



GLOBAL JOURNAL OF MEDICAL RESEARCH: F
DISEASES

Volume 24 Issue 2 Version 1.0 Year 2024

Type: Double Blind Peer Reviewed International Research Journal

Publisher: Global Journals

Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Pulmonary Zygomycosis in a Patient with X-CGD

By Claudia Plech Garcia Barbosa, Matheus Cana Brasil Xavier da Silva, Rafael Burlacchini de Carvalho Magalhães, Victor Farias Coelho, Thainá Catão Lopes & João Carlos Coelho Filho

Abstract- Objective: To report a case of an X-CGD diagnosed patient presenting atypical zygomycosis. The X-CGD is a genetic disorder, autosomal recessive linked to the X, characterized by recurrent infections and granulomas formation.

Description: Male patient, five years, admitted at the hospital experiencing fever and shortness of breath for two months. The patient was hospitalized and given Ceftriaxone and discharged after improved clinical condition, but continued showing dyspnea and fever. The persistent clinical state demanded lung biopsy which revealed mucorales fungi.

Comment: This study has shown the importance of the correlation among infectious diseases from distinct pathogens in one individual.

Keywords: chronic granulomatous disease; cgd; immunodeficiency; primary immunodeficiency; zygomycosis; fungal pneumonia.

GJMR-F Classification: LCC: RC280.S5, RC280.L8



Strictly as per the compliance and regulations of:



RESEARCH | DIVERSITY | ETHICS

© 2024. Claudia Plech Garcia Barbosa, Matheus Cana Brasil Xavier da Silva, Rafael Burlacchini de Carvalho Magalhães, Victor Farias Coelho, Thainá Catão Lopes & João Carlos Coelho Filho. This research/review article is distributed under the terms of the Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0). You must give appropriate credit to authors and reference this article if parts of the article are reproduced in any manner. Applicable licensing terms are at <https://creativecommons.org/licenses/by-nc-nd/4.0/>.

Pulmonary Zygomycosis in a Patient with X-CGD

Claudia Plech Garcia Barbosa ^α, Matheus Cana Brasil Xavier da Silva ^σ,
Rafael Burlacchini de Carvalho Magalhães ^ρ, Victor Farias Coelho ^ω, Thainá Catão Lopes ^χ
& João Carlos Coelho Filho ^ξ

Abstract- Objective: To report a case of an X-CGD diagnosed patient presenting atypical zygomycosis. The X-CGD is a genetic disorder, autosomal recessive linked to the X, characterized by recurrent infections and granulomas formation.

Description: Male patient, five years, admitted at the hospital experiencing fever and shortness of breath for two months. The patient was hospitalized and given Ceftriaxone and discharged after improved clinical condition, but continued showing dyspnea and fever. The persistent clinical state demanded lung biopsy which revealed mucorales fungi.

Comment: This study has shown the importance of the correlation among infectious diseases from distinct pathogens in one individual.

Keywords: chronic granulomatous disease; cgd; immunodeficiency; primary immunodeficiency; zygomycosis; fungal pneumonia.

I. INTRODUCTION

The pulmonary zygomycosis is an unusual fungi infection which occurs mostly in immunodepressive patients¹¹. In the CGD, the lung infection from fungi etiology is the one with higher prevalence, with the *Aspergillus* fungus as the more prominent reason².

Our report describes a patient with CGD plus pulmonary zygomycosis.

II. CASE REPORT

Male patient, five years, coming from Alagoinhas-BA, admitted at the hospital Martagão Gesteira (HMG) in Salvador-BA, diagnosed with pneumonia for five months and not responding to large spectrum antibiotic therapy. The patient developed fever and dyspnea five months back; he had received previous medical treatment in his hometown with the following antibiotics in sequence: Ceftriaxone and Oxacillin, Azithromycin, Tazocin, Sulfamethoxazole (plus Trimethoprim, Vancomycin, Meropenem and Fluconazole). The recurrent fever and tachypnea persisted, only the respiratory discomfort showed improvement.

The genitor denied knowledge on the disease although reported previous recurrent pneumonia since the patient was two-years old and abscesses episodes (1 scalp abscesses when newborn; 1 perianal and 1

cervical) that in turn led to many hospitalizations and previous use of antibiotics. Two maternal cousins were reported deceased in the family.

Regarding physical examination, low stature (Z-2 Height) and very thin (BMI Z-2), presenting tachypnea (40 BPM), SaO₂ at 92% in room air, widely distributed murmur with crackles, mild intercostal retractions.

Examinations results held at reference hospital:

Author : e-mail: victorfariascoelho@gmail.com

Computerized tomography (CT) of the chest (FIGURE 1)

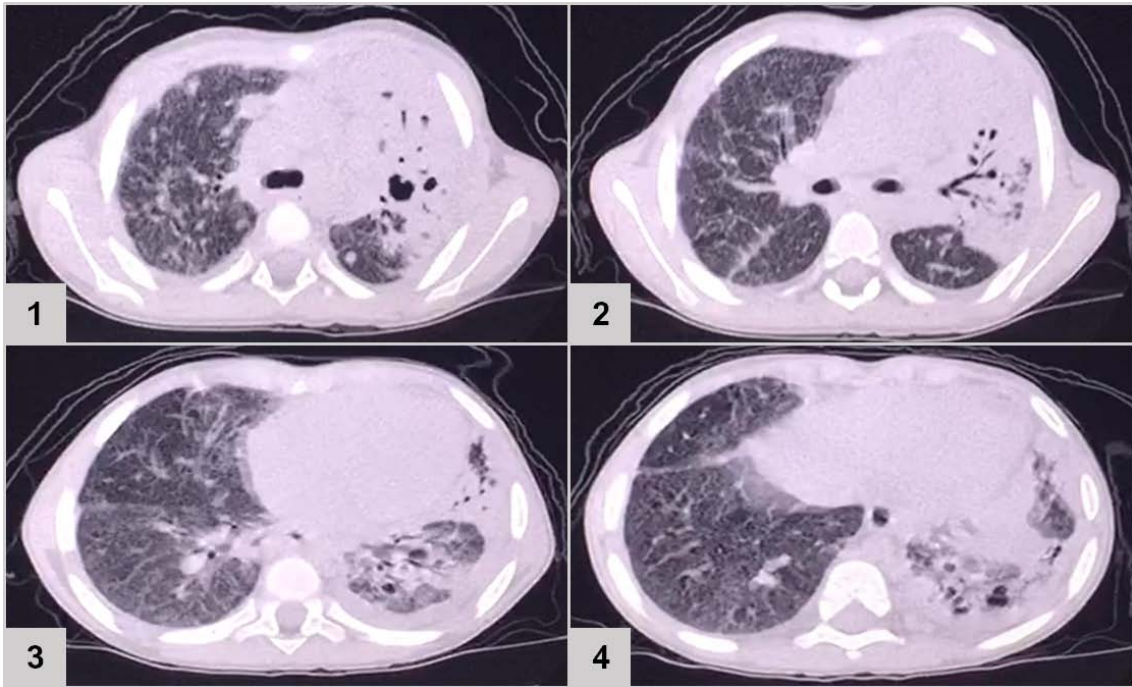


Figure 1: CT of the chest results: extensive consolidation, with air bronchograms and cystic images in between, in the left lung (3 and 4); ground-glass opacities, diffusion in the lower left lobe (1 and 2); nodular opacity, no sign of calcification in between, on both lungs (1, 2 and 3); reticular and linear opacity and parenchymal bands in the upper lobes (3 and 4); small pleural effusion on the left (1 and 2); adjacent subsegmental atelectasis (2 and 4)

Hemogram: hemoglobin: 10g/l; White blood cell count: 9400/mm³; lymphocytes: 1692/mm³; neutrophils: 7144/mm³; eosinophil:188/mm³; platelets: 425.000/mm³. Negative blood culture. PPD no reaction. Normal range for Alpha-1 antitrypsin. Negative HIV. Normal sweat chloride values.

Primary immune evaluation (dose of complement, serum immunoglobulin and immune-phenotyping) all set in normal values for the patient's age.

Lungbiopsy (FIGURE 2)

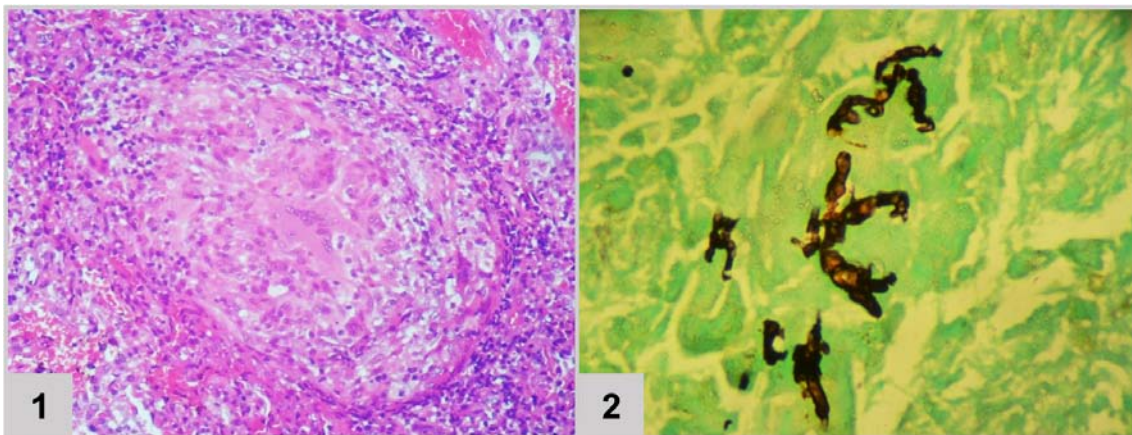


Figure 2: Lung biopsy (200x magnification). (1) Pulmonary tissue in hematoxylin and eosin showing granulomatous reaction with epithelioid histiocytes and multinucleated giant cells. (2) Pulmonary tissue in Grocott's stain revealing fragments of broad, wavy and short hyphae, matching Zygomyces by mucorales, longitudinal and cross-sectioned

With the fungal lung infection diagnosis (zygomycosis), without previously response to Fluconazole, Amphotericin B was administered. The fever disappeared and there was no need for supplemental oxygen, the patient was discharged from the hospital with mild tachypnea.

With the medical record of pneumonia and recurrent abscesses, as well as fungal pneumonia, Bactrim and Itraconazole were prescribed as a prophylactic measure and a dihydrorhodamine test (DHR) was ordered to evaluate the oxidase burst of phagocytes.

DHR test has revealed no sign of oxidation after stimulation with phorbol myristate acetate, PMA (from

59,2 to 48,1) has shown in comparison with the threshold an increase (from 34,7 to 91,6) which in turn confirmed the Chronic Granulomatous Disease (CGD) diagnosis. The antibiotic and antifungal prophylaxis has demonstrated good evolution and weight-stature gain (reverting FTT), the patient is listed for transplant.

III. DISCUSSION

The CGD is an innate immunity disorder that is inherited, mostly characterized as an X-linked recessive mode, marked by the presence of two early childhood deaths of first-degree male cousins in the patient's family history (FIGURE 3).

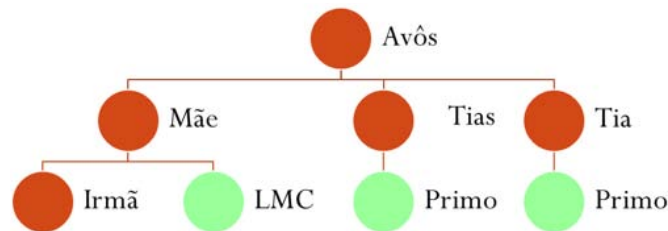


Figure 3: Patient Family history showing two childhood deaths of first-degree male cousins

This transmission pattern has been present in approximately 67%¹ of cases, more prominent and susceptible in male sex, linked to mutations in the CYBB gene, located on locus Xp21.1¹, which cause a functional deficit of gp91-phox, an enzyme complex component NADPH oxidase of phagocytes. This protein complex is responsible for producing oxygen metabolism intermediates in phagocytes, including oxidants with antifungal and antibacterial action.

Phagocytes, neutrophils, monocytes, macrophages and dendritic cells are cells capable of binding to pathogens and providing phagocytosis of these, through trapping within a phagosome. Several mechanisms, such as the release of lysozymes, acid hydrolases and toxic oxidants, are used by these cells of the immune system to destroy the pathogen. To carry out the production and release of oxidative compounds, phagocytic cells are able to assemble NAPH-oxidase complexes in the phagolysosome membrane, which are responsible for catalyzing the production of these compounds¹³. The protein complex provides the generation of O²⁻, which is unstable and has a weak bactericidal action, through the transfer of electrons from intracellular NADPH molecules to molecular oxygen. The generated O²⁻ will later undergo dismutation reactions, catalyzed by the enzyme superoxide dismutase (SOD), which will convert it into hydrogen peroxide (H₂O₂). Finally, the enzyme myeloperoxidase (MPO) present in primary granules (mainly from neutrophils) is released into the phagosome and converts H₂O₂ into oxidants with great bactericidal power, reactive oxygen species (ROS), such as hypochlorous acid and radicals free (such as OH⁻

and O⁻)¹⁴. After activation and assembly of the complex, the phagocytic cell enters a transient stage of oxidative explosion, where there is a significant increase in oxygen consumption¹³.

Thus, CGD patients possess dysfunctional neutrophils and incapable oxidative burst, which in turn disable catalase-positive and intracellular microorganisms' elimination¹¹. There is also granuloma formation, mostly sterile, a characteristic that may be directly connected to the hyperinflammatory state common in CGD patients¹⁰. Granuloma is a means of containing the proliferation of the microorganism that is difficult to eliminate and isolating it from the rest of the organism¹⁰.

Morphologically, granulomas in patients with CGD, in general, have the following histopathological organization:

- Neutrophils located predominantly in the central portion, with extremely reduced activity and some even in the apoptotic phase.
- Lymphocytes located both in the central and peripheral portions, being highly induced to apoptosis.
- Macrophages located essentially in the peripheral portion, usually with high expression of TNF-alpha cytokines, which recruit and induce the action of inflammatory cells, IL-10, which inhibits the function of neutrophils and induces cell healing and the IDO enzyme (Indoleamine 2, 3-dioxygenase), which converts L-tryptophan, an important bacterial substrate, into L-kynurenine, a protective inflammatory agent that induces apoptosis in lymphocytes.

- Epithelioid cells located in the central portion of the granuloma are modified, squamous and almost dysfunctional macrophages, due to their intense activity in the attempt to remove the infectious agent that is difficult to eliminate. Multinucleated giant cells, formed from the fusion of epithelioid cells, can also be observed.

Those are patients with a phenotype of life-threatening early life infections¹, where diagnosis usually occurs between 2 and 3 years, and more aggressive. Our patient had shown abscesses and pneumonia since his first months of life, weight-stature gain compromise. As the individual with CGD has dysfunctional phagocytes, catalase-positive microorganisms become difficult to eliminate by the immune system, so that the patient diagnosed with CGD has a tendency of developing several infections through life; pneumonia is the most infectious and prominent, followed by lymphadenitis, suppuration, infectious dermatitis and abscesses formation in the skin, lungs, brain and liver, as well as osteomyelitis, meningitis and sepsis. There has also been manifestation related to the obstruction of gastrointestinal and urinary tract due to granuloma formation².

On the one hand, the most common gram-positive bacteria are *Staphylococcus aureus* and *Nocardia* spp. On the other hand, gram-negatives which stand out are *Serratia marcescens*, *Burkholderia cepacia* e *Klebsiella pneumoniae*^{1,2}.

The most frequent fungus in CGD is the *Aspergillus* spp., constantly associated with pneumonias (generally the most prevalent agent), osteomyelitis, suppurative lymphadenitis, and also lung and brain abscesses².

Our patient had persistent pulmonary infection by fungi of the Mucorales order (Zygomycosis), a rare fungal type whose pathogenicity consists of the invasion of blood vessels of infected tissues, resulting in infarction and tissue necrosis¹².

The patient's chest CT scan for the evaluation of pulmonary zygomycosis showed suggestive findings of fungal balls in both lungs, visualized as non-calcified nodular opacities and pleural effusion on the left, which is an infrequent radiological sign⁶, but of great importance for diagnosis, because the mutual presence of multiple fungal balls with pleural effusion are independent predictors of pulmonary zygomycosis⁵.

The identification of the etiologic agent was possible through microscopy (FIGURE 2) that showed granulomatous tissue, and, through Grocott staining, fragments of hyphae compatible with Mucorales fungi. Histopathological examination represents the most reliable method for diagnosing pulmonary zygomycosis⁶. Direct histomorphological visualization allows differentiation between Zygomycetes (short, tortuous broad hyphae of variable caliber with random

branching at right angles) and *Aspergillus* fungi, and is extremely important because, clinically, lung infections caused by these fungi are indistinguishable⁷.

In this case report, the patient's clinical improvement was achieved after taking Amphotericin B, the drug of choice for zygomycosis therapy⁴. This drug is available from the Ministry of Health in two formulations: Amphotericin B deoxycholate (lower cost and higher toxicity) and Liposomal Amphotericin B (higher cost and lower toxicity), both with high efficacy. The starting dose tends to be 5 mg/Kg/day, usually increasing to 10 mg/Kg/day, much higher than the usual dose (1.5 mg/Kg/day), and therapy should be continued until there is complete resolution of clinical and radiological signs of infection¹². To avoid the toxic effects of Amphotericin B, especially on the kidneys, bone marrow, and cardiovascular system, the use of the later less toxic liposomal form is indicated³.

Posaconazole is an important therapeutic alternative, since it also has activity against zygomycosis. Itraconazole has low effectiveness, while other azole antifungals, such as fluconazole and voriconazole, as well as flucitocin and echinocandin, are ineffective against mucorales fungi⁴.

The diagnosis of CGD should be suspected in patients with a family history of first-degree relatives with early death, clinical history of severe infections (pneumonias, abscesses, osteomyelitis, lymphadenitis) and recurrent, early onset infections by catalase-positive germs, and it can be confirmed by biochemical tests which evaluate the oxidative function of phagocytes. In this report, measurement of superoxide anion production using the dihydrorhodamine (DHR) method demonstrated that after stimulation with PMA there was no oxidative burst (increased production of superoxide) in the phagocytes⁸.

Prophylactic treatment is indicated for CGD patients to prevent fungal and *Staphylococcus* infections in addition to removing sources of pathogens. The recommended prophylaxis for these patients is a daily oral regimen of Sulfamethoxazole + Trimethoprim and Intraconazole, but since the latter drug has low activity against mucorales fungi, a substitution with Posaconazole may be considered. The patient should continue to receive routine vaccinations, except those containing live bacteria¹.

If a patient has pneumonia that is unresponsive to broad spectrum antibiotics, an investigation for fungal pneumonia should be extended to indicate specific treatment, and immunologic investigation in the care of a specialist for innate immune error should be initiated. Early diagnosis allows treatment of the infection as well as prophylactic management to decrease morbidity and mortality and discuss bone marrow transplantation, improving chances of survival and quality of life.

ACKNOWLEDGEMENTS

This case report was supported by the Liga Acadêmica de Imunologia da Bahia (Academic League of Immunology in Bahia), linked to Universidade Salvador (Salvador University).

Conflict of Interest

The authors declare that this report was produced without any commercial or funding relationship that could build a potential conflict of interest.

Financial Support

The authors declare that they did not obtain any payment, investment, or any financial support for the construction of this report.

REFERENCES RÉFÉRENCES REFERENCIAS

- Leiding JW, Holland SM. Chronic Granulomatous Disease [Internet]. Pub Med. 2012 [cited 2021 Dec 15]. Available from: <https://pubmed.ncbi.nlm.nih.gov/22876374/>.
- Winkelstein JA, Marino MC, Johnston RB, Boyle J, Curnutte J, Gallin JI, et al. Chronic Granulomatous Disease: Report on a National Registry of 368 Patients. *Medicine* [Internet]. 2000 May [cited 2021 Dec 15]; 79 (3):155–69. Available from: <https://pubmed.ncbi.nlm.nih.gov/10844935/>.
- Filippin FB, Souza LC. Eficiência terapêutica das formulações lipídicas de anfotericina B. *Revista Brasileira de Ciências Farmacêuticas* [Internet]. 2006 Jun; 42 (2):167–94. Available from: <https://www.scielo.br/pdf/rbcf/v42n2/a03v42n2.pdf>
- Rogers TR. Treatment of zygomycosis: current and new options. *Journal of Antimicrobial Chemotherapy* [Internet]. 2008 Jan 1 [cited 2021 Dec 15]; 61(Supplement 1): i35–40. Available from: https://academic.oup.com/jac/article/61/suppl_1/i35/738783.
- Methee Chayakulkeeree, Ghannoum MA, Perfect JR. Zygomycosis: The re-emerging fungal infection [Internet]. Research Gate. Springer Verlag; 2006 [cited 2021 Dec 15]. Available from: https://www.researchgate.net/publication/7211593_Zygomycosis_The_re-emerging_fungal_infection
- Lee FYW, Mossad SB, Adal KA. Pulmonary Mucormycosis. *Archives of Internal Medicine* [Internet]. 1999 Jun 28 [cited 2021 Dec 15]; 159 (12):1301. Available from: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/485069>.
- Severo CB, Guazzelli LS, Severo LC. Capítulo 7 - Zigomicose. *Jornal Brasileiro de Pneumologia* [Internet]. 2010 Feb [cited 2021 Dec 15]; 36(1): 134–41. Available from: <https://www.scielo.br/j/jbpneu/a/sdjsjwztzq4QYXx5vzhcq8Xy/>.
- Fontequê JH, Saito ME, Rizelo PA, Teixeira WT, Kohayagawa A. Comparação entre duas metodologias para a realização do teste de redução do tetrazólionitrozol (NBT) em caprinos. *Pesquisa Veterinária Brasileira* [Internet]. 2015 Dec [cited 2021 Dec 15]; 35 (suppl 1): 1–4. Available from: <https://www.scielo.br/j/pvb/a/ktYB9BZ67JnDj53t5QzRnSf/?lang=pt>.
- Kontoyiannis DP, Lewis RE. Agents of Mucormycosis and Entomophthoromycosis. *Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases* [Internet]. 2015 [cited 2021 Dec 15]; 69 (7-15): 2909-2919.e3. Available from: <https://www.sciencedirect.com/topics/immunology-and-microbiology/mucorales>.
- Kuijpers T, Lutter R. Inflammation and repeated infections in CGD: two sides of a coin. *Cellular and Molecular Life Sciences* [Internet]. 2011 Nov 15 [cited 2021 Dec 15]; 69 (1): 7–15. Available from: <https://link.springer.com/article/10.1007/s00018-011-0834-z>.
- Rider NL, Jameson MB, Creech CB. Chronic Granulomatous Disease: Epidemiology, Pathophysiology, and Genetic Basis of Disease. *Journal of the Pediatric Infectious Diseases Society* [Internet]. 2018 May [cited 2021 Dec 15]; 7 (suppl_1): S2–5. Available from: https://academic.oup.com/jpids/article/7/suppl_1/S2/4994080?login=true.
- Cox GM. Mucormycosis (zygomycosis) [Internet]. Kauffman CA, Hall KK, editors. Up To Date. 2021 [cited 2021 Dec 15]. Available from: <https://www.uptodate.com/contents/mucormycosis-zygomycosis?csi=4bd5f8bc-a307-4fea-bb5d-f42681dc0ff7&source=contentShare>.
- Biologia molecular da célula / Bruce Alberts ... [et al.]; tradução: [Ardala Elisa Breda Andrade ... et al.]; revisão técnica: Ardala Elisa Breda Andrade, Cristiano Valim Bizarro, Gaby Renard. – 6. ed. – Porto Alegre: Artmed, 2017.
- Meischl, C., Roos, D. The molecular basis of chronic granulomatous disease. *Springer Semin Immunopathol* 19, 417–434 (1998). Available from: The molecular basis of chronic granulomatous disease | SpringerLink.