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LETTER TO EDITOR

# Successful Lung Transplantation in a Patient with Chronic Granulomatous Disease

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## Introduction

Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder caused by defective NADPH oxidase and impaired production of superoxide that is necessary for effective intracellular killing of pathogens. Patients with CGD are prone to severe, recurrent bacterial and invasive fungal infections of the lungs, skin, GI tract, and liver. Pulmonary complications are common and include pneumonia, abscess, granulomatous disease, and chronic inflammation that can lead to fibrosis and bronchiectasis [1]. For those patients with CGD who develop end-stage lung disease, lung transplantation is a potential life-saving treatment, but necessitates life-long therapy with immunosuppressive medications. We present the first case of a successful double-lung transplant in a CGD patient with severe bronchiectasis and end-stage lung disease.

This case report was previously presented as an abstract [2].

## Case Description

The patient is a 32-year-old male from Trinidad with CGD who presented to our clinic for pre-lung transplant evaluation. Beginning at 19 months old, he experienced frequent respiratory infections requiring prolonged hospitalizations and antibiotic therapy. Prior infectious pathogens included *Methicillin-resistant Staphylococcus*, *Pseudomonas*, *Klebsiella*, *Serratia*, *Acinetobacter*, *Proteus*, *Moraxella*, *Empedobacter*, *Achromobacter*, and *Stenotrophomonas*, as well as *Mycobacterium tuberculosis* for which he was treated in his teens. Other non-pulmonary infections in his youth included skin pustules, soft tissue abscesses, mouth ulcers, and cervical lymphadenitis. He did not have sinus disease.

At age 26 years, he developed respiratory failure from pneumonia requiring mechanical ventilation for 40 days. He was started on chronic systemic steroid therapy and supplemental oxygen. At age 28, he was diagnosed with CGD by nitroblue tetrazolium testing. The subsequent dihydrorhodamine (DHR) 123 oxidation test showed complete absence of neutrophil oxidative burst after stimulation with phorbol 12-myristate 13-acetate. He began prophylaxis with trimethoprim-sulfamethoxazole and itraconazole and his overall frequency of pneumonias decreased. However, at age 31, he developed New York Heart Association Class III symptoms with significant dyspnea and occasional exertional presyncopal episodes followed by acute on chronic respiratory failure requiring a tracheostomy. He subsequently moved to the USA for lung transplant evaluation. Hematopoietic stem cell transplant (HSCT) was deferred due to the patient's limited financial resources.

Pre-transplant evaluation included spirometry showing severely depressed lung function with forced expiratory volume in 1 s ($FEV_1$) of 16% predicted and forced vital capacity (FVC) of 30% predicted. Chest computed-tomography (CT) revealed advanced, diffuse bronchiectasis with air trapping (Fig. 1a). His CGD diagnosis was confirmed in our center by genetic testing that demonstrated two mutations in exon 2 of the NCF1 gene: a novel missense mutation (p. His51Pro or c.152A>C) and a common GT deletion.

Over the next 2 years, the patient continued to require hospital admissions twice yearly for respiratory failure while awaiting transplant. At age 34, while dependent on

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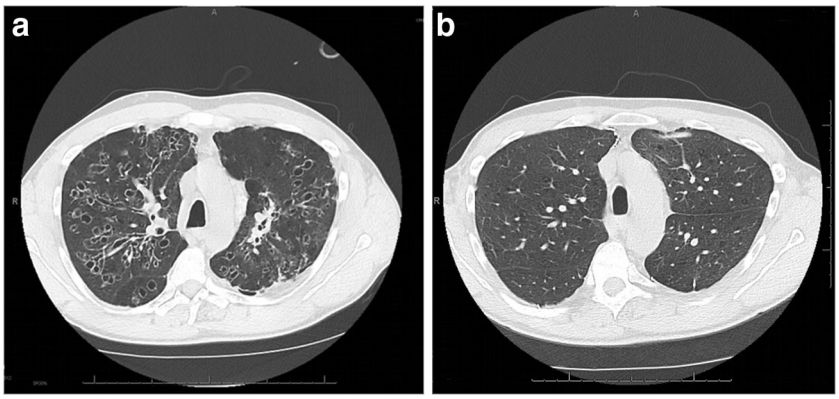


**Fig. 1** **a** Advanced bronchiectasis and calcified lymph nodes on CT chest prior to lung transplant. **b** Resolution of bronchiectasis. Emphysema from the donor lung present on CT chest after lung transplant

mechanical ventilatory support via tracheostomy, he underwent successful double-lung transplant on Veno-arterial ECMO with alemtuzumab induction. The donor was a middle-aged man with a 20-year tobacco history. Native lung pathology revealed bronchiectasis with pleural and parenchymal scar and necrotizing, culture-negative hilar lymph nodes (Fig. 2a, b). His initial post-transplant course was complicated by dense adhesions and oversized lungs that were corrected by lung graft volume reduction surgery. His long-term immunosuppression regimen consisted of azathioprine (75 mg daily or 1.5 mg/kg), tacrolimus (the therapeutic range of 12–15 ng/ml in the first year post-transplant, 8–12 ng/ml in the second year post-transplant, and 6–10 ng/ml after 2 years post-transplant), and hydrocortisone (20 mg in the morning and 10 mg in the evening). Additionally, he was placed on antibiotic prophylaxis with trimethoprim-sulfamethoxazole, voriconazole, valganciclovir (during the first 6 months post-transplant), and inhaled colistin due to pre-transplant bronchial colonization with *Acinetobacter* and *Stenotrophomonas*. In the first year post-transplant, he experienced one episode of *Aspergillus lentulus* pneumonia that was resistant to amphotericin, itraconazole, and voriconazole. He was treated successfully with posaconazole and caspofungin and subsequently maintained on posazonazole prophylaxis. Remarkably, in the subsequent 3.5 years, he has had no hospitalizations and experienced no further severe pulmonary infections. At 5 years after transplant, he has no respiratory limitations as he volunteers while applying to graduate school. He has no evidence of chronic lung allograft dysfunction thus far.

## Discussion

CGD is a rare primary immunodeficiency often presenting within the first 2 years of life with severe recurrent infections. Early diagnosis, antimicrobial prophylaxis, aggressive treatment of infections, and HSCT have led to substantial improvements in morbidity and mortality, with most patients now surviving to adulthood. Despite improved survival, recurrent pulmonary infections and poorly understood inflammatory processes can lead to chronic pulmonary changes including restrictive fibrotic lung disease and less frequently bronchiectasis [3]. In some patients, these chronic changes result in end-stage lung disease.

We present the first reported case of a successful double-lung transplant in a CGD patient with severe bronchiectasis. Our patient had autosomal recessive CGD with a defect in $p47^{phox}$ subunit of NADPH oxidase which has been associated with a better prognosis compared with X-linked CGD [1]. However, he was diagnosed with CGD at a relatively late age (28 years) due to misdiagnosis in childhood. At diagnosis, he

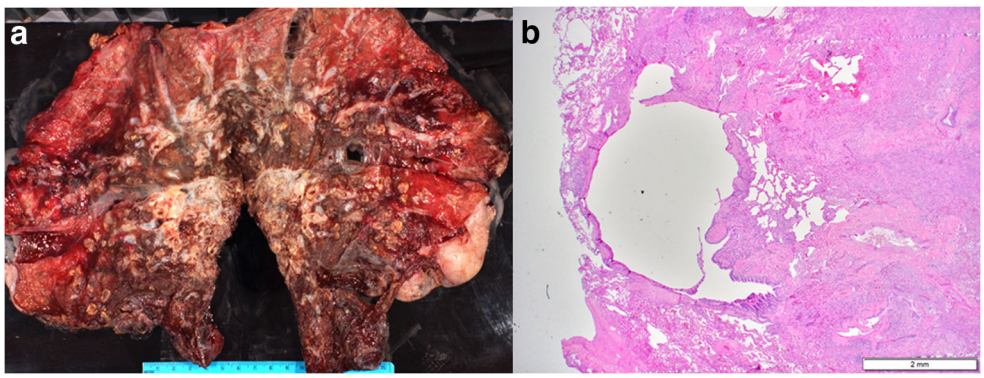


**Fig. 2** **a** Explanted lung with bronchiectasis. **b** Bronchiectasis with scarring

had already developed severe bronchiectasis and had complete absence of reactive oxygen intermediate activity with DHR testing which has been associated with more severe disease [4]. Despite the introduction of prophylactic antimicrobial therapy, his lung disease continued to progress, leading to chronic respiratory failure. The etiology of his severe bronchiectasis could be explained by previous tuberculosis infection as well as frequent infections with other catalase-positive organisms. While his bronchiectasis was diffuse and non-cystic, post-tuberculosis bronchiectasis tends to be more upper lobe predominant and less bilateral [5].

The only successful solid organ transplantations in patients with CGD have been liver and kidney [6–8]. To our knowledge, lung transplant has not been previously performed. In the general population, the overall median survival rate for kidney and liver transplant recipients has been significantly greater (9.2 years and 11.6 years respectively) compared with lung transplant recipients (5.7 years) [9–11]. Importantly, infections are common complications of lung transplant, accounting for 37.4% of all known causes of death in the first year post-lung transplantation [6]. In our case, the patient had only one serious fungal infection with *Aspergillus lentulus* in the first year post-transplant which was successfully treated. While most lung transplant recipients receive prophylaxis with an azole antifungal antibiotic during the first 3–6 months post-transplant, in our center, lung transplant patients with an underlying primary immunodeficiency receive life-long prophylaxis with azole antibiotics. Moreover, his overall infection frequency significantly decreased post-transplant which can be explained by the reversal of bronchiectasis and early antibiotic prophylaxis (Fig. 1b). Our patient has not experienced other post-transplant complications such as acute rejection or chronic lung allograft dysfunction. His lung function has been stable and he has been fully functional. Although HSCT is not considered at this time, this may change in the future.

We present the first successful case of double-lung transplant in CGD with end-stage lung disease secondary to advanced bronchiectasis. While HSCT is a potentially curative option, it does not improve severe bronchiectasis [12]. Therefore, lung transplantation should be considered in patients with CGD and chronic respiratory failure from bronchiectasis and combined lung/HSCT transplantation may be an option for some patients. Additional larger studies are needed to further explore the benefits of lung transplantation with or without HSCT in CGD.

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## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

## References

1. Arnold DE, Heimall JR. A review of chronic granulomatous disease. Adv Ther. 2017;34(12):2543–57. https://doi.org/10.1007/s12325-017-0636-2.
2. Israelsen RB, Fajt ML, Crespo MM, Petrov AA. Successful lung transplant for bronchiectasis in an adult male with autosomal recessive chronic granulomatous disease with a novel NF1 gene mutation. J Allergy Clin Immunol. 2016;137(2):AB222.
3. Godoy MCB, Vos PM, Cooperberg PL, Lydell CP, Phillips P, Müller NL. Chest radiographic and CT manifestations of chronic granulomatous disease in adults. AJR Am J Roentgenol. 2008;191(5):1570–5. https://doi.org/10.2214/AJR.07.3482.
4. Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. N Engl J Med. 2010;363(27):2600–10. https://doi.org/10.1056/NEJMoa1007097.
5. Wang H, Ji XB, Li CW, Lu HW, Mao B, Liang S, et al. Validation of bronchiectasis severity score systems for post-tuberculosis bronchiectasis. Clin Respir J. 2018;12:2346–53. https://doi.org/10.1111/crj.12911.
6. Caliskan B, Yazici H, Gulluoglu M, Caliskan Y, Turkmen A, Sever MS. Renal transplantation in a patient with chronic granulomatous disease: case report. Transplant Proc. 2015;47(1):158–60. https://doi.org/10.1016/j.transproceed.2014.07.069.
7. Bolanowski A, Mannon RB, Holland SM, Malech HL, Aschan J, Palmblad J, et al. Successful renal transplantation in patients with chronic granulomatous disease. Am J Transplant. 2006;6(3):636–9. https://doi.org/10.1111/j.1600-6143.2006.01232.x.
8. Cale CM, Jones AM, Goldblatt D. Follow up of patients with chronic granulomatous disease diagnosed since 1990. Clin Exp Immunol. 2000;120(2):351–5.
9. Seaberg EC, Belle SH, Beringer KC, Schivins JL, Detre KM. Liver transplantation in the United States from 1987-1998: updated results from the Pitt-UNOS Liver Transplant Registry. Clin Transpl. 1998:17–37.
10. Hariharan S. Long-term kidney transplant survival. Am J Kidney Dis. 2001;38(6 Suppl 6):S44–50. https://doi.org/10.1053/ajkd.2001.28925.
11. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, et al. The registry of the International Society for Heart and Lung Transplantation: thirty-second official adult lung and heart-lung transplantation report–2015; focus theme: early graft failure. J Heart Lung Transplant. 2015;34(10):1264–77. https://doi.org/10.1016/j.healun.2015.08.014.
12. Seger RA, Gungor T, Belohradsky BH, Blanche S, Bordigoni P, di Bartolomeo P, et al. Treatment of chronic granulomatous disease with myeloablative conditioning and an unmodified hemopoietic allograft: a survey of the European experience, 1985-2000. Blood. 2002;100(13):4344–50. https://doi.org/10.1182/blood-2002-02-0583.