Chronic granulomatous disease presenting at age 52 with fulminant mulch pneumonitis

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Chronic granulomatous disease should be considered in adults of any age in the presence of refractory and/or atypical or fulminant pulmonary infections. This case of new large deletions in *NCF1* was presented with mulch pneumonitis without a significant history of infections. (J Allergy Clin Immunol Global 2022;1:322-4.)

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Chronic granulomatous disease (CGD) is caused by inherited nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2) defects, resulting in severely reduced phagocyte-derived superoxide (O_2^-) production that manifests as recurrent infections and autoinflammation. Approximately 65% of patients with CGD have X-linked mutations in the *CYBB* (the gp91^{phox} subunit of the NOX2 complex), with the remainder harboring autosomal recessive mutations, the most common being in *NCF1* (the p47^{phox} subunit [occurring in 25% of patients with CGD]). Although the majority of patients have their CGD diagnosed before the age of 10 years, it is occasionally detected only in adulthood. However, diagnosis after the fourth decade of life is exceptionally rare, with only a handful of such cases described.[1,2] Moreover, there is usually a history of childhood infections. We present an atypical case of a 52-year-old male with no significant medical history who was diagnosed with p47^{phox}-deficient CGD during an episode of diffuse pulmonary granulomatosis secondary to *Aspergillus fumigatus* sp.

A 52-year-old male, known only for having chronic rhinitis without any history of hospitalization or pulmonary or intestinal disease was admitted with a 3-day history of fever, nausea, and headaches. As an excavator driver for several years, he reported a recent significant exposure to volatile organic compounds while plowing a sumac field. A thorough family history revealed 1 episode of endocarditis in a nephew and a maternal aunt with psoriatic arthritis. The patient's only medication was a statin for the treatment of his dyslipidemia.

On admission, blood tests revealed a C-reactive protein level of 238 mg/L and a white blood cell count of 13 $\times$ 10^9/L. A chest radiograph showed small multicentric opacities, and empiric treatment with ceftriaxone and azithromycin was started for community acquired pneumonia along with corticosteroids. Despite initial improvement, the patient's respiratory condition rapidly deteriorated, with an increase in inflammatory markers (a C-reactive protein level of 299 mg/L and a white blood cell count of 24 $\times$ 10^9/L), leading to his transfer to the intensive care unit on day 3 of hospitalization. A follow-up chest radiograph showed the progression of bilateral opacities (Fig 1, *A-D*) and a chest computed tomography scan showed diffuse ground-glass and reticulonodular opacities. Cardiac ultrasound showed a left ventricular function of 60% to 65% without evidence of pulmonary hypertension. The results of serial blood cultures, cerebral spinal fluid analyses, and computed tomography scan of the head remained negative. Surgical lung biopsy revealed extensive suppurative granulomatosis associated with branching septate hyphae compatible with *Aspergillus* spp (Fig 2). Culture of the lung biopsy specimen confirmed *Aspergillus fumigatus* sp. Three bronchoalveolar lavages were positive for galactomannan at a level higher than 3.56. The patient began receiving voriconazole and caspofungin but developed refractory acute respiratory distress syndrome requiring extracorporeal membrane oxygenation. The patient's unique histologic pattern and rapid clinical deterioration raised suspicion for an inborn error of immunity. A dihydrorhodamine 123 (DHR) assay demonstrated a marked reduction in neutrophil O_2^- production (Fig 1, *F*), consistent with a diagnosis of CGD. Because reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase dysfunction in CGD can lead to dysregulated inflammation and an overexuberant response to pathogens, we added intravenous methylprednisone to the patient's antifungal regimen, followed by an IL-1 receptor antagonist 72 hours later. Nevertheless, the patient died within 28 days of hospitalization following withdrawal of care according to the wishes of the family in the context of multiorgan damage. No autopsy was performed.

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Informed consent: The authors obtained the consent of the patient's family for the publication of this case.

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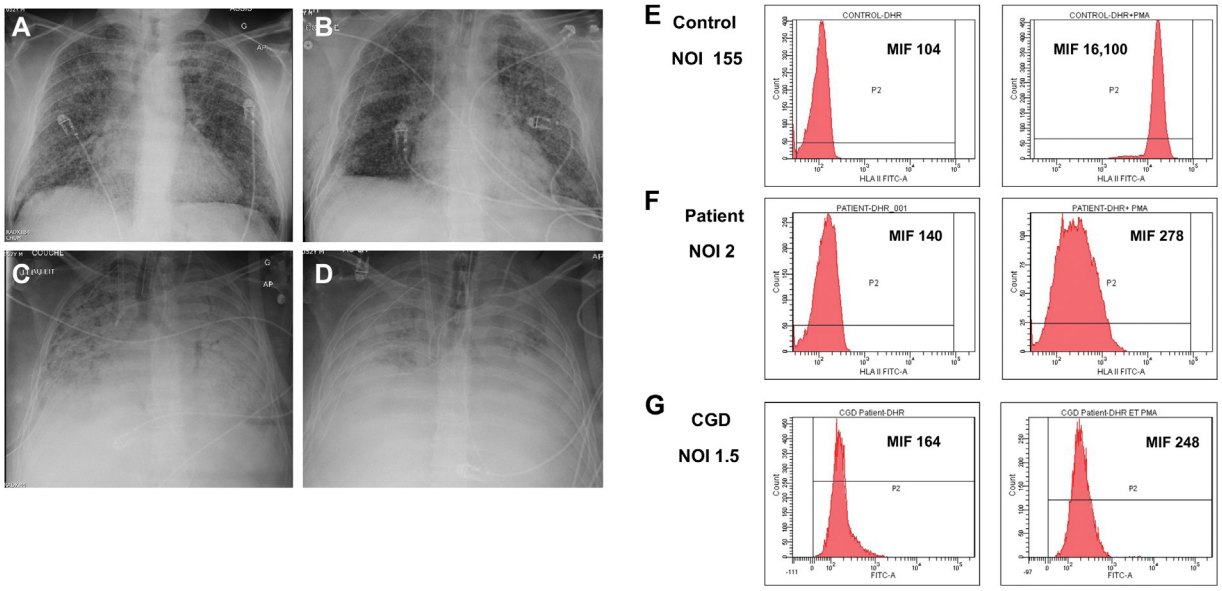

FIG 1. Chest radiograph at admission (**A**), day 3 (**B**), day 15 (**C**), and day 28 (**D**) of hospitalization. DHR 123 flow cytometry assay showing normal neutrophil oxidation index (NOI) (>70) from the control (**E**) and reduced NOI from neutrophils from the case patient (NOI 2) (**F**) and from a patient with X-linked CGD (**G**) tested in the same laboratory. *MIF,* Mean intensity fluorescence.

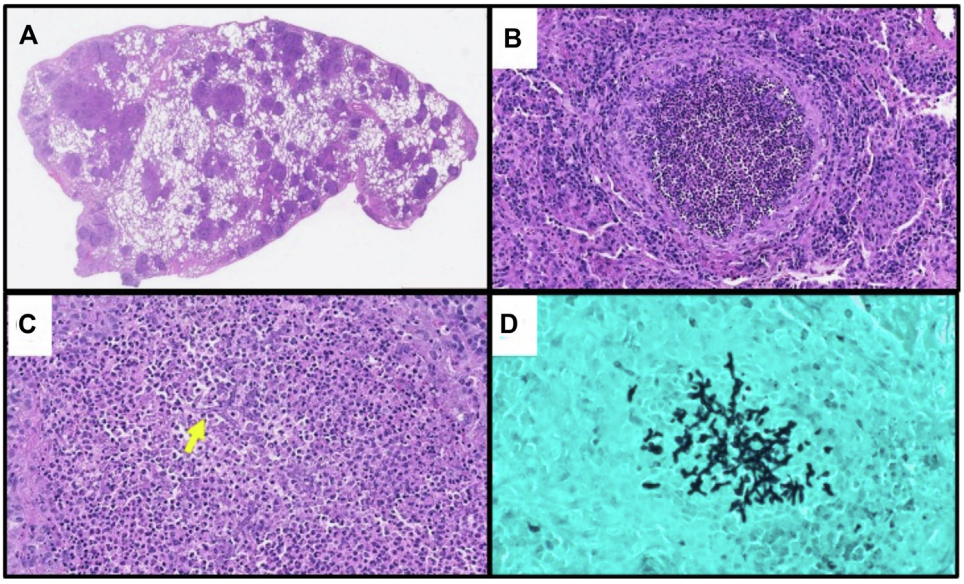

FIG 2. Hematoxylin and eosin (HE)-stained lung parenchyma showing multiple randomly distributed interstitial micronodules (**A**) consisting of suppurative granulomas (**B**) (dense central collections of neutrophils surrounded by a rim of epithelioid histiocytes) (HE staining; original magnification, ×100). Hyphal structures (**C,** *arrow*) can be seen on routine stain (HE staining; original magnification, ×200), with the silver stain confirmed to be acute angle branching septate hyphae consistent with *Aspergillus* spp (**D**) (Gömöri methenamine silver stain staining; original magnification, ×200).

Next-generation sequencing revealed a homozygous deletion in the $p47^{phox}$ subunit gene *NCF1* c.(7+1_73–1)_(1051+1_1052–1) del encompassing exons 2 to 10, thereby confirming the diagnosis of CGD. The deletion was classified as pathogenic according to the 2015 American College of Medical Genetics guidelines, and Sanger sequencing was performed to confirm that the deletion was located in *NCF1* and not in its pseudogenes. Although some large deletions of *NCF1* have been reported in databases (the Human Gene Mutation Database and the University of California Santa Cruz Genome Browser), these seem to extend into adjacent genes, and the few published cases reporting similar deletions do not describe the associated patient phenotypes.[3,4] Thus, our case appears to be the first report of a clinical presentation associated with an *NCF1* deletion including almost

the entire gene. Because the patient did not have any children and his parents were deceased, a family genetic investigation was performed only on his 2 healthy sisters. It revealed that both are heterozygous for the same mutation.

We have described the sudden and fatal presentation of CGD associated with a large *NCF1* deletion in a previously healthy man in the fifth decade of life. Although the average age of diagnosis for CGD is before 5 years, cases diagnosed in adults have been reported.[1,2] These later presentations may be due to several factors, including residual reactive oxygen species production in phagocytes, misdiagnosis, and a low level of suspicion on the part of health care providers. When the patient's DHR assay result (Fig 1, *F*) was compared with that of a patient with X-linked CGD analyzed in the same laboratory (Fig 1, *G*), the larger cytometry peak profile suggested the presence of a small residual NADPH oxidase activity, which may partly explain the very late manifestation of CGD in this patient. In the handful of cases of autosomal recessive CGD diagnosed in adulthood, the average age of presentation was in the second or third decade of life and patients often presented with evidence of chronic lung pathology (eg, bronchiectasis) due to clinical or subclinical recurrent infections.[1] In our 52-year-old patient, the diagnosis of CGD was made during his first serious infection, which was associated with an exuberant inflammatory response. Other rare cases of individuals being diagnosed with CGD later in life have been reported; they include a 69-year-old patient diagnosed with gp91^{phox}-deficient CGD[2] and a 44-year-old patient who had a homozygous *NCF1* mutation with granulomatous colitis that was falsely diagnosed at an early age as Crohn disease and who later presented with recurrent scrotal cellulitis.[5] Similar to our patient, the patients in these cases illustrate the importance of considering the diagnosis of CGD in patients of any age who present with a characteristic or very severe infection and/or recurrent infections, especially if there is also a history of inflammatory bowel disease. In other words, patients with recurrent and/or difficult-to-treat infections or atypical presentations of *de novo* infections must be investigated promptly to rule out primary immunodeficiency, regardless of age at presentation. Although diagnosing largely asymptomatic patients with pathogenic NOX2 subunit mutations is challenging, the diagnosis of CGD should be considered when a patient presents with a refractory infection associated with granulomatous inflammation.

Although the diagnosis of CGD was suspected and confirmed by genetic analysis in our patient, a broader differential diagnosis should nonetheless be considered by clinicians evaluating a fulminant pulmonary process. In addition to testing to rule out various infections (eg, repeated bacterial and fungal cultures, evaluation for blastomycosis, testing for HIV, performance of hepatitis and other viral serologic tests [to detect EBV, cytomegalovirus, and COVID-19]), rheumatologic (antinuclear antibody, myositis antibody, extractable nuclear antigen antibody, antineutrophil cytoplasmic antibody, anticyclic citrullinated peptide, and rheumatoid factor tests), paraneoplastic (blood LDH and uric acid tests), and pathologic (lung biopsy) assessments should be performed to rule out an underlying secondary immunodeficiency.

Early identification of an underlying inborn error of immunity is key to managing infection-associated inflammation and to beginning timely evaluations for possible allogeneic hematopoietic cell transplantation, which is often curative.[6] Moreover, macrophages from patients with CGD have defective autophagy and increased inflammasome activity, resulting in elevated systemic IL-1β levels. Given that certain infections exacerbate this hyperinflammatory response in the context of CGD, the addition of immunomodulators (eg, steroids, IL-1Ra) may be warranted depending on the clinical context.[7]

Our case demonstrates that in a previously asymptomatic individual, autosomal recessive CGD can present with pulmonary aspergillosis beyond the fourth decade of life. This susceptibility to invasive filamentous fungal infections, particularly *Aspergillus* spp, is unique to CGD, and it typically causes lung damage that is difficult to treat. One particular form of pulmonary aspergillosis that has been reported only in CGD, is referred to as "mulch pneumonitis" and is characterized by an abrupt-onset massive hypersensitivity reaction to aerosolized fungi, with a triad of fever, dyspnea, and diffuse pulmonary infiltrates as its clinical presentation.[8] Significant environmental exposure to soil and organic plant matter preceding the development of rapidly progressive diffuse lung disease, especially if associated with granulomatous inflammation, should prompt health care providers to consider DHR testing. Although nonspecific, the nodular radiologic presentation evoking a diffuse fungal infection is also an important finding that should lead clinicians to suspect an underlying immune deficiency and consider CGD in the differential diagnosis.[9] The severe and rapidly deteriorating clinical course in this seemingly healthy older individual underlines the importance of maintaining a high index of suspicion for inborn errors of immunity in adults of any age with refractory infections and/or atypical or fulminant presentations of infections with common or environmental pathogens. Consequently, rapid and comprehensive infectious, radiologic, pathologic, and immunologic investigations, including the DHR assay, must be undertaken under these circumstances.

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