A 60-Year-Old Asymptomatic Woman With Pulmonary Lesions and Cervical Lymphadenopathy

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A 60-year-old asymptomatic woman was referred to our hospital because of an abnormal chest roentgenogram during a routine medical checkup. The patient had no history of memorable infectious diseases, except a liver abscess caused by *Serratia marcescens* at age 46 years. Her son was diagnosed with chronic granulomatous disease at the age of 1 year. She had never smoked cigarettes and drank only occasionally. CHEST 2015; 147(2):e48-e51

Physical Examination Findings

The patient's vital signs were as follows: temperature, 36.8°C; BP, 136/72 mm Hg; heart rate, 72 beats/min; respiratory rate, 16 breaths/min; and oxygen saturation, 98% on room air. Lungs were clear to auscultation. Nontender enlargement of the left cervical and submental lymph nodes (10 and 8 mm in diameter, respectively) was observed. The rest of the physical examination was unremarkable.

Diagnostic Studies

Laboratory data revealed a normal WBC count (6,300/ μ L) and a slight increase in the C-reactive protein level (0.32 mg/dL; normal range, < 0.30 mg/dL). The interferon- γ release assay and 1,3- β -glucan content were negative. Consolidations were observed in the bilateral lung field on chest roentgenography. Chest CT scan revealed multiple consolidations with

Figure 1 – CT scan of the chest showing multiple consolidations with surrounding ground-glass opacities in bilateral lung field (arrow). A, Right apical segment. B, Lingular segment.

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surrounding ground-glass opacities (Fig 1). Transbronchial biopsy and bronchial washing showed no evidence of malignancy with negative bacterial and fungal culture results.

What is the diagnosis?

Diagnosis: Pulmonary aspergillosis as diagnosed by cervical lymph biopsy samples that contained *Aspergillus* hyphae in this patient with underlying chronic granulomatous disease

Discussion

Chronic granulomatous disease (CGD) is a rare, inherited immunodeficiency disorder caused by defects in superoxide-generating nicotinamide adenine dinucleotide phosphate oxidase in phagocytes and leading to recurrent, life-threatening bacterial and invasive fungal infections. CGD has at least five different mutations in genes involved in assembly and activation of the nicotinamide adenine dinucleotide phosphate oxidase. Most of patients in Western countries have an X chromosome-linked mutation in *gp91phox* (CYBB). Other less frequent mutations are inherited in autosomal recessive forms that involve *p22phox*, *p47phox*, *p67phox*, or *p40phox*. Approximately two-thirds of CGD cases are X-linked (*gp91phox* deficient). Consequently, the disorder is much more common in men and boys.

CGD involves multiple organs, including the lung, lymph node, bone, and GI tract. Pneumonia is the most frequent infection. Most common pathogens are catalase-positive organisms including *Aspergillus* species, *Staphylococcus*, *Burkholderia* species, *Serratia*, and *Nocardia*. Patients with CGD may not manifest typical signs of infection, despite the presence of significant infection. In a review of aspergillosis in patients with CGD, one-third of patients are asymptomatic at diagnosis, and only about 20% are febrile. Another important manifestation of CGD is abnormally exuberant inflammatory responses leading to granuloma formation, such as granulomatous enteritis resembling Crohn's disease.

Patients suspected of having CGD should initially undergo neutrophil function test. The most common diagnostic assays are the nitroblue tetrazolium reduction test and dihydrorhodamine 123 (DHR) test. Genetic testing, such as immunoblotting and direct gene sequencing, can be used to confirm the diagnosis of CGD.

Long-term antibacterial and antifungal prophylaxis with trimethoprim-sulfamethoxazole and itraconazole has been shown to reduce the rate of infection among patients with CGD. Treatment of acute infection must be performed by early and aggressive therapies. Patients should be treated empirically for gram-negative bacteria,

gram-positive bacteria, and fungal infections until the pathogen is identified.

The prognosis of CGD has been improved dramatically during the last decade by prophylaxis. Delayed diagnosis of CGD may lead to fatal outcome due to infectious and noninfectious complications. Most patients with CGD are diagnosed during childhood, but the presentation of adult-onset CGD has been reported in a few cases; this is considered to be due to age-related skewing of lyonization. Thus, the appropriate testing for CGD might be considered at any age if the patient has a suspicious history.

Meanwhile, the CT scan halo sign of ground-glass opacity surrounding a pulmonary nodule was first described in the patient with invasive pulmonary aspergillosis (IPA). Patients with such lesions on CT scan may have other invasive fungal infection (eg, candidiasis, cryptococcosis, and mucormycosis). *Aspergillus* galactomannan antigen and capsular antigen of *Cryptococcus neoformans* in serum are also useful as indirect diagnostic test. The main host factors for IPA development are neutropenia, receipt of an allogeneic stem cell transplant, and immunosuppressive agents (for example, corticosteroids and cyclosporine). Other immunocompromised patients, such as patients with CGD, have high risk for developing IPA.

Clinical Course

The patient's serum *Aspergillus* galactomannan antigen level was elevated at 4.5 (normal range, <0.5), and polysaccharide antigens of the capsule of *Cryptococcus neoformans* were negative. Based upon the clinical presentation of CT scan halo sign and elevated *Aspergillus* galactomannan antigen level, she was considered to have pulmonary aspergillosis. Thus, we performed cervical lymph node biopsy, which detected *Aspergillus* fungal elements (Fig 2) and suggested the presence of underlying immunocompromise. The history of a liver abscess and the son's history of CGD prompted neutrophil function testing, which demonstrated that the patient had CGD. Direct sequencing of the *gp91phox* gene revealed a missense mutation (Gly408Arg) in exon 10. The patient was treated with IV voriconazole 4 mg/kg q12h after two loading doses of 6 mg/kg. Three months after initiation of voriconazole, chest roentgenogram and CT scan images showed improvement of consolidations, and the *Aspergillus* galactomannan antigen level was normalized. She was switched to oral antimicrobial prophylaxis with itraconazole (200 mg/d) and

Figure 2 – A, Histopathologic analysis of cervical lymph node biopsy specimen showing suppurative granuloma containing necrosis and neutrophils (magnification $\times 100$). B, Grocott stain demonstrating the presence of fungal filament (arrow) (magnification $\times 400$).

trimethoprim-sulfamethoxazole after approximately 6 months of voriconazole therapy. The patient has no clinical signs of infection and currently remains stable.

Clinical Pearls

1. Appropriate testing for CGD might be considered at any age if the patient has a suspicious history.
2. Neutrophil function test should be initially performed for patients suspected of having CGD.
3. CGD is a genetically heterogeneous disorder characterized by recurrent life-threatening bacterial and fungal infections and granuloma formation.
4. One-third of *Aspergillus* infections in patients with CGD were asymptomatic at diagnosis, despite the presence of significant infection.

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Suggested Readings

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