Actinomycosis and Nocardiosis Co-infection in Chronic Granulomatous Disease

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Abstract
Chronic granulomatous disease (CGD) is an inherited disease of the phagocyte NADPH oxidase system that causes defective production of toxic oxygen metabolites, leading to impaired bacterial and fungal killing, and recurrent life threatening infections; mostly by catalase producing organisms. Nocardiosis in CGD is well described, however actinomycosis is rare. We describe a patient of CGD with actinomycosis and nocardiosis co-infection. A 43-year-old male with history of recurrent discharging sinuses presented with fever, dyspnea and cough. He had multiple discharging sinuses over neck and anterior chest wall. There was only partial response to intravenous penicillin. Needle aspirate from chest wall showed co-infection with actinomyces and nocardia. His nitroblue tetrazolium (NBT) reduction test was negative. He was treated with penicillin, amikacin and trimethoprim-sulfamethoxazole and had good clinical and radiological response.

Introduction
CGD is a rare inherited disease that affects the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system, which leads to defective production of toxic oxygen metabolites and ineffective microbial killing. These patients develop recurrent life-threatening infections, especially due to catalase producing organisms including nocardia. Actinomyces are catalase-negative organisms, previously thought to be non-pathogenic in CGD. However, recently 10 cases of actinomycosis have been described in these patients, challenging this concept.¹

Actinomyces and nocardia have been called the “great masqueraders,” as the diagnosis of infections caused by these organisms is often delayed. Hallmark of both infections is abscess formation and chronic progression of infection without regard to anatomic barriers. Patients frequently present with fistulous tracts and draining sinuses. Nocardiosis in CGD is well described, however actinomycosis is rare.²³ We report a case of actinomycosis and nocardiosis co-infection in a previously undiagnosed case of CGD. To our knowledge, this is the first report of such a case in literature.

Case Report
A 43-year-old male, working in a cotton mill, presented to us with history of recurrent multiple discharging sinuses for the last 8 years. He sustained fracture of the left humerus in a road traffic accident 8 years back. Few months later, he noticed a painless swelling over left elbow which gradually increased in size over one year. He was operated with a diagnosis of bursitis; however, the suture site developed multiple boils which converted to discharging sinuses. Over the next two years he developed new discharging sinuses on the arm and axilla on the same side. Meanwhile, he was treated with multiple courses of antibiotics without any improvement. Sinus tract biopsy was performed which revealed granulomatous inflammation; stains for acid fast bacilli and fungus were negative and no organism was identified on gram stain. He received anti-tubercular therapy for one year with good compliance. However, he continued to develop new lesions which now involved the neck. Repeat biopsy of the sinus tract and stain of the discharging pus revealed no definitive diagnosis. The patient received intravenous penicillin for 1 month followed by oral amoxicillin (500 mg three times daily) for 6 months. He improved clinically and his lesions dried up. Two years later, he had recurrence of symptoms with appearance of new lesions over the chest and discharge from old sinuses. This time he also had fever, dyspnea, cough with anorexia and significant weight loss. He was again started on intravenous penicillin; however the response was inadequate.

He presented to us with high grade fever and prostration. On examination, he had healed scars of sinuses on left elbow, arm and neck and discharging sinuses over anterior chest wall, neck and left axilla (Figure 1A). There was pallor, mild pedal edema and decreased breath sounds over the left hemithorax. Investigations revealed haemoglobin of 9.2 gm/dl, elevated leukocyte count (13.8 x 10⁹ cells/L), elevated erythrocyte sedimentation rate (102 mm/1st hr), and reversal of albumin: globulin ratio (3.2/5.9 gm/dL). Serum levels of blood urea, creatinine and electrolytes were normal as were bilirubin and transaminases. Computed tomography (CT) of the chest showed left upper lobe collapse-consolidation, soft tissue shadow in anterior chest wall invading the pectoralis muscles, and axillary lymph nodes (Figure 2A). Gram stain and Ziehl-Neelsen (ZN) stain of the pus did not show any organism and bacterial, anaerobic and fungal cultures were negative. Needle aspirate from anterior chest wall collection showed dense acute inflammatory exudates along with histiocytes and giant cells. Colonies of actinomyces and nocardia were identified on Papanicolaou, Grocott methenamine silver and modified ZN stains (Figure 3 A, B). His blood sugar level was normal, serology for retrovirus was negative and immunoglobulin levels were normal. His NBT reduction test was negative (50% positive cells). Final diagnosis of CGD with actinomycosis and nocardiosis co-infection was reached. He was started on intravenous penicillin, amikacin and trimethoprim-sulfamethoxazole which he received for one month and patient...
Discussion

The patient had presented to us with recurrent multiple discharging sinuses which had been treated on the lines of actinomycosis previously. At this presentation, he had disease involving subcutaneous tissue and the lungs. On evaluation, he was found to have CGD with co-infection of actinomyces and nocardia. Actinomyces are almost invariably isolated as part of a polymicrobial flora, however there are no reports of co-infection with nocardia in CGD. Moreover, actinomycosis is rarely described in CGD.

Skin, lymph nodes and lung are the most frequent sites of infection in CGD. Nocardiosis is amongst the five commonest infections described in these patients whereas; only 10 patients with actinomycosis have been reported. Actinomyces are part of the normal flora of the mouth and gastrointestinal tract and are generally of low virulence. They invade via damaged mucosa, leading to bacteraemia and systemic infections in both healthy individuals and immunocompromised patients. Reichenbach et al have described 10 patients of CGD with actinomycosis; however, none of them had pulmonary disease. In contrast, nocardiosis is well recognized in CGD. In a retrospective review Dorman et al analyzed 29 episodes of Nocardia infection in 24 of 150 patients with CGD and found that all patients had pulmonary involvement, dissemination occurred in one-quarter of episodes, and concomitant fungal infections were common.

Actinomyces and nocardia cause similar clinical syndromes involving the lung and soft tissue. Patients frequently present with fistulous tracts and draining sinuses. The onset of pulmonary disease may be acute, subacute, or chronic and is not distinguished by any specific signs or symptoms. Fever, night sweats, fatigue, anorexia, weight loss, dyspnea, cough, hemoptysis, and pleuritic chest pain have all been described.

A definitive diagnosis of actinomycosis or nocardiosis requires the isolation and identification of the organism from a clinical specimen. Actinomyces and nocardia are morphologically similar; however staining differences allow reasonably accurate classification and differentiation between the two. Actinomyces are characterized by tangles of slender filaments branching at acute angles; whereas nocardia are delicate, thin, faintly stained filaments branching at right angles. Nocardia are acid fast unlike actinomyces on staining with modified ZN stain. Difficulty in diagnosis arises as isolation of the causative organisms from patients who have received antibiotics within 7 to 10 days is extremely rare. Further as the diagnosis is delayed, chronicity of the disease course and fibrosis is further encouraged. The enhanced fibrosis also hinders the identification of typical sulphur granules on histological examination. At presentation, our patient had already received prolonged courses of antibiotics and repeated efforts to reach a microbiological diagnosis had been unsuccessful. Moreover, he had high fever along with pulmonary involvement, necessitating rapid diagnosis and treatment. Deep needle aspiration and prompt handling of samples helped in identifying the organisms.

Treatment for both actinomycosis and nocardiosis require long-term administration of parenteral and oral antibiotics. Surgical intervention may be required in selective cases. Actinomyces are susceptible to penicillins and extended spectrum penicillins, cephalosporins, clindamycin, carbapenems, and tetracycline. In nocardiosis with pulmonary involvement, combination therapy with trimethoprim-sulfamethoxazole and amikacin is recommended. Our patient received combination therapy with penicillin, amikacin and trimethoprim-sulfamethoxazole.

The cornerstone of clinical care in CGD is lifelong antibiotics and antifungal prophylaxis with trimethoprim-sulfamethoxazole and itraconazole. Judicious use of corticosteroids is warranted for exuberant inflammation. Haematopoietic stem cell transplantation; the definitive cure for CGD, was refused by our patient.

The susceptibility of CGD patients to infection with actinomyces suggests that catalase production is neither necessary nor sufficient for microbial virulence in CGD. Recently, the central role of superoxide in potassium flux into the phagolysosome and potassium’s role in activating killing has been elucidated. This explains the lack of importance of microbial hydrogen peroxide and, therefore, catalase in the pathogenesis of infections in CGD. High level of suspicion for actinomyces infection is essential in CGD patients to prevent the
chronic debilitating effects of inadequately treated infection and the unnecessary toxic effects of antibiotics.

**Abbreviations**

CGD- chronic granulomatous disease, NBT- Nitroblue tetrazolium, NADPH- nicotinamide adenine dinucleotide phosphate, CT- computed tomography, ZN stain-Ziehl-Neelsen stain.

**References**


