Pediatr Nephrol (2008) 23:831–834
DOI 10.1007/s00467-007-0702-0

BRIEF REPORT

Renal amyloidosis in a child with chronic granulomatous disease and invasive aspergillosis

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Received: 1 June 2007 / Revised: 4 October 2007 / Accepted: 2 November 2007 / Published online: 11 January 2008

Abstract A boy who had been diagnosed with chronic granulomatous disease (CGD) at the age of 6.5 years had a medical history of multiple bacterial infections, including pneumonia, staphylococcal liver abscesses and septicemia, from birth. At the age of 10 years and 4 months he developed an infection that was accompanied by high fever and pulmonary, mediastinal and paravertebral infiltrations. *Aspergillus niger* was cultured on bronchial secretions obtained by bronchoscopy. Shortly thereafter, proteinuria manifested and progressed to the nephrotic level. A skin biopsy indicated a diagnosis of amyloidosis. An anti-fungal treatment with amphotericin B and other agents, along with surgical pus drainage, intravenous leukocyte mass, interferon-γ and immunoglobulin infusions, was ineffective, and the patient eventually died from multi-organ failure. The postmortem examination revealed the presence of disseminated aspergillosis and systemic amyloidosis. Although no direct evidence is available that would confirm the causative role of aspergillosis in the development of systemic amyloidosis, to the best of our knowledge this is the first report of a CGD case with complications of both invasive aspergillosis and systemic amyloidosis.

Keywords Amyloidosis · Aspergillosis · Chronic granulomatous disease · Nephrotic syndrome

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Introduction

Chronic granulomatous disease (CGD) is a diverse group of genetic disorders characterized by the inability of phagocytes to kill the ingested organisms. One of the most important killing mechanisms depends on the respiratory burst, i.e. the release of bactericidal oxygen metabolites. This process is catalyzed by a nicotinamide-adenine-dinucleotide phosphate (NADPH) oxidase enzyme system that consists of multiple subunits each encoded by a distinct gene locus. To date, defects in at least four of the oxidase components have been identified in the patients suffering from CGD [1]. Approximately 65% of all CGD cases belong to a subtype inherited as an X-linked pattern.

In the first year of its presence, CGD usually manifests itself with severe recurrent bacterial and fungal infections that can appear at any site in the body, although they occur most often in those organs and tissues where bacteria and fungi would colonize. The most common CGD infections are pneumonia (70–80%), lymphadenitis (60–80%), impetigo and other skin infections (60–70%), liver and perihepatic abscesses (30–40%), osteomyelitis (20–30%), perirectal abscesses and fistulas (15–30%), septicemia (10–20%) and otitis media (20%) [2, 3]. Catalase-producing bacteria, such as *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp., *Salmonella* spp., *Pseudomonas aeruginosa*, among others, are the usual causes of these infections. Of the fungi, *Aspergillus* spp. are the most prevalent organisms; for example, lung aspergillosis can spread to the adjacent soft tissues and bones.

Urinary tract involvement has been reported in 7–48% of the patients [1]. Its presentation may vary broadly and include chronic granulomatous cystitis, pyelonephritis, the kidney and paranephric abscesses. Immune complex glomerulonephritis may also sometimes develop [4].

Renal amyloidosis is a very rare complication of CGD, and very few cases have been reported to date [5–7], none of which have been associated with *Aspergillus* infection. We report here a patient presenting with CGD complicated by invasive aspergillosis, renal amyloidosis and nephrotic syndrome.

Case report

A 10.5-year-old boy was admitted to Vilnius University Children's Hospital with a history of recurrent infections that affected the boy since birth. He was discharged from the neonatal department with signs of pyoderma and purulent conjunctivitis. Other severe infections which appear in his medical history are: paraproctitis (age of 1 month); sepsis with septic pneumonia and purulent otoantritis (age of 2 months); purulent cervical lymphadenitis that recurred several times later (age of 5 months); pneumonia and salmonellosis (4 years); otogenic sepsis and the liver abscess (age of 6 years); recurrent liver abscesses (age of 8 years).

His pus cultures revealed the growth of *Staphylococcus aureus, Escherichia coli,* and *Klebsiella* spp. at different times. The oral thrush without signs of systemic fungal infection was occasionally observed. The patient was treated with multiple courses of various antibiotics, including rifampicin, and the pus was drained on these occasions by surgical interventions. At the age of 6.5 years the patient was examined by Dr. K.M. Debatin, Dr. B. Selle, and Dr. T. Böhler of the Children's Clinic of Ruprecht-Karls University Heidelberg. Their examination of the oxygen radical production in the granulocytes resulted in a diagnosis of CGD. The disease appeared to be X-linked since the same defect was detected in the patient's mother. A detailed study of the family history revealed that the uncle of the patient's mother – to be exact, the brother of her mother – had died of pneumonia at the early age of 5 or 6 years. The consultants prescribed prophylactic treatment with trimethoprim and itraconazole for the patient; however, the precise duration of the treatment course was not documented.

At the age of 10 years and 4 months, the patient contracted an infection which presented as fever, cough and dyspnea. Upon admission to another hospital, his first peripheral blood examination revealed Hb, 121 g/L; red blood cell (RBC) count, 5.09×10^{12}/L; hematocrit (Hct), 37.6%; mean cell volume (MCV), 74 fL; mean corpuscular hemoglobin (MCH), 23.8 pg; white blood cell (WBC), 13.4×10^{9}/L; polymorphs, 59.6%; lymphocytes, 25.2%; monocytes, 9.4%; eosinophils, 5.8%; platelets, 413×10^{9}/L; erythrocyte sedimentation rate (ESR), 50 mm/h; serum creatinine, 52 μmol/L. His urinalysis showed slight proteinuria (0.3 g/L) without abnormal formed elements, with the exception of the occasional hyaline casts. It is worth mentioning that there was no mention of urinary changes in his medical history. The results of the renal ultrasound examination was unremarkable, although X-ray disclosed pneumonia in the right upper lobe. The pulmonary changes did not resolve under intense antibacterial treatment, and the symptoms of the disease progressed. The computed tomography (CT) scan showed infiltration in the upper lobe of the right lung with involvement of the pleura, the mediastinum and the adjacent rib. A culture of the bronchial secretions, obtained by bronchoscopy, indicated the growth of *Aspergillus niger*. Itraconazole was not effective in treating the infection and, in addition to the persisting fever and the peripheral blood changes characteristic of purulent infection, nephrotic syndrome with gross edema and proteinuria up to 3 g/L developed.

Two months after contracting this infection, the patient was transferred to Vilnius University Children's Hospital for further treatment. His peripheral blood examination did not show any essential changes. The blood chemistry of the patient was as follows: total protein, 43 g/L (concentration of albumin was not measured); BUN (blood urea nitrogen), 3.6 mmol/L; creatinine, 27 μmol/L; K^{+}, 2.8 mmol/L; Na^{+}, 142 mmol/L; Ca^{++}, 1.03 mmol/L; Cl^{-}, 99 mmol/L. Urinalysis revealed the protein to be in the range of 1 to 3 g/L (initially) with a small number of leukocytes and erythrocytes as well as the occasional hyaline and granular casts. For the first time in the history of this patients, the renal ultrasound examination showed remarkable changes – namely, the kidneys (right 124.7×48 mm, left 124.1×47.1 mm) grew large with thick and hyperechogenic cortical layers, the pyramids were round and small and the pelves and calyces were depressed.

The repeated plain chest films and CT scans showed a marked involvement of the mediastinum, the destruction of the adjacent ribs and the vertebrae as well as the formation of several abscesses along the vertebral column. Since conservative therapy was not successful and the disease continued progressing, the first solution was to perform a mediastinotomy on the boy. Some weeks later, a paravertebral incision was also performed, accompanied with pus drainage. His pus cultures confirmed the diagnosis of aspergillosis. The skin and the lung biopsies showed the presence of deposits positive for amyloid staining and granulomas in the connective tissue fragments with abundant giant cells filled with fungal hyphae (Fig. 1). In response to the results of these tests, treatment with amphotericin B, interferon-γ and alternate-day moderate doses of prednisolone was introduced. Along with antifungal therapy, the patient received several courses of antibiotics, including co-trimoxazole, for the prophylaxis of

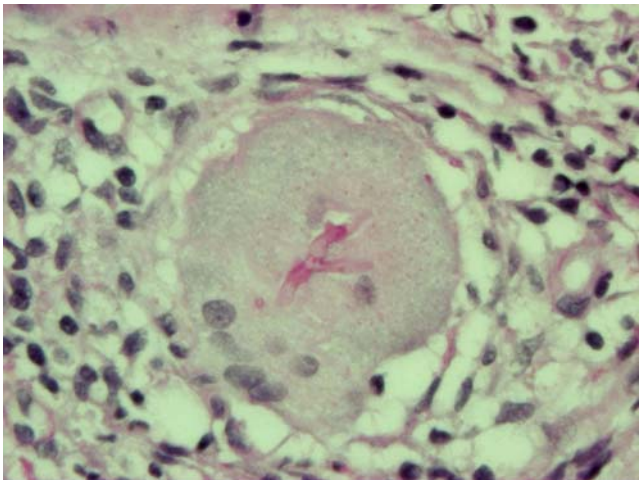

Fig. 1 *Aspergillus* hyphae in the cytoplasm of the giant cell [Periodic Acid Schiff (PAS) stain, ×400]

bacterial infections, especially after the surgical interventions. The introduction of amphotericin B, including its liposomal form, resulted in a slight decrease of fever; however, it caused phlebothrombosis and increased proteinuria and, due to these side effects, treatment with this agent had to be interrupted temporarily. A further switch to an oral antifungal agent (itraconazole) was ineffective, and the patient's state continued to deteriorate. One of the newer antifungal agents, voriconazole, was not available in Lithuania at this time. The reintroduction of amphotericin B did not lead to any improvement despite therapy involving intravenous leukocyte mass, interferon-γ and immunoglobulin infusions. The patient started suffering from the abdominal pain with increased amylase activity. An intractable diarrhea also started. Although the kidney function remained stable for a considerably long time, proteinuria increased up to 10–15 g/L; renal failure eventually occurred, and the patient died of the multi-organ failure. Postmortem examination of the patient confirmed the presence of disseminated aspergillosis and the systemic amyloidosis (Figs. 2 and 3).

Discussion

The case presented here is typical of inherited X-linked CGD and associated recurrent infections. The medical history of the family suggests that the mother's uncle, who died of pneumonia during early childhood, also suffered from CGD, similar to our young patient. The aspergillosis of the bones, concurrent amyloidosis and the nephrotic syndrome were factors that interfered with the treatment and aggravated the patient's disease. It is likely that the nephrotic syndrome was an expression of the renal amyloidosis because the autopsy detected the presence of the amyloid deposits in the glomeruli (Fig. 3).

A simultaneous search on PubMed for three terms "chronic granulomatous disease", "aspergillosis" and "amyloidosis" did not yield any items. The failure of this search has led us to believe that this report is the first to be published case of CGD with the concomitant complications of invasive aspergillosis and systemic amyloidosis. To date, however, there is no direct evidence showing a causative relation between these two conditions.

The case under discussion is illustrative of the complex problems usually encountered by healthcare providers when treating patients with CGD. Invasive aspergillosis in an immunocompromised host is particularly resistant to antifungal therapy, as clearly illustrated by the case of the 10-year-old boy reported here. For many years, the most effective agent in the treatment of aspergillosis was

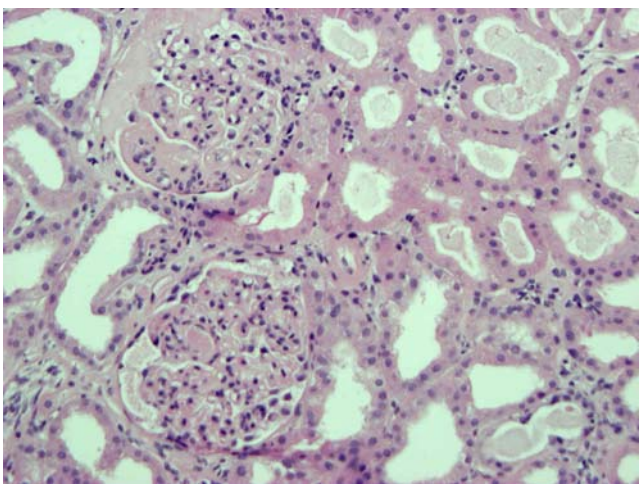

Fig. 2 Amyloid deposition in the glomeruli (hematoxylin and eosin stain, ×200)

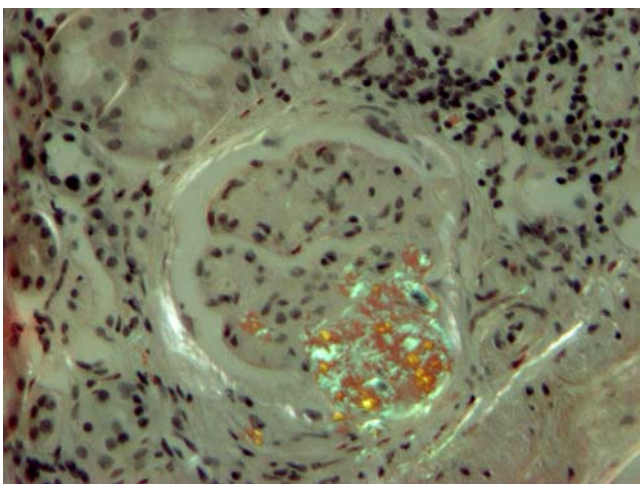

Fig. 3 Positive reaction for amyloid in the glomerulus (Congo red stain with polarization, ×200)

amphotericin B. The use of this agent, however, is limited due to its toxicity. Less toxic are the lipid formulations of amphotericin B [8]. According to Segal and Walsh [9] and Antachopoulos et al. [10], the second-generation triazole, voriconazole, is superior to the conventional form of amphotericin B as a primary therapy for invasive aspergillosis. Voriconazole has become a new standard in the care for this infection. However, this agent was unavailable in Lithuania when our patient was being treated.

Some complications caused by granulomas can be reduced using glucocorticoids. However, it is dangerous to use these agents in the presence of invasive aspergillosis because they can activate the infection, which might result in a fatal outcome. The bactericidal activity of granulocytes can be enhanced by interferon-γ whose long-term prophylactic use may reduce the incidence of infectious complications. Leukocyte (granulocyte) mass transfusions are usually used in the treatment of life-threatening infections. However, these measures were ineffective in the case reported here. Finally, despite reports on the successful grafting of marrow from HLA-matched donors [11], no attempt was made to perform this intervention in our patient because of the uncontrollable infections and renal amyloidosis. Given all of the aggravating factors, the case reported here was extremely complicated by the development of systemic amyloidosis resulting in nephrotic syndrome and leading to renal failure, intractable diarrhea and a fatal outcome.

Acknowledgments This case was presented at the following venues: (1) the 17th Annual Meeting of the European Society for Paediatric Infectious Diseases, Heraklion, Crete, Greece, May 19–21, 1999; (2) the 33rd Annual Meeting of the European Society for Paediatric Nephrology, 2–5 September 1999, Prague, Czech Republic.

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