunately, none of the side effects was observed.

Finally the infant was discharged with a general improvement, after healing the abscesses and after receiving four weeks of intravenous antibiotics with oral therapy.

DISCUSSION

Immune deficiency disease was to be thought in each infant was infected with a serious but uncommon infectious disease.

We have encountered a baby with unusual multiple abscesses in various parts of the body. Because the hallmark of the clinical presentation of CGD is recurrent infections at epithelial surfaces in direct contact with the environment such as the skin, lungs and gut (34) we took steps to diagnose this disease, too. CGD is caused by defects in the phagocyte NADPH oxidase (phox). These genetic defects result in the inability of phagocytes (neutrophils, monocytes, and macrophages) to destroy certain microbes (35) but Predominant symptoms are different in patients with CGD at several studies (20, 30 and 36-7). Ahlin A et al and a few other studies showed that Lymphadenitis is the most common presenting feature (20, 30). Cale CM et al showed the most commonly described complications were pneumonia (79%), followed by lymphadenitis (53%), subcutaneous abscess (42%), liver abscess (27%), osteomyelitis (25%) and sepsis (18%). (23). Carnide EG et al Suggested that the initial clinical manifestations of the disease vary among series, according to the reference center qualification and they showed in their study, pneumonias were the most common initial manifestation, followed by skin abscesses (39).In our

patient multiple skin abscesses, skin cellulitis, liver abscesses and then osteomyelitis was observed but CXR showed no evidence in favor of pneumonia.

The majority of affected individuals are diagnosed before the age of 2 years (23, 40). The pathogens responsible for the majority of infections in CGD are characteristic bacteria and fungi. Catalase-positive bacteria are the most important and include S.aureus and the Gram-negative enterobacteria (34, 41). Infections are generally caused" by catalase-positive microorganisms (most bacterial and all fungal pathogens are catalase-positive)" (35). Microbiologic confirmation of the cause of infection helps confirm the likelihood of CGD, since the spectrum of infection in CGD is distinct and narrow (38). In our patient, in the smears and cultures from the abscess drainage, gram-negative bacilli and enterobacter was found, respectively.

The diagnosis is made by neutrophil function testing and then the exact defect is determined by genotyping (35, 38). Historically, in many studies, the NBT test is used to diagnose disease (34-5, 37-8) and NBT test of our patient have been 100% disrupted. Mateos M et al showed immunological study revealed high humoral and cellular immune responses, with polyclonal hypergammaglobulinemia and large increase in IgG and IgA. These levels remained high even in periods of non-infection (37). IgA serum level were normal in our patient. Goldblatt D et al Suggested that a raised erythrocyte sedimentation rate (ESR) can be found, even in the apparently uninfected patients, and probably reflects ongoing, subclinical inflammation. The level of C-reactive protein is rarely raised when the patient is apparently infection-free and thus remains a better marker of bacterial sepsis in the acutely ill patient (34) .The our patient ESR and CRP were serial controlled which reached to high level , but with beginning and persistence of treatment returned low levels gradually. Anemia (hemoglobin <12.5 g %) and leukocytosis (leukocytes >8500/mm3) were common findings in some studies and in our patient (23, 39).

CONCLUSION

Ultimately it is true that this disease is rarely seen in neonates but in any case, that the

neonate has multiple abscesses must be thought to have this condition and it should be treated.

REFERENCES

1. Winkelstein JA, Marino MC, Johnston RB Jr, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 2000; 79:155.

2. Suliaman F, Amra N, Sheikh S, et al. Epidemiology of chronic granulomatous disease of childhood in Eastern Province, Saudi Arabia. Pediatr Asthma Allergy Immunol 2009; 22:21.

3. Jones LB, McGrogan P, Flood TJ, et al. Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. Clin Exp Immunol 2008; 152:211.

4. Martire B, Rondelli R, Soresina A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin Immunol 2008; 126:155.

5. Soler-Palacín P, Margareto C, Llobet P, et al. Chronic granulomatous disease in pediatric patients: 25 years of experience. Allergol Immunopathol (Madr) 2007; 35:83.

6. Dorman SE, Guide SV, Conville PS, et al. Nocardia infection in chronic granulomatous disease. Clin Infect Dis 2002; 35:390.

7. Segal BH, DeCarlo ES, Kwon-Chung KJ, et al. Aspergillus nidulans infection in chronic granulomatous disease. Medicine (Baltimore) 1998; 77:345.

8. Towbin AJ, Chaves I. Chronic granulomatous disease. Pediatr Radiol 2010; 40:657.

9. Segal BH, Leto TL, Gallin JI, et al. Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine (Baltimore) 2000; 79:170.

10. Reichenbach J, Lopatin U, Mahlaoui N, et al. Actinomyces in chronic granulomatous disease: an emerging and unanticipated pathogen. Clin Infect Dis 2009; 49:1703.

11. Vowells SJ, Sekhsaria S, Malech HL, et al. Flow cytometric analysis of the granulocyte respiratory burst: a comparison study of fluorescent probes. J Immunol Methods 1995; 178:89.

12. Vowells SJ, Fleisher TA, Sekhsaria S, et al. Genotype-dependent variability in flow cytometric evaluation of reduced nicotinamide adenine dinucleotide phosphate oxidase function in patients with chronic granulomatous disease. J Pediatr 1996; 128:104.

13. Margolis DM, Melnick DA, Alling DW, Gallin JI. Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis 1990; 162:723.

14. Gallin JI, Alling DW, Malech HL, et al. Itraconazole to prevent fungal infections in chronic
granulomatous disease. N Engl J Med 2003; 348:2416.

15. A controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. The International Chronic Granulomatous Disease Cooperative Study Group. N Engl J Med 1991; 324:509.

16. Seger RA. Modern management of chronic granulomatous disease. Br J Haematol 2008; 140:255.

17. Marciano BE, Wesley R, De Carlo ES, et al. Long-term interferon-gamma therapy for patients with chronic granulomatous disease. Clin Infect Dis 2004; 39:692.

18. Kobayashi Y, Amano D, Ueda K, et al. Treatment of seven cases of chronic granulomatous disease with sulfamethoxazole-trimethoprim (SMX-TMP). Eur J Pediatr 1978; 127:247.

19. Weening RS, Kabel P, Pijman P, Roos D. Continuous therapy with sulfamethoxazole-trimethoprim in patients with chronic granulomatous disease. J Pediatr 1983; 103:127.

20. Mouy R, Fischer A, Vilmer E, et al. Incidence, severity, and prevention of infections in chronic granulomatous disease. J Pediatr 1989; 114:555-60.

21. Petropoulou T, Liese J, Tintelnot K, et al. [Long-term treatment of patients with itraconazole for the prevention of Aspergillus infections in patients with chronic granulomatous disease (CGD)]. Mycoses 1994; 37 Suppl 2:64.

22. Mouy R, Veber F, Blanche S, et al. Long-term itraconazole prophylaxis against Aspergillus infections in thirty-two patients with chronic granulomatous disease. J Pediatr 1994; 125:998

23. Cale CM, Jones AM, Goldblatt D. Follow up of patients with chronic granulomatous disease diagnosed since 1990. Clin Exp Immunol 2000; 120:351-5.

24. Beauté J, Obenga G, Le Mignot L, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France. Pediatr Infect Dis J 2011; 30:57.

25. Lublin M, Bartlett DL, Danforth DN, et al. Hepatic abscess in patients with chronic granulomatous disease. Ann Surg 2002; 235:383.

26. Seger RA. Hematopoietic stem cell transplantation for chronic granulomatous disease. Immunol Allergy Clin North Am 2010; 30:195.

27. Kang EM, Marciano BE, DeRavin S, et al. Chronic granulomatous disease: overview and hematopoietic stem cell transplantation. J Allergy Clin Immunol 2011; 127:1319.

28. Martire B, Rondelli R, Soresina A, et al. Clinical features, long-term follow-up and outcome of a large cohort of patients with Chronic Granulomatous Disease: an Italian multicenter study. Clin Immunol 2008; 126:155.

29. Jones LB, McGrogan P, Flood TJ, et al. Special article: chronic granulomatous disease in the United Kingdom and Ireland: a comprehensive national patient-based registry. Clin Exp Immunol 2008; 152:211.

30. Liese J, Kloos S, Jendrossek V, et al. Long-term follow-up and outcome of 39 patients with chronic granulomatous disease. J Pediatr 2000; 137:687-93.

31. Winkelstein JA, Marino MC, Johnston RB Jr, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine (Baltimore) 2000; 79:155.

32. Kobayashi S, Murayama S, Takanashi S, et al. Clinical features and prognoses of 23 patients with chronic granulomatous disease followed for 21 years by a single hospital in Japan. Eur J Pediatr 2008; 167:1389.

33. Wolach B, Gavrieli R, de Boer M, et al. Chronic granulomatous disease in Israel: clinical, functional and molecular studies of 38 patients. Clin Immunol 2008; 129:103.

34. Goldblatt D, Thrasher AJ, Chronic granulomatous disease. Clin Exp Immunol 2000; 122:1-9

35. Holland SM, Rosenzweig SD, Chronic granulomatous disease: Pathogenesis,

clinical manifestations, and diagnosis. Uptodate.2012,Mon Nov 19 00:00:00.

36. Arnide EG, Jacob CA, Castro AM, Pastorino AC. Clinical and laboratory aspects of chronic
granulomatous disease in description of eighteen patients.Pediatr Allergy Immunol 2005: 16: 5–9.

37. Mateos M, Alvaro, Giner M, Plaza A , López M, et al, Chronic granulomatous disease: six new cases.PediatrAllergy Immunol,1998;26:241-9.

38. Leiding JW, Holland SM, Chronic granulomatous disease. GeneReviews,2012, Bookshelf ID: NBK99496PMID: 22876374.

39. Carnide EG, Jacob CA, Castro AM, Pastorino AC. Clinical and laboratory aspects of chronic
granulomatous disease in description of eighteen patients.Pediatr Allergy Immunol 2005: 16: 5–9.

40. Finn A, Hadzic N, Morgan G, Strobel S, Levinsky RJ. Prognosis of chronic granulomatous disease. Arch Dis Child 1990; 65:942-5.

41. Dorman SE, Gill VJ, Gallin JI, Holland SM. Burkholderia pseudomallei infection in a Puerto Rican patient with chronic granulomatous disease: case report and review of occurrences in the Americas. Clin Infect Dis 1998; 26:889-94.