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Chronic granulomatous disease presenting as refractory pneumonia in late adulthood

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Abstract

We present a case of refractory pneumonia in an adult patient with underlying chronic granulomatous disease (CGD). Her lobectomy tissue grew *Burkholderia cepacia* and histopathology revealed diffuse severe pneumonic consolidation with suppurative/necrotizing granulomata. An initial attempt to find an underlying immune deficiency was unsuccessful. Following recurrent invasive infections, repeat immunological assessment revealed reduced neutrophil function, demonstrating skewed carrier status (lyonization) for X-linked CGD (only 3% normal cells). A pathogenic mutation in the *CYBB* gene was found on sequencing. *CYBB* gene encodes the gp91phox, a catalytic subunit of nicotinamide adenine dinucleotide phosphate-oxidase that produces reactive oxygen species in phagocytes. Lyonization increases with age, explaining the delayed clinical CGD. CGD is a rare neutrophil disorder that usually presents in early life with recurrent infections due to bacteria and fungi primarily involving lungs and skin. It is secondary to a defective NADPH oxidase system needed to kill intracellular organisms and activate the formation of neutrophil extracellular traps.

Introduction

A 53-year-old woman presented with refractory pneumonia with underlying undiagnosed chronic granulomatous disease (CGD). CGD is a neutrophil defect that leads to recurrent and persistent intracellular bacterial and fungal infections and also to granuloma formation. Presentation is usually in early childhood.

Infections commonly encountered in patients with CGD include *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* and *Aspergillus* spp. Other uncommon organisms include *Neisseria meningitidis*, *Acinetobacter junii*, *Candida* species, *Klebsiella pneumoniae*, *Mycobacterium tuberculosis*, nontuberculous mycobacteria, *Proteus* species, and *Leishmania* species [1].

Case Report

A 53-year-old woman presented with left lower lobe pneumonia in 2005 with a past medical history of four lower respiratory tract infections treated with oral antibiotics. She was an ex-smoker of 12 months with a 35 pack year history, but otherwise well. Despite intravenous ceftriaxone then intravenous piperacillin/tazobactam, each in combination with oral azithromycin, her infection remained refractory to treatment. Blood, sputum, bronchial lavage, and

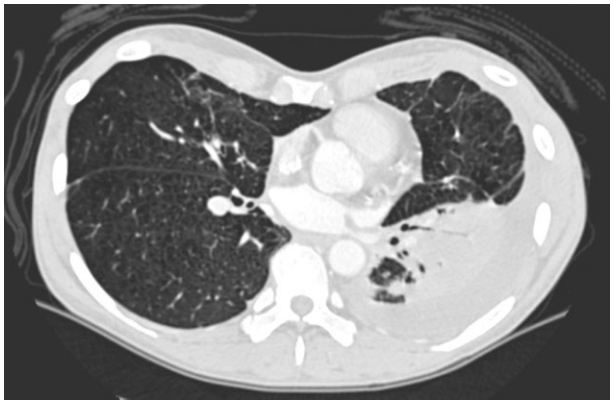

Figure 1. Cross-sectional computed tomography scan of lower lungs showing collapse/consolidation in the lower lobe of left lung.

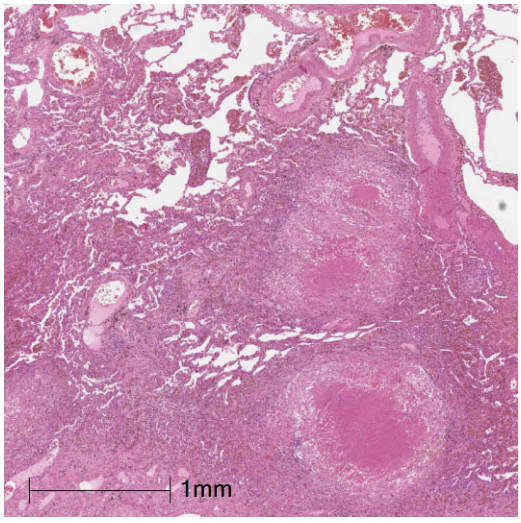

Figure 2. Microscopic section of lower lobe of left lung showing multiple necrotizing granulomata and hematoxylin and eosin stain.

transbronchial biopsy cultures did not grow any organisms. Computed tomography of the chest revealed left lower lobe collapse/consolidation with an associated small pleural effusion (Fig. 1).

A diagnostic thoracoscopic left lower lobe wedge resection grew *B. cepacia*. Following this, therapy was changed to parenteral ceftazidime, tobramycin, meropenem, and ciprofloxacin for 6 weeks. Subsequent therapeutic left lower lobectomy was performed to debulk the remaining necrotizing tissue. Histology showed diffuse severe pneumonic consolidation with suppurative/necrotizing granulomata, organizing granulomatous pleuritis, and suppurative granulomatous lymphadenitis (Fig. 2). Histochemical stains for fungi and acid fast bacilli were negative. Parenteral therapy was followed by oral treatment with sulfamethoxazole-trimethoprim and ciprofloxacin for 3 months resulting in clinical resolution.

Shortly after surgery, immunoglobulins, HIV testing, autoantibodies, *CFTR*, sweat chloride, and a single flow cytometric neutrophil function test were all reported as normal.

Subsequently, she suffered from 17 episodes of pneumonia in the remaining lobes of both lungs, and one episode of invasive salmonellosis, requiring hospital admissions and parenteral antibiotics. She also had two episodes of cervical herpes zoster (C2 and C3) in 2008 and 2013, respectively. She has not to date suffered a significant fungal infection. Due to her recurrent chest and skin infections, she was again investigated for immune dysfunction in 2012. A reduced neutrophil oxidative burst was found, contrary to the result reported in 2005. The oxidative burst of neutrophil was measured by capacity of neutrophil to oxidize dihydrorhodamine 123 (DHR 123) to the highly fluorescent compound rhodamine 123 when stimulated with phorbol-12-myristate 13-acetate (PMA). Rhodamine 123 can be detected by flow cytometry providing a quantitative means of functional neutrophils. Analysis showed that only 3% of her neutrophil were able to oxidize DHR 123 and remaining 97% neutrophil did not show oxidative burst.

Reduced neutrophil oxidative burst led to sequencing of the *CYBB* gene that demonstrated two heterozygous changes: 1152-2A>G, previously reported as pathogenic and diagnostic of CGD, and 1190G>C of less clear clinical significance. Following the discussion of the diagnosis of CGD, more family history came to light; her younger brother had died at the age of 6, disease consistent with granulomatous disease of the lungs. An older brother and two sisters are well and declined testing.

Discussion

Mutations in all five genes coding for components of the NADPH enzyme complex have been reported. Mutations in *CYBB*, on the X chromosome, account for up to 70% of cases of CGD, while mutations in the other four proteins lead to rarer autosomal recessive forms [2, 3].

Our patient had two rare mutations in the *CYBB* gene with extremely skewed lyonization resulting in CGD. Such a presentation in late adulthood is very unusual. Lyonization is an epigenetic process that occurs in all female mammalian cells whereby one of the two X chromosomes are randomly rendered inactive, such that all subsequent gene expression is derived from the other (active) chromosome. Preferential inactivation leads to skewed lyonization. The 1152-2A>G mutation has been previously reported as pathogenic [2, 3], whereas a patient with heterozygous 1190G>C mutation showed normal oxidative burst, sug-

gesting this is benign [4]. We were unable to test other family members to establish whether these mutations were co-located on the same allele or not. Our patient had extremely skewed lyonization with only 3% of the circulating neutrophils demonstrating normal oxidative burst activity, the result of expression of a functional *CYBB* gene, insufficient to protect against infection.

The original data for the neutrophil function test performed in 2005 could not be found. This may have been incorrectly interpreted, and was only tested once. It is also possible that the degree of reduction of ROS was less marked at that time, but should still have demonstrated two populations of neutrophils. Lyonization is a progressive process [5], and neutrophil function may have declined with age. Extremely skewed lyonization has been reported to cause adult onset CGD. Wolach et al. reported a 66-year-old woman who presented with multiple infections in different body systems and 8 years later found to have reduced oxidative burst on neutrophil function testing [6]. Her *CYBB* gene sequencing demonstrated heterozygous CYBB (CCG[90-92]→GGT) mutation and only 2% of her neutrophils produced oxidative burst consistent with skewed lyonization. Physicians, particularly immunologists and respiratory physicians, need to be aware of unusual cases of CGD that may present in late adult life. Neutrophil function testing is relatively simple and should be considered in patients with unusual or recurrent infections. Repeat testing should also be considered in those considered likely to have neutrophil defects.

Recommended antibacterial prophylaxis for CGD patients includes trimethoprim-sulfamethoxazole, a macrolide, or penicillin. Our patient is taking doxycycline, which is currently effective. Previous prophylactic macrolide and penicillin were ineffective. Interferon-gamma prophylaxis in CGD patients may be considered if prophylactic antibiotics are not effective [7]. Allogenic bone marrow transplantation should be considered, particularly in younger patients without significant morbidity [8].

Disclosure Statements

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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