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Chronic Granulomatous Disease Presenting as *Aspergillus Fumigatus* Pneumonia in a Previously Healthy Young Woman

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Conflict of interest: None declared

Patient: Female, 23
Final Diagnosis: Chronic granulomatous disease
Symptoms: Fever • shortness of breath
Medication: —
Clinical Procedure: Bronchoscopy
Specialty: Pulmonology

Objective: Unusual clinical course

Background: Chronic Granulomatous Disease (CGD) is a rare immunodeficiency disease caused by a genetic defect in the NADPH (nicotinamide adenine dinucleotide phosphate) oxidase enzyme, resulting in increased susceptibility to bacterial and fungal infections. The inheritance can be X-linked or autosomal recessive. Patients usually present with repeated infections early in life. We present an unusual case of a 23-year-old patient diagnosed with CGD.

Case Report: A 23-year-old white woman with no previous history of recurrent infections presented with complaints of fever, shortness of breath, and diffuse myalgia. She had been treated twice for similar complaints recently, but without resolution. She was febrile, tachypneic, tachycardic, and hypoxic at presentation. Physical examination revealed diffuse inspiratory rales. Laboratory results showed leukocytosis. Her initial chest X-ray and CT chest showed reticular nodular interstitial lung disease pattern. Despite being on broad-spectrum antibiotics for 5 days, she continued to require supplemental oxygen and continued to be tachypneic, with minimal activity. Initial diagnostic tests, including bronchoscopy with biopsy and lavage, did not reveal a diagnosis. She then underwent a video-assisted thoracoscopic surgery (VATS) lung biopsy. The biopsy slides showed suppurative granulomatous inflammation affecting greater than 50% of the parenchymal lung surface. Fungal hyphae consistent with *Aspergillus* were present in those granulomas. A diagnosis of CGD was made and she was started on Voriconazole. She improved with treatment. Her neutrophil burst test showed negative burst on stimulation, indicating phagocytic dysfunction consistent with CGD. Autosomal recessive CGD was confirmed by genetic testing.

Conclusions: CGD can present in adulthood without any previous symptoms and signs. Clinicians should consider this disease in patients presenting with recurrent or non-resolving infections. Timely treatment and prophylaxis has been shown to reduce serious infections as well as mortality in these patients.

MeSH Keywords: *Aspergillus Fumigatus* • Granulomatous Disease, Chronic • Pneumonia

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/902764

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Background

Chronic granulomatous disease (CGD) is a rare immunodeficiency disorder caused by a genetic defect in the NADPH oxidase enzyme, leading to increased susceptibility to bacterial and fungal infections. The inheritance of the defect can be X-linked or autosomal recessive. As a result of this defect, phagocytes (neutrophils and monocytes) fail to kill the organisms that they have engulfed due to inability to release their own toxic free radicals. This is also known as the failure of the respiratory or oxidative burst pathway [1]. This failure leads to undigested cellular debris and gives way to areas of increased inflammation and granuloma formation [2].

Patients typically develop several infections early on in life (usually within the first 2 years of life). This may involve any organ or tissue, but the lungs, skin, gastrointestinal tract, lymph nodes, liver, and bones are the usual sites of infection [3–5]. Being a predominately X-linked disease, CGD is much more common in males, who accounted for up to 86% in a registry [3]. CGD affects about 1 in 200 000 people in the United States, with about 20 new cases diagnosed each year [3]. There are milder forms of the disease, generally related to the autosomal recessive defects that are less severe. Patients with the milder form of disease usually present at around 5–7 years of age [6,7]. We present the unusual case of a 23-year-old woman diagnosed with CGD.

Case Report

A 23-year-old white woman presented with complaints of shortness of breath, minimal cough, and chills at an outpatient clinic. She was thought to have an upper-respiratory tract infection and/or pneumonia and was given a course of oral antibiotics. A week later, she returned to the clinic similar complaints and a high fever. She was again treated for pneumonia and discharged with oral antibiotics. However, after 2 days, she presented to the local Emergency Department (ED) with worsening shortness of breath and high fever (39°C at home per patient). She also complained of diffuse body aches but no specific arthralgia. Initial evaluation showed a temperature of 37°C, respiratory rate of 44/min, heart rate of 132/min, and a room air oxygen saturation of 80%. She was immediately started on 4 L/min supplemental oxygen via nasal cannula, with improvement in saturations. The physical examination revealed diffuse inspiratory rales. Her white blood cell (WBC) count was 28 000, with 76% neutrophils and 7% eosinophils. Other laboratory results, including lactic acid, were within normal limits. Her PaO_2 on ABG was 79 mmHg while on supplemental oxygen. Her initial chest X-ray and CT chest showed reticular nodular interstitial lung disease pattern (Figure 1). Her past medical history was significant only for hypothyroidism. She had no previous history of recurrent infections. There was no family history of any immunodeficiency or autoimmune disease. She did landscaping work and was frequently around soil and mulch. She was started on broad-spectrum antibiotics (Vancomycin, Zosyn, and levofloxacin) and high-dose corticosteroids and was admitted to the Intensive Care Unit (ICU) for close observation.

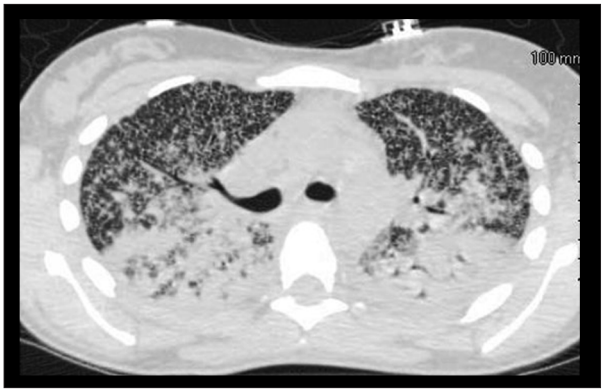

Figure 1. CT chest at presentation showing reticular nodular interstitial pattern throughout both lungs.

Further investigations were done to rule out possible infectious and inflammatory lung disease. She had negative ANA (antinuclear antibody) and ANCA (anti-neutrophil cytoplasmic antibody). Her C3 and C4 were 62 mg/dl and 4 mg/dl, respectively. Her immunoglobulins were normal except for an elevated IgE level of 2280. Results were negative for HIV, *Legionella,* and *S. pneumoniae*. Her sputum gram and acid-fast bacilli stain, sputum culture, and blood and urine cultures were also negative. Serum fungal antigen and antibody levels for *Aspergillus, Blastomyces, Coccidioides, Cryptococcus, and Histoplasma* were also negative. Bronchoscopy with bronchoalveolar lavage (BAL) and trans-bronchial biopsy was done. BAL fluid cultures were also negative, with a differential showing neutrophils 67%, lymphocytes 14%, and Macrophages 17%. Trans-bronchial biopsies showed benign bronchial mucosa with mild chronic inflammation. Polymerase chain reaction and galactomannan test were sent in an initial BAL sample and were negative.

Despite being on broad-spectrum antibiotics for 5 days, she continued to require 3–4 L/min supplemental oxygen and continued to be tachypneic with minimal activity. Her WBC remained over 25 000 despite antibiotics. She underwent a video-assisted thoracoscopic surgery (VATS) with biopsy of the right middle and lower lobes. During surgery, the lung surface appeared grossly nodular. The bedside frozen pathology showed suppurative granulomatous inflammation. The final surgical pathology showed suppurative granulomatous inflammation affecting greater than 50% of the parenchymal lung surface (Figure 2), with fungal hyphae consistent with *Aspergillus* present within the granulomas (Figure 3). With her clinical and pathological

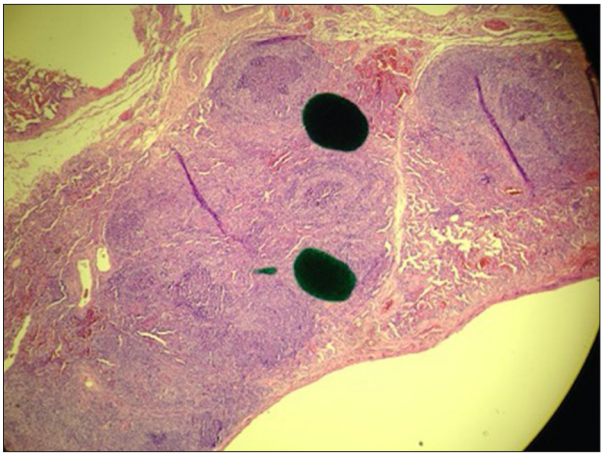

Figure 2. Full tissue sample showing multiple granulomas throughout the lung parenchyma (over 50% by report).

findings, a diagnosis of chronic granulomatous disease was made along with *Aspergillus* pneumonia, and she was started on Voriconazole.

With anti-fungal treatment, her WBC improved and returned to normal levels. After VATS biopsy, she required mechanical ventilation with high PEEP (up to 12 cm H_2O) and FIO2 (as high as 65%). She had copious bronchial secretions and initially required serial bronchoscopies for clearance. Interestingly, subsequent BAL fluids grew *Aspergillus* species. She was successfully extubated on day 7 after VATS biopsy.

She underwent neutrophil burst test that showed negative burst on stimulation indicating phagocytic dysfunction consistent with CGD. She continued to recover well and was discharged home. She was continued on Voriconazole for a total of 90 days with plans to start on prophylactic antibiotics (Trimethoprim/Sulfamethoxazole for bacterial and Itraconazole as tolerated) after that. Prophylaxis will have to be lifelong. During follow up, she had confirmatory genetic testing done which detected 2 copies of the GT deletion causing frameshift mutation in neutrophil cytosolic factor 1 {p47phox (NCF1)} exon 2.

Discussion

CGD is a rare genetic disease leading to life-threatening recurrent infections of various organ systems in the body. The lungs are a common site of infection, with patients presenting with pneumonia or pulmonary abscess [3–5,8]. The most common causative organisms are catalase-positive microbes, including *S. aureus*, *Enterobacteriaceae* family, *Nocardia* sp., *Burkholderia cepacia*, and *Aspergillus* species [4,5,9]. The catalase is able to break down the little amount of superoxides that are formed in the defective phagocytes, leaving the WBC incapable of destroying these microorganisms. Patients often

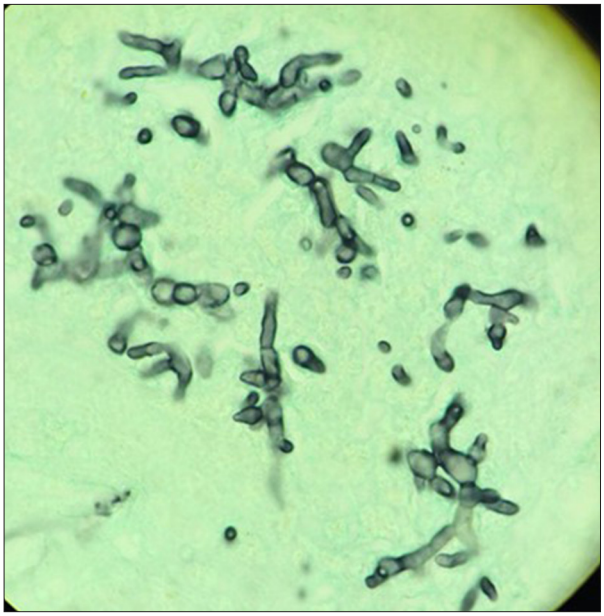

Figure 3. *Aspergillus* hyphae.

can resist most catalase-negative bacteria. *Aspergillus* typically accounts for up to 15% of infections in CGD [9].

In our case, the patient's exposure to soil and mulch due to her landscaping work likely lead to *Aspergillus* exposure. The diagnosis of *Aspergillus* pneumonia can usually be made by bronchoscopy with BAL and serum fungal antigen detection [10]. However, in this case, the initial cultures were negative and antigen levels were normal. She required open lung biopsy to help with diagnosis. The unusual aspect of this case is that the *Aspergillus* did not grow in cultures until later in the course of disease.

This case is also intriguing in that the patient did not have any obvious manifestations of CGD, such as recurrent infections, until the age of 23 years. As mentioned above, autosomal recessive pattern CGD usually presents at around 5–7 years of age, and such a late presentation is unusual. There are other reported cases of CGD in which a patient was diagnosed in late adulthood, but these are rare [11–13]. Up to 30–40% of CGD occurs in an autosomal recessive pattern. These patients typically have genetic defects in one of 5 genes: $gp91^{phos}$ (CYBB), $p22^{phos}$ (CYBA), p47phox (NCF1), $p67^{phox}$ (NCF2), and $p40^{phox}$ (NCF4) [14]. The type of inheritance pattern defect present determines the degree of superoxide anion production and thus the degree of neutrophil activity available to fight infections [2,14,15]. Our patient's genetic defect is the most common genetic mutation in autosomal recessive CGD, and accounts for approximately 20% of all CGD cases [15]. Knowing the inheritance pattern, and thus the degree of a patient's neutrophil's ability to provide respiratory burst, is helpful in determining the possible clinical course and therapy.

The management of patients known to have CGD includes avoiding common exposures and antibiotic prophylaxis against common bacterial and fungal infections. It is recommended that patients avoid any exposure to mulch and to they stay indoors while neighbors are laying mulch. Prophylaxis includes Trimethoprim/sulfamethoxazole for bacterial infections and itraconazole for fungal infections, as tolerated [9]. If infections do occur, prompt and appropriate workup and treatment should be initiated. Interferon gamma prophylaxis reduces the frequency of serious infections by 70% [16], achieved by increasing the production of superoxides in CGD patients. Another option is stem cell transplantation, which has been reported to be curative [17].

Conclusions

CGD can present late in adulthood without any previous symptoms or signs. Clinicians should consider this disease in patients presenting with recurrent infections or non-resolving infections. Timely treatment and prophylaxis have been shown to reduce serious infections and mortality in these patients.

Conflict of interest

No financial support was available, no conflict of interest exists.

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