Aspergillus myofasciitis in a chronic granulomatous disease patient: first case report

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SUMMARY

Aspergillus myofasciitis is a rare infection of the muscles and their fascial sheaths that has been reported in patients with immune deficiencies of various kinds but, until now, not with chronic granulomatous disease (CGD). Patients affected by CGD are at high risk of invasive aspergillus infections. The case described involves a 14-year-old boy with a severe autosomal recessive CGD who was admitted to hospital with an Aspergillus myofasciitis of the left forearm. He was treated with liposomal amphotericin for 14 days and then with oral voriconazole for three months with an excellent clinical outcome. He did not evidence any recurrence in the following 30 months using itraconazole prophylaxis.

Keywords: myofasciitis, aspergillus, chronic granulomatous disease, voriconazole, itraconazole.

INTRODUCTION

Chronic granulomatous disease (CGD) is an inherited immunodeficiency disorder that affects the phagocytes and has an incidence of 1 to 200000-250000 births [1]. CGD patients have a partial or complete reduction of the enzymatic and therefore microbicidal activity. The disease is caused by mutations in the genes that encode subunits of nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase, an enzyme that produces superoxide and its metabolites [2]. The X-linked recessive form is by far the most common and the affected gene is CYBB, which encodes the membrane-bound glycoprotein gp91-phox. In autosomal recessive (AR) forms of CGD the affected genes are CYBA, NCF1, NCF2 and NCF4, encoding the membrane-bound protein p22-phox and cytoplasmatic components p47phox, p67phox, and p40phox [2].

Although the immune system has difficulty to eliminate pathogenic microorganisms, it can still produce an inflammatory response that very often is exuberant, with tendency to the formation of granulomas [3].

CGD patients usually present moderate, non specific symptoms and sometimes they can be asymptomatic. Fever and leukocytosis are often present and a high erythrocyte sedimentation rate (ESR) can be the only haematological alteration. Clinical manifestations include recurrent or persistent infections of the soft tissues, lymph nodes, liver, spleen, lungs and gastrointestinal tract, failure to thrive and granulomatous complications. A severe and resistant acne of the face is very common, as well as severe gingivitis and canker sore without periodontal disease [4]. A lymphadenitis with abscess formation and leakage usually affects the cervical lymph nodes. Pneumonia can be complicated with abscesses formation, cavitations and empyema. Hepatosplenomegaly is reported in almost all patients affected by CGD while in about one third of the cases the formation of abscesses or hepatic granulomas can be detected [5]. The diagnosis of CGD requires clinical suspicion and a test that reveals a flaw in the activity of granulocytes: Nitroblue tetrazolium test (NBT) or

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dihydrorhodamine 123 (DHR) test.
The NBT test is a semiquantitative test in which, in a CGD patient, the nitroblue tetrazolium is not reduced to formazan in the absence of superoxide. DHR is a highly sensitive test based on the use of dihydrorhodamine (DHR) as a fluorescent substrate detector of oxidase activity; it can distinguish X-linked from the AR forms of the disease and detect the carrier state.
Molecular tests are used to confirm clinical or laboratory diagnosis and to determine the genotype of the CGD: they include serial single-gene testing, a multi-gene panel, and more comprehensive genomic testing [3,6].
The prognosis for CGD patients has improved considerably in recent years due to the prophylaxis with trimethoprim-sulfamethoxazole and itraconazole, the use of γ-IFN and aggressive treatment of acute infections. Unfortunately granulomatous complications and infectious morbidity remain significant, particularly in patients with X-linked CGD. The estimated overall mortality rate is approximately 5% per annum for patients with X-linked CGD and 2% per annum for patients with autosomal recessive form of CGD [1, 6].

CASE REPORT

A 14-years-old boy with an autosomal recessive CGD was admitted in our hospital after a 7-day history of pain, functional impairment, progressive swelling and hot and slightly hyperemic skin in the left forearm. The diagnosis of CGD had been established at 18 months of age.
Past history was positive for major infectious complications related to his underlying disease: the infections are shown in Table 1.
On admission, the physical examination revealed that the boy was febrile at 37.5°C, his weight was 48 kg, he had normal vital signs as well as heart and abdominal objectivity. He had hyperemic pharynx and reduction of vesicular murmur without any pathological chest sound at auscultation and dull sound at percussion in the basal area of left hemithorax (well known and stable clinical signs).
He showed some swelling on the proximal half of the left forearm with a warm and hyperemic overlying skin. He had reduced flexion-extension movements of the forearm and of the III and IV fingers of the left hand.
Blood tests carried out at admission showed normal absolute and differential white blood cell count but high levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (13.11 mg/dl and 99 mm/h, respectively). The blood cultures were negative for aerobic and anaerobic bacteria and fungi.
The boy was in prophylaxis with trimethoprim-sulfamethoxazole and γ-IFN but not with itraconazole.
An empirical treatment with intravenous vancomycin, 650 mg every 8 hours combined with gentamicin 80 mg every 8 hours was started on hospital day 1 and continued for 14 days and 9 days respectively. Despite the administered antibiotic treatment his clinical and haematological conditions did not improve so the patient underwent an MRI of the forearm on day 3 that showed "an extensive alteration of the signal at the dorsal compartment of the left forearm. There was solid tissue, dishomogeneously isointense if compared to muscle parenchyma in T1w, moderately hyperintense in T2w (but without edema or fluid signal) with an intra and interfascial distribution and extra end intramuscular localization. The extension on the major axis was of about 10 cm. In particular the extensor region, with areas of replacement and infiltration of the parenchyma of the muscle

Table 1 - Infectious complications of our patient.

Age	*Infections*
1 year	Multiple abscesses of the back Pustulosis of genital area Purulent conjunctivitis
18 months	Basal right Bronchopneumonia Left lymphadenitis and laterocervical abscess Erythemato-Staphylococcal Pustular Skin Syndrome
3 years old	Recurrent urinary tract infections
5 years old	Acute diffuse peritonitis from acute appendicitis with subsequent intestinal subocclusion
7 years old	Hepatic abscesses
8 years old	Group B Salmonella gastroenteritis Cerebellar abscess Left basal pneumonia that developed in pulmonary fibrosis

bellies was involved. Also the anterior and posterior interosseous vessels and nerves region were involved. No bone changes".
The same day a drainage and debridement surgery with leaking of copious purulent material was performed. Intravenous ceftriaxone 1.5 g/day was added on day 4 and continued for 14 days. The growth of *Aspergillus fumigatus* was detected in the purulent material, it was sensitive to amphotericin, caspofungin and voriconazole but resistant to fluconazole and ketoconazole. A liposomal amphotericin therapy (Ambisome) was added at a dose of 150 mg/day for 10 days (the initial dose was gradually increased to 3 mg/kg/day). When he discontinued amphotericin, he was administered oral voriconazole, 200 mg every 12 hours and he experienced a mild cutaneous rash that lasted about 7 days. A continuous improvement of local inflammation and recovery of both forearm and fingers movements was detected. The patient was discharged after 14 days from surgery. He completed 3 months of therapy with oral voriconazole 200 mg every 12 hours. He was then prescribed an antifungal prophylaxis with itraconazole 200 mg daily. The healing was complete, without outcomes, and after 30 months of observation there were no local fungal recurrences. He still continues his therapy with itraconazole 200 daily and with trimethoprim-sulfametoxazolo and γ-IFN.

DISCUSSION

Aspergillus myofasciitis is a rare infection of the muscles and their fascial sheaths that has been reported in patients with immune deficiencies of various kinds but, until now, not with Chronic Granulomatous Disease (CGD).
CGD patients develop recurrent bacterial and fungal infections from the first year of life and are susceptible to numerous pathogens [3]. Children with X-linked CGD have more severe clinical presentation: earlier disease onset, frequent obstructions caused by granulomas, more frequent infections and higher mortality rate [7].
Although our patient had an autosomal recessive CGD, he had already experienced many severe infectious complications. Pyomyositis and muscular abscesses are purulent infections of skeletal muscles: in CGD patients *Staphylococcus aureus* is the main etiologic agent followed by *B. cepacia*, *Serratia marcescens* and Nocardia spp [8]. Aspergillus spp is a frequent cause of morbidity and mortality in patients with CGD: it can cause invasive and scattered infections of lungs, bones and brain. *Aspergillus fumigatus* seems to be the most frequent cause of fungal infections while *Aspergillus nidulans* appears to be the most virulent in terms of mortality rate and propensity to spread [9].
Prophylaxis with trimethoprim-sulfamethoxazole decreases the rate of infections and is effective against most bacteria commonly involved in CGD. Currently available data indicate that the trimethoprim-sulfamethoxazole prophylaxis has brought neither to raising the rate of fungal infections nor to raising infections caused by pathogens resistant to trimethoprim-sulfamethoxazole [10]. Alternatives for antibiotic prophylaxis are trimethoprim and doxycycline.
Currently available data show a significant reduction in the rate of infections by Aspergillus in patients receiving prophylaxis with itraconazole and the drug is well tolerated [11]. In patients with CGD, treatment with γ-IFN, reduces the incidence of bacterial or fungal opportunistic infections by 70% [12]. The medication is usually well tolerated and the benefits are probably better and longer lasting than those achieved with antibacterial prophylaxis alone. The use of allogeneic bone marrow transplant in this disease is not frequent due to the high morbidity and mortality associated with this procedure.
We emphasize the absence of azole prophylaxis before admission of our patient.
We used drugs of choice for aspergillus infection with an excellent clinical outcome and we observed the absence of recurrences at 30 months with the use of prolonged therapy with itraconazole.

Conflicts of interest
None

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