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CASE REPORT

Chronic Granulomatous Disease: a Case Report

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Abstract

Chronic granulomatous disease is a rare disorder characterized by genetic mutations that causes defects in the NADPH oxidase of phagocytes, resulting mainly in higher predisposition to fungal and bacterial infections that threatens life. Our objective, with this study, is to report a case of chronic granulomatous disease diagnosed in a patient followed in a pediatric institute in Rio de Janeiro. A male teenage, presented while an infant with many recurrent, difficult to solve cutaneous infections. The patient evolved, as years passed by, with *Mycobacterium tuberculosis* hepatic abscess and severe fungal pneumonia, before confirming the CGD diagnosis. Currently, the patient is using the indicated prophylactic drugs and his clinical condition is controlled. Early diagnosis aiming to start suitable antimicrobial and antifungal prophylaxis is fundamental to achieve better disease control and mainly to improve patients' prognosis and quality of life.

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INTRODUCTION

Chronic Granulomatous Disease (CGD) is a heterogeneous genetic disease that affects about 1:200,000 people living in the US, caused by defects in NADPH oxidase in phagocytes (phox)[1,2]. These defects result in the inability of phagocytes to destroy certain pathogens, leading to recurrent, often fatal, fungal and bacterial infections and the formation of systemic granulomas[3,4].

The most common sites of infection are the lungs, skin, lymph nodes and liver[5].

Its diagnosis consists of performing tests that measure the function of intracellular digestion of phagocytes, such as the dihydrorhodamine test (DHR) and is confirmed by genotyping studies[6].

Disease control is achieved with antifungal and antimicrobial prophylaxis, in addition to timely treatment of acute infections[3,5].

The description of the proposed case aims to elucidate this rare disease, demonstrate the severity of the infections that it can cause, as well as point out the importance of adequate control and follow-up of the patient, showing how the good management of the disease contributes to the improvement of the prognosis and quality of life.

CASE REPORT

A 14-year-old patient started follow-up at the immunology service at a pediatric institute in September 2017, due to recurrent infections.

During the period of early childhood, he presented several skin infections that were difficult to heal, with frequent use of antibiotics; at 10 years of age, a contact with a relative with tuberculosis, developed a liver abscess caused by *Mycobacterium tuberculosis* , diagnosed through liver biopsy. On this occasion, he received a six-month RIP regimen, with resolution of the condition; at the age of 12 years, he developed persistent fever refractory to common antibiotics, significant weight loss and respiratory symptoms. He received the initial diagnosis of community-acquired pneumonia complicated with pleural effusion, and after 10 days of intravenous amoxicillin- clavulanate , fever persisted and progressed to deterioration in his general condition. cervical adenomegaly and hepatosplenomegaly. Examinations revealed screening for TORCH, viral hepatitis and HIV negative, non-reactive PPD, sputum AFB (three samples) negative. Chest ultrasound compatible with pulmonary consolidation, without areas suggestive of necrosis. After 48 hours afebrile, he was discharged. One month after the fever returns, associated with pain in the right hemithorax, productive cough and new weight loss. Readmitted for diagnostic clarification and the hypothesis that the patient had immunodeficiency syndrome was raised. Computed tomography of the chest was performed, with a tree-in-bud image, ground-glass opacities, and a juxtacisural cystic image in the apicoposterior segment of the left upper lobe, suggestive of fungal pneumonia. Serologies for histoplasmosis , aspergillosis and paracoccidioidomycosis were negative. Treatment with itraconazole and amoxicillin- clavulanate was initiated , progressing with resolution of the condition.

At 13 years of age, the patient presented with hidradenitis suppurativa in the right armpit, with fever refractory to outpatient cephalexin. He needed a venous regimen with high-dose oxacillin for resolution.

Based on the patient's history, immunoglobulin dosage, lymphocyte profile and vaccine response were performed at the specialized service, with normal results and altered DHR, configuring the diagnosis of CGD. Prophylactic trimethoprim-sulfamethoxazole was started in conjunction with itraconazole. Currently, the patient remains under follow-up, using the prophylactic regimen, without having new infectious episodes or new hospitalizations.

COMMENTS

CGD was first identified and described in the 1950s in a 12-month-old child in Minnesota who presented with an exuberant clinical presentation, including chronic suppurative lymphadenitis, hepatosplenomegaly, pulmonary infiltrates, and dermatitis[7].

Although its incidence varies according to ethnicity, its estimate is 1 in 200,000 live births. The case patient is male, and studies show that men are more affected than women by a ratio of 2:1, due to the predominant model of genetic transmission (X-linked disease)[7].

The immune system is a complex system capable of recognizing a wide variety of external agents through different biological processes. The generation and release of reactive oxygen species (ROS) in the form of an oxidative burst represents the main mechanism by which phagocytic cells destroy pathogens. On the other hand, defects in oxidative balance are also implicated in the pathogenesis of inflammatory complications, which can affect the function of various organ systems. NADPH oxidase (NOX) plays a key role in the production of ROS, and defects in its different subunits lead to the development of CGD[9].

Activation of phagocyte NOX requires stimulation of neutrophils and involves the binding of essential membrane and cytoplasmic subunits ($p47^{phox}$, $p67^{phox}$, $p22^{phox}$, $p40^{phox}$, $gp91^{phox}$), playing a key role in killing microorganisms on phagocytes[8,9].

The disease is caused by genes that affect one X-linked chromosome or three autosomal recessive chromosomes[4]. X-linked CGD is caused by mutations in the CYBB gene, which encodes the $gp91^{phox}$ protein; the autosomal recessive form is due to mutations in the CYBA gene (encoding p22 phox protein), NCF1 (encoding p47 phox protein), NCF2 (encoding

p67 phox protein) or NCF4 (encoding p40phox protein)[3]. Approximately two-thirds of CGD cases in the US are caused by mutations in CYBB. Mutations in NCF1 are the second leading cause of CGD[5,10]. X-linked CGD is more common in areas with miscegenation, while the autosomal recessive form is more common in areas with a history of inbreeding[8].

Taking into account the patient in the case, we assume that he has an X-linked disease. Although we do not know the genetic origin of his relatives, we know that there is no history of consanguinity in his family, in addition to having been generated in a of the most mixed countries in the world.

Children with CGD have recurrent fungal and bacterial infections. Infections are caused by catalase-positive microorganisms , and the most common sites are the lungs, skin, lymph nodes, and liver. In North America and Europe, the most frequent pathogens are *Aspergillus* spp., *Staphylococcus aureus, Burkholderia cepacia , Serratia marcescens , Nocardia* spp. and *Salmonella.* In developing countries, Bacillus Calmette - Guerin (BCG) and *Mycobacterium tuberculosis* are important pathogens. There are a variety of bacteria that are virtually pathognomonic for the diagnosis of CGD (*Chromobacterium violaceum , Francisella philomiragia , Granulibacter bethesdensis)*[5,6]. It is observed that the patient in the case presented both bacterial and invasive fungal infections, affecting the main sites mentioned (lung, skin, liver). The pathogen *Mycobacterium tuberculosis ,* prevalent in Brazil, affected the patient, who was a contact with a case of tuberculosis without adequate treatment. This shows the importance of epidemiological data in conducting the clinical case.

CGD has the highest prevalence of invasive fungal infections of all primary immunodeficiencies, and *Aspergillus fumigatus* followed by *A. nidulans ,* the most common isolated pathogens. After *Aspergillus spp., Rhizopus spp.* and *Trichosporon spp.* are the fungi most commonly identified in patients with CGD[5,6].

Symptoms typically appear in the first two years of life, and the median age at diagnosis is 2.5-3 years of age[1]. In this case, his final diagnosis was made late, at the age of 14, despite the initial symptoms having started in early childhood.

At the cellular level, CGD can be diagnosed by measuring the ability of phagocytic leukocytes to form superoxide or hydrogen peroxide[1]. Well-known assays for measuring NOX activity are the Nitro-Blue cytochrome c reduction test Tetrazolium (NBT), both measure superoxide. The dihydrorodamine-1,2,3 (DHR) test is a well-known study that measures hydrogen peroxide in this context[2], It is currently considered the gold standard for the diagnosis of CGD[6].

Positive findings must be confirmed by an additional test, such as genotyping or immunoblotting[1,4].

The patient's diagnosis was confirmed by the DHR, but genotyping was not performed as an additional test, due to the difficulty of performing this test in our country. Its performance would be indicated, but not essential for diagnostic definition.

Management of CGD is based on indefinitely antifungal and antibiotic prophylaxis; early diagnosis of infections; aggressive management of infectious complications. Medications recommended for use as they have been proven to reduce the risk of serious infections are trimethoprim-sulfamethoxazole (SMX-TMP) (5mg/kg/day 12/12h) and itraconazole (5mg/kg/day 24/24h)[1]. The use of IFN gamma as prophylaxis is still controversial[2,5,10]. Currently, several studies indicate the benefit of using steroids in conjunction with antimicrobials to treat cases of exacerbated inflammation[5].

Hematopoietic stem cell transplantation (HSCT) is well described as potentially curative in CGD (>90%). Transplantation as an early treatment option has been gaining ground, with high success rates, being beneficial not only in preventing infectious and inflammatory complications, but also in reducing exposure to prophylactic medications[1,5,8,10]. It is the only curative therapy for CGD[8].

Gene therapy is an attractive alternative to HSCT, being an option for patients without compatible donors. As gene repair technology becomes more advanced, DNA editing using the short palindromic repeat/CRISPR (CRISPR/Cas9) could be used to repair defective genes in cases of X-linked CGD. This method of gene therapy has been shown to restore cellular NADPH oxidase *in vitro*[1,8].

Our patient has been using antimicrobial and antifungal prophylaxis since the diagnosis of CGD for about a year, and since then he has not had new episodes of infection, proving the effectiveness of the indicated medications. During this time, we were able to observe the improvement in the adolescent's quality of life during their outpatient consultations.

REFERENCES

1. Lent-Schochet D, Jialal I. Chronic granulomatous disease. Treasure Island (FL): StatPearls Publishing; 2020.
2. Roos D. Chronic granulomatous disease. Br Med Bull. 2016 Jun;118(1):50-63.
3. Chiriaco M, Salfa I, Di Matteo G, Rossi P, Finocchi A. Chronic granulomatous disease: clinical, molecular, and therapeutic aspects. Pediatr Allergy Immunol. 2016 Mai;27(3):242-53.
4. Boxer LA, Newburger PE. Distúrbios da função dos fagócitos. In: Kliegman RM, Stanton BF, Schor NF, Geme III JWS, Behrman RE, eds. Nelson, tratado de pediatria; tradução da 19ª edição. In: Rio de Janeiro: Elsevier; 2014. p. 745-6.
5. Arnold DE, Heimall JR. A review of chronic granulomatous disease. Adv Ther. 2017 Dez;34(12):2543-57.
6. Yu JE, Azar AE, Chong HJ, Jongco III AM, Prince BT. Considerations in the diagnosis of chronic granulomatous disease. J Pediatr Infect Dis Soc. 2018 Mai;7(Supl 1):6-11.
7. Rider NL, Jameson MB, Creech CB. Chronic granulomatous disease: epidemiology, pathophysiology, and genetic basis of disease. J Pediatr Infect Dis Soc. 2018 Mai;7(Supl 1):2-5.
8. Gennery A. Recent advances in understanding and treating chronic granulomatous disease. F1000Res. 2017 Ago;7:1427.

9. Giardino G, Cicalese MP, Delmonte O, Migliavacca M, Palterer B, Loffredo L, et al. NADPH oxidase deficiency: a multisystem approach. Oxidative Med Cell Longev. 2017;2017:ID4590127.

10. Thomsen IP, Smith MA, Holland SM, Creech B. A comprehensive approach to the management of children and adults with chronic granulomatous disease. J Allergy Clin Immunol Pract. 2016 Nov/Dez;4(6):1082-8.