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Dermacoccus nishinomiyaensis brain abscesses as the first manifestation of chronic granulomatous disease

Jesica Triguy[a], Ana L. Tolin[a], Sonia Peña[a], Celeste Ballester[a], Ángela Gallardo[a], María J. Aguilar Fixman[b]

ABSTRACT

Chronic granulomatous disease is a rare primary immunodeficiency characterized by defects in one of the subunits of the nicotinamide adenine dinucleotide phosphate oxidase enzyme complex, which causes a deficiency in the capacity of phagocytes to generate superoxide anion. Within this group, the X-linked form is the most frequent.

Here we report the case of a 2-year-old female patient with autosomal recessive chronic granulomatous disease, with a mutation in the *CYBA* gene, whose initial manifestation was brain abscesses caused by an opportunistic microorganism (*Dermacoccus nishinomiyaensis*). The infection led to an early diagnostic suspicion, so treatment and prophylaxis were administered in a timely manner. Currently, she is infection-free, awaiting hematopoietic progenitor cell transplantation.

Key words: *chronic granulomatous disease;* Dermacoccus nishinomiyaensis; *brain abscess.*

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[a] Department of Immunology; [b] Department of Pediatric Hospitalization; Hospital Pediátrico Dr. Humberto Notti, Mendoza, Argentina.

Corrrespondence to *Jesica Triguy: jesicatriguy@hotmail.com*

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INTRODUCTION

Primary immunodeficiencies or inborn errors of immunity (IEI) are genetic diseases in which there is a functional alteration in the immune system. IEI may present with various clinical manifestations, from asymptomatic disorders to diseases associated with severe infections, autoimmunity, and neoplasms.[1,2] More than 400 entities have been described, and this number continues to grow rapidly, with an annual incidence of 1/10 000 persons based on ethnicity.[1–4]

Chronic granulomatous disease (CGD) is part of the group of diseases caused by phagocyte defects. The most common of these is the X-linked form (70%).[1,5] Its incidence is estimated at 1 in 125 000–250 000 live births.[1]

It is caused by defects in one of the subunits of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex (gp91phox, p22phox, p47phox, p67phox, p40phox), a transmembrane electron transport system, responsible for the generation of superoxide anion by phagocytes, necessary for their bactericidal and fungicidal activity.[1]

This disease has a broad spectrum of clinical presentation and may debut from infancy to adulthood. Most individuals are diagnosed before the age of 5, although autosomal recessive forms may manifest symptoms later, with a consequent delay in diagnosis.[1,4,6,7]

The most common manifestations are infections of the skin, lung, lymph nodes, liver, bone, central nervous system, and perianal region. The most frequent microorganisms are catalase-positive bacteria, such as *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia*, and fungi, such as *Aspergillus*. Another characteristic is the formation of granulomas in the skin and in the gastrointestinal, genitourinary, and respiratory tracts, together with other signs of hyperinflammation, autoimmune manifestations, and growth failure.[1,3,5,6]

The dihydrorhodamine (DHR) assay is used for diagnosis, which may distinguish the X-linked form from the autosomal recessive form in most cases.[1,3,6]

Here we report the clinical case of a 2-year-old female patient with autosomal recessive chronic granulomatous disease with a mutation in the *CYBA* gene. The initial manifestation of the disease was brain abscesses caused by an opportunistic microorganism, *Dermacoccus nishinomiyaensis*, which had not been previously reported as a cause of brain abscesses in healthy or immunocompromised patients.

CASE REPORT

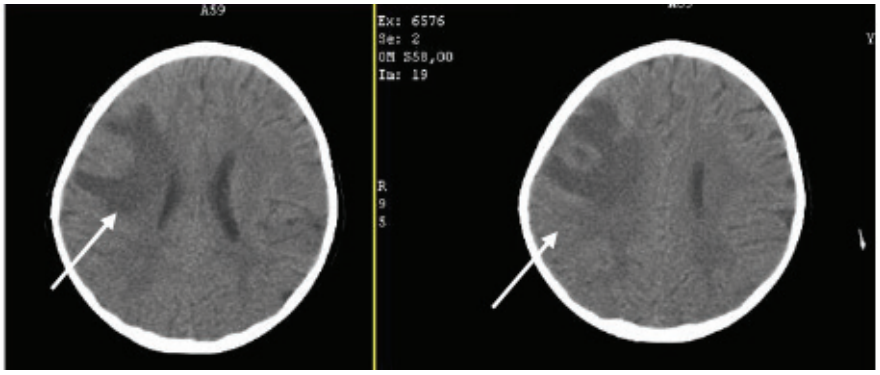
Female, 2-year-old patient, second child of a healthy non-consanguineous couple. No relevant medical history.

She consulted due to afebrile focal seizure on the right side of the face, which subsided spontaneously at home, with full recovery. No other accompanying signs or symptoms were observed on admission. A computed tomography (CT) of the brain (*Figure 1*) showed a right, temporoparietal, cortico-subcortical hypodense image. Surgical drainage was decided, with postoperative diagnosis of brain abscess. *Dermacoccus nishinomiyaensis* was isolated in the specimen culture, which was considered contaminating. She completed antibiotic treatment with intravenous piperacillin-tazobactam 240 mg/kg/day and vancomycin 60 mg/kg/day for 1 week, followed by ceftriaxone 100 mg/kg/day and metronidazole 30 mg/kg/day for 3 weeks. She received anticonvulsant therapy with diphenylhydantoin 5 mg/kg/day. Her clinical course was adequate, her electroencephalogram was normal; diphenylhydantoin was discontinued. She was discharged after 35 days of hospitalization.

She was readmitted 72 hours later due to left focal facial-brachial-crural seizure. A magnetic resonance imaging of the brain showed multiple brain abscesses (*Figure 2*). A drainage and a biopsy were performed; the biopsy results reported brain abscess, osteomyelitis of the calotte, and subdural and epidural empyema. A culture isolated *Acinetobacter iwoffy haemolyticus* (sensitive to meropenem, amikacin, ciprofloxacin), methicillin-resistant *Staphylococcus epidermidis* (sensitive to vancomycin, rifampicin, trimethoprim-sulfamethoxazole, and linezolid), and again *Dermacoccus nishinomiyaensis* (no sensitivity). On this occasion, the isolates were considered pathogenic given the persistence and extent of the lesions.

The patient's sequelae included brachial-crural hemiparesis. The fundus examination and echocardiogram were normal; the CT showed that the mastoid air cells and paranasal sinuses were occupied. She received intravenous treatment with meropenem 120 mg/kg/day for 7 weeks, then levofloxacin 20 mg/kg/day for 7 weeks, and vancomycin at 60 mg/kg/day for 14 weeks. Treatment was restarted with diphenylhydantoin,

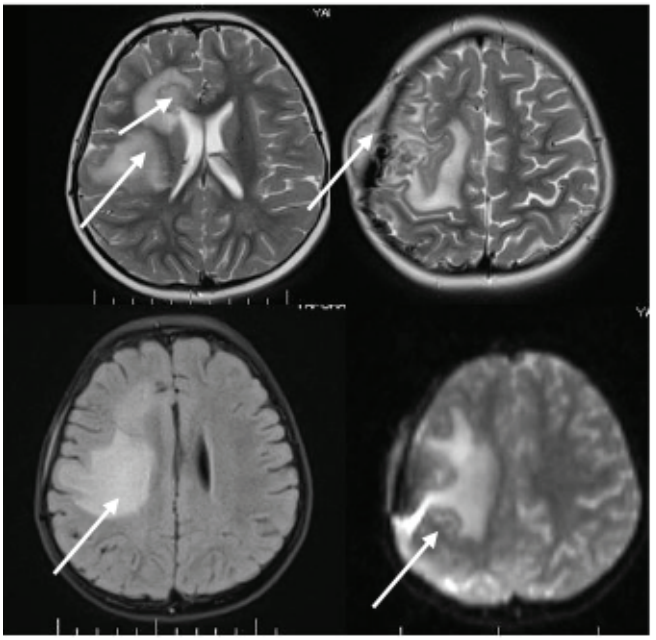
Figure 1. Computed tomography of the brain from first hospitalization



Hypodense cortico-subcortical image, predominantly in the right temporoparietal region, associated with perilesional edema.

which was later replaced by levetiracetam at 50 mg/kg/day. During the patient's course, she developed pulmonary aspergillosis (*Figure 3*), diagnosed by pulmonary infiltrates observed in her chest CT, and positive galactomannans in bronchoalveolar lavage. She was treated with itraconazole for 2 weeks and then voriconazole for 6 weeks, with clinical and CT improvement.

Figure 2. Magnetic resonance imaging of the brain from second hospitalization



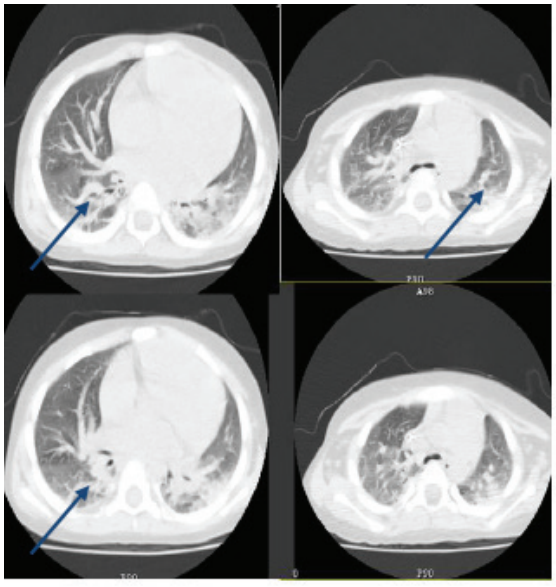
Subgaleal fluid collection with peripheral enhancement after intravenous contrast administration. Cortico-subcortical lesion at the right parietal level, with intense post-contrast enhancement surrounded by moderate perilesional edema. Two rounded lesions are observed in the right cerebral hemisphere, one at the level of the frontal periventricular white matter (18 mm) and the other in the projection of the right lenticular nucleus (6 mm). These images show intense enhancement after intravenous contrast administration, showing restriction in the diffusion sequence inside and signal drop in the ACD map. At these levels, spectroscopy ROIs are placed; and CHO, lactate, and lipid peaks are observed, with a decrease in the NAA peak. The lesions are surrounded by vasogenic edema and exert discrete compression effects on adjacent structures, with partial collapse of the right lateral ventricle. These findings together could be related to lesions of infectious/inflammatory origin (abscesses).

ADC: apparent diffusion coefficient; ROI: region of interest; NAA: N-acetylaspartate.

Due to suspected immunodeficiency, tests for immunoglobulins, specific antibody response, complement, and lymphocyte populations were performed and resulted normal. The test for neutrophil degranulation was altered and the DHR assay showed a pathological histogram, suggestive of autosomal recessive chronic granulomatous disease (*Figure 4*). The DHR assay was performed on the family group, and their findings were normal.

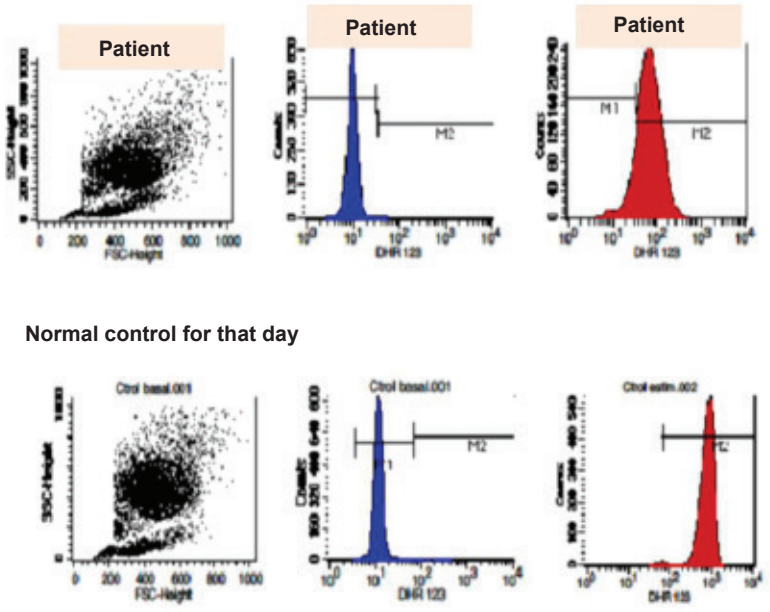
The diagnosis was confirmed at a molecular level, with a previously undescribed homozygous mutation in exon 4 of the *CYBA* gene (p.Leu96Pro/Leu96Pro), validated by the Sanger technique at the Laboratory of Human Genetics of Infectious Diseases of the University of Paris

Figure 3. Computed tomography of the lung



Interstitial-alveolar infiltrates in bilateral lower lobes. Bilateral posterior subpleural fibrous tracts.

Figure 4. Test for neutrophil degranulation



DHR test: altered.

René Descartes (France). This variant causes p22phox protein deficiency.

The patient is currently receiving rehabilitation for her left facial-brachial-crural hemiparesis. She has not had new seizure episodes. She is currently on prophylaxis with trimethoprim-sulfamethoxazole and voriconazole, with monitoring of toxic effects, awaiting for a hematopoietic progenitor cell transplantation (HPCT).

DISCUSSION

CGD is a very heterogeneous disease, both in terms of the genetic perspective and in its clinical manifestations.[1,3,8]

Here we report the clinical case of a 2-year-old female patient with multiple brain abscesses caused by a non-pathogenic opportunistic microorganism as initial manifestation of CGD, which was wrongly construed as a contaminant, since the culture was collected in aseptic conditions from a closed cavity.

The diagnosis was made in an early manner because, unlike X-linked CGD, autosomal recessive forms have a later debut, generally between the second and third decade of life, and are diagnosed late.[1,3,4,6,8–10]

The frequency of central nervous system manifestations in CGD is variable according to the bibliography; it may affect up to 9% of individuals.[1,3,8–12] However, to date, brain abscesses had not been reported as an initial manifestation of CGD, unlike what was observed in our patient.[10–12]

Dermacoccus spp is an aerobic, non-motile, Gram-positive coccus, formerly referred to as *Micrococcus*. It is considered a skin commensal and is frequently found on the skin of the head and extremities. There are few reports of this microorganism causing disease,[13] including colonizing infection of aortic aneurysm,[14] among others, always in patients who are immunocompromised or have a predisposing condition. To date, there are no reports of this microorganism as a causative agent of brain abscesses or infections in patients with CGD.

In contrast, *Aspergillus* is a microorganism commonly isolated in CGD patients with brain involvement.[1,3,10,11] It is the most common fungal infection with a great morbidity and a high rate of complications.

In recent years, morbidity and mortality in CGD patients have improved remarkably. Prophylaxis with sulfamethoxazole trimethoprim reduces the frequency of catalase-positive infections without increasing the number of fungal infections.[1,3,4,6,7] Prophylactic use of azoles has markedly reduced the frequency and severity of fungal infections. Itraconazole, voriconazole, or posaconazole are effective and very well tolerated.[1,3,4,7,9,15]

Interferon-gamma is a cytokine responsible for activating oxidative metabolism and increasing the antimicrobial activity of macrophages. Multiple studies have been conducted to assess the effect of its subcutaneous use in patients with CGD, and results have been controversial. Many experts recommend its use in patients with X-linked CGD to prevent invasive infectious complications. Some adverse effects related to the injection site have been observed, such as redness and swelling, and general flu-like symptoms, which may be reduced with dose adjustment.[1,6,7]

HPCT is the only known cure for this disease.[1,4,6,7]

Reporting this case is very important in order to raise the level of suspicion of primary immunodeficiency in the presence of invasive, severe and/or unusual location infections, and thus get different specialists involved in its detection and timely referral to an immunologist. This will allow to make an early diagnosis, start a targeted treatment, and reduce morbidity and mortality. ■

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