

## Case Reports

### Disseminated Nocardiosis in a Patient with Chronic Granulomatous Disease: A Case Report

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#### Introduction

Infection with *Nocardia* poses a diagnostic challenge in patients with chronic granulomatous disease (CGD), because the signs and symptoms are often nonspecific, delay in diagnosis is common. Physicians caring for patients with CGD need to maintain a high index of suspicion for nocardiosis, especially in those receiving chronic steroid therapy. Early diagnosis remains critical for decreased morbidity and occasional mortality.

Chronic granulomatous disease (CGD) is a rare inherited disorder of the nicotinamide adenine dinucleotide phosphate-oxidase complex in which phagocytes fail to generate superoxide and toxic oxygen metabolites, which are key elements in host defense against a variety of microbes<sup>1</sup>. As a result, CGD patients are susceptible to recurrent, severe infections at an early age with catalase-positive organisms such as *Staphylococcus*, *Burkholderia cepacia*, *Aspergillus*, and *Nocardia*<sup>1</sup>. Two thirds of patients inherit CGD in an X-linked pattern attributable to mutations in the gene encoding the membrane-bound cytochrome b558 gp91-phox subunit of the nicotinamide adenine dinucleotide phosphate-oxidase. One third follows an autosomal recessive pattern attributable to gene mutations encoding the remaining three oxidase components: p47-phox, p67-phox, and p22-phox<sup>2</sup>.

*Nocardia* species (spp) are ubiquitous soil-borne aerobic actinomycetes usually causing invasive disease in patients with immunodeficiency, such as

those receiving corticosteroids or antineoplastic chemotherapy, solid-organ transplant recipients, and patients with CGD and lymphoreticular malignancies<sup>3,4</sup>. The most common pathogenic *Nocardia* species are the *Nocardia asteroides* complex followed by *N. brasiliensis*, *N. otitidiscavarium*, and *N. transvaliensis*<sup>5</sup>. Reports of nocardiosis in pediatric patients with CGD have been few. No case of CGD with disseminated Nocardiosis had been reported from Bangladesh till now. A rare case is presented below.



**Fig.-1:** Multiple discharging sinuses in patient's right inguinal region

#### Case report

A 6½ yr old immunized male child, only issue of consanguineous parents hailing from Manikdia, Dhaka presented with multiple nodular swelling in axilla and groin for 5½ years, purulent discharge from the site for 4½ years. At 9 months of age he developed multiple nodular swelling at left axilla and was diagnosed as a case of tubercular lymphadenitis and was treated with anti-tubercular drugs for 6 months. Following treatment he was apparently well for 1 year. Again he developed

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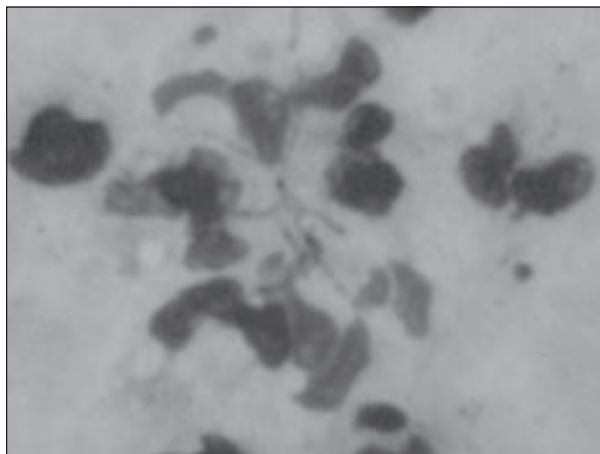
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multiple nodular swelling involving left submandibular, axillary and both inguinal

regions. Axillary and inguinal lymph nodes were subsequently ulcerated producing purulent discharge. Thereafter, he developed low grade irregular fever and painless scrotal swelling for the last 6 months. He got anti-tubercular drugs for a total of 4 occasions during the last 4 years with adequate dose & duration along with second line drugs without significant improvement. He had a suggestive family history. One of his cousins died of similar disease and another cousin had similar problem; their

parents also had consanguinity. On examination, the child was moderately pale, febrile; left submandibular, axillary, right and left inguinal lymph nodes were palpable, discrete, non-tender, with honey coloured purulent discharge from right inguinal lymph nodes (Fig.1). BCG mark was present. There was mild hepatomegaly. Kidneys were not palpable and other systems were found normal on examination.

Blood hemogram showed normocytic normochromic anemia with neutrophilic leucocytosis and reactive thrombocytosis in the peripheral smear. ESR was raised (114 mm in 1<sup>st</sup> hour).



**Fig.-2:** A modified acid-fast stained smear of pus on admission showing acid-fast and filamentous bacilli with branching

USG of whole abdomen showed moderate obstructive features in right kidney with dilated right upper ureter. Pus from inguinal region was examined by Gram stain and modified AFB stain which revealed filamentous branching Gram positive acid fast bacteria suggesting *Nocardia* spp (Fig.2). Culture revealed growth of *Nocardia* spp. Mantoux test was negative. Lymph

node biopsy yielded microgranulomata without any necrosis. CT scan of whole abdomen revealed para-aortic, para-caval & mesenteric lymphadenopathy. IVU showed that excretory function of right kidney was grossly impaired; left kidney was normal. DMSA Scan revealed non visualized right kidney, left kidney was normal. DTPA renogram also showed nonfunctioning right kidney.

The patient was treated with Inj. Cefotaxime [100 mg/kg/day] & Inj. Amikacin

[15 mg/kg/day] for 4 weeks, then Syp. Cotrimoxazole [15 mg/kg/day] & Syp. Cefixim [10 mg/kg/day] were prescribed for 6 months. Patient improved appreciably with resolution of discharging sinuses. Fever had subsided, appetite returned and weight gained. But excretory function of right kidney was impaired.

### Discussion

Chronic granulomatous disease is characterized by the ability of neutrophil and monocyte to ingest but their inability to kill catalase positive microorganisms, because of a defect in the generation of microbial oxygen metabolites. Granuloma formation and inflammatory processes are hallmark of CGD<sup>6</sup>.

Nocardiosis in children with CGD is rare. Ballenger and Goldring reported the first case of *Nocardia* spp (species) infection in a child with presumed CGD in 1957. To date, 17 cases have been reported in the English language literature<sup>7-9</sup>. Neutrophils are critical to the initial containment of infection with *Nocardia* spp, but infection progresses until the appearance of cell-mediated immunity, triggered by activated macrophages and induction of a T cell population capable of direct lymphocyte-mediated toxicity to *N. asteroides*; both of these cells kill nocardiae in vitro<sup>4</sup>. Suppression of cellular immunity appears to play a key role in the establishment of *Nocardia* infections<sup>3,4</sup>. *Nocardia* infections are almost exclusively seen in immunocompromised patients. Typical sites of dissemination include the lungs, skin, brain, and musculoskeletal system. Less common sites include the pericardium, kidney, adrenal glands, eye, spleen, and liver. Ours is a very rare case of CGD with the involvement of lymph nodes at multiple sites with renal involvement. Although no controlled trial has been done, extensive clinical experience has shown that antibiotic prophylaxis in patients with CGD reduced the incidence of infections and prolongs patients' survival<sup>10</sup>. Hematopoietic stem cell transplantation is

the only known cure for CGD. As part of supportive care, patient with CGD should be given daily oral trimethoprim-sulfamethoxazole for prophylaxis of infection. Granulocyte transfusions may be necessary if antibiotics are ineffective<sup>6</sup>.

### Conclusion

Due to low incidence and nontypical manifestations, nocardiosis is frequently misdiagnosed while recognition of this infection is important for the choice of appropriate antibiotic treatment in CGD. In the absence of any specific therapy, it is very important to identify carriers of CGD, especially in families in which a known case is already present. Genetic counseling of such families may help in reducing the incidence of the disease, especially the autosomal recessive form<sup>11</sup>. Fetal blood sampling and the nitroblue tetrazolium (NBT) slide test analysis of fetal neutrophils can be used for prenatal diagnosis of CGD<sup>6</sup>.

### References

- Gallin JI, Buescher ES, Seligmann BE, Nath J, Gaither T, Katz P. NIH conference: recent advances in chronic granulomatous disease. *Ann Intern Med.* 1983; 99(5): 657-74.
- Curnutte JT. Chronic granulomatous disease: the solving of a clinical riddle at the molecular level. *Clin Immunol Immunopathol.* 1993; 67:S2-S15
- McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. *Clin Microbiol Rev.* 1994; 7(3): 357-417.
- Beaman BL, Beaman L. *Nocardia* species: host-parasite relationships. *Clin Microbiol Rev* 1994; 7(2): 213-264.
- Steingrube VA, Brown BA, Gibson JL. DNA amplification and restriction endonuclease analysis for differentiation of 12 species and taxa of *Nocardia*, including recognition of four new taxa within the *Nocardia asteroides* complex. *J Clin Microbiol* 1995; 33(12): 3096-3101.
- Boxer LA, Disorders of Phagocytic function. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF editors. *Nelson Textbook of Pediatrics.* 18<sup>th</sup> ed. Philadelphia: Elsevier; 2007.P.908-9.
- Beaman BL, Boiron P, Beaman L, Brownell GH, Schaal K, Gombert ME. *Nocardia* and nocardiosis. *J Med Vet Mycol.* 1992; 30 (suppl 1): 317-31
- Avinash K. Shetty, Ann M. Arvin, and Kathleen M. Gutierrez. *Nocardia farcinica* Pneumonia in Chronic Granulomatous Disease. *Pediatrics* 1999; 104: 961-4.
- Bujak JS, Ottesen EA, Dinarello CA, Brenner VJ. Nocardiosis in a child with chronic granulomatous disease. *J Pediatr* 1973; 83(1): 98-100
- Woodman RC, Curnutte JT. Chronic granulomatous disease. *West J Med* 1991; 154(4): 460-1
- Nawaz H, Ahmed TA, Ali S, Ahmed D. Wazar MA. Chronic granulomatous disease. *J Pak Med Assoc* 2008; 58(9): 516-8.