Mastoidectomy in a child with chronic granulomatous disease

Introduction

Chronic granulomatous disease is a rare inherited primary immunodeficiency with a defect in one of the subunits of the phagocyte nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. This defect results in the failure of phagocytes to generate reactive oxygen species, and consequently fail to kill invading microorganisms, such as bacteria and fungi (Battersby et al, 2013). In addition to infections, chronic granulomatous disease is characterized by abnormally prolific inflammatory responses leading to granuloma formation, such as granulomatous enteritis (Segal et al, 2011).

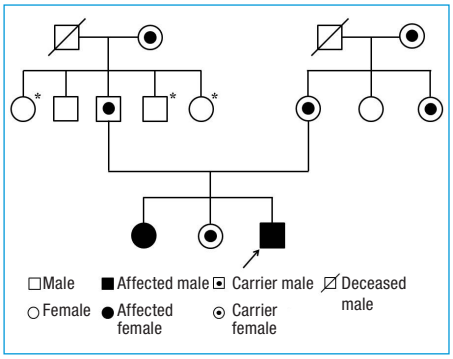
The common clinical manifestations of chronic granulomatous disease include pneumonia, pyoderma, lymphadenitis, liver abscess, colitis and osteomyelitis (Winkelstein et al, 2000). The majority of infections in chronic granulomatous disease are caused by *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia* spp. and *Aspergillus* spp. However, a few cases of otological manifestations in patients with chronic granulomatous disease have been reported (Blayney and Burch, 1984; Wilson et al, 2008). This article presents a case of otomastoiditis and its surgical treatment in a child with chronic granulomatous disease.

Discussion

The incidence of chronic granulomatous disease is 3–4 per 1 000 000 individuals, and the prevalence of chronic granulomatous disease in Korea (0.4–1.7 in 1 000 000) is similar to that in other regions (Kim et al, 2009; Shin and Lee, 2016). However, the incidence of chronic granulomatous disease on Jeju Island, Korea is 20.7 per 1 000 000 individuals, 10–50-fold higher than in other regions (Kang et al, 2015). The family of this patient reside on Jeju Island. It is reported that all patients from Jeju Island who were positive for chronic granulomatous disease had an identical and homozygous mutation in the CYBA gene and were presumed to be the A220 phenotype (Kim et al, 2009; Cho and Shin, 2013). This patient and his sister also have the mutation in the CYBA gene.

The NADPH oxidase complex is composed of five major subunits. Two of these, gp91phox and p22phox, are membrane-bound components encoded by the CYBB and CYBA genes respectively.

Figure 1. Pedigree of the patient. *Not analysed.



CASE REPORT

A 9-year-old boy with chronic granulomatous disease was referred with a 3-week history of left ear discharge. He was diagnosed with p22phox-deficient (phox = phagocytic oxidase) chronic granulomatous disease at 1 month of age, and his elder sister had also been diagnosed with chronic granulomatous disease at 12 months of age (*Figure 1*). He had suffered repeated episodes of pneumonia, lymphadenitis, cellulitis, gastroenteritis and acute otitis media.

Examination of the left ear revealed granulation tissue on the tympanic membrane and otorrhoea. This granulation tissue was partially removed and submitted for culture analysis. Topical ciprofloxacin/fluocinolone otic solution was administered and local ear care was commenced. The culture from the otorrhoea was positive for *Streptococcus sanguinis*.

After 1 month, the ear discharge had not decreased and the granulation tissue had enlarged despite systemic administration of amoxicillin, so a temporal bone computed tomography scan, magnetic resonance imaging and audiometry were performed. Computed tomography showed opacification of the mastoid air cells with cortical bone erosion, as well as erosion of the ossicles (*Figure 2*). Magnetic resonance imaging revealed enhancing soft tissue in the external auditory canal and mastoid air cells. The pure tone audiometry showed mixed hearing loss in the left ear.

Because otomastoiditis was diagnosed, a radical mastoidectomy was performed. The middle ear and mastoid air cells were completely filled with granulation tissue, and all ossicles were eroded. The facial nerve was exposed but intact. Neither the dura nor sigmoid sinus was involved. After removal of the granulation tissue, the cavity was lined with the temporalis muscle fascia of the patient. The exposed facial nerve and oval window were covered with cartilage. Histological findings from the middle ear and mastoid air cell lesion demonstrated chronic granulomatous inflammation.

Following surgery, vancomycin, imipenem and interferon-gamma were administered for 3 weeks because the culture from the granulation tissue was positive for methicillin-resistant *Staphylococcus aureus*. The patient was treated with prophylactic trimethoprim-sulfamethoxazole for 6 weeks. Follow-up temporal bone computed tomography showed no residual lesion, and there has been no evidence of recurrence for 2 years after the surgery (*Figure 3*).

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Figure 2. Preoperative temporal bone computed tomography scan showed opacification of the mastoid air cells with cortical bone erosion, as well as the erosion of ossicles in the left ear. **a.** Axial images. **b.** Coronal images.

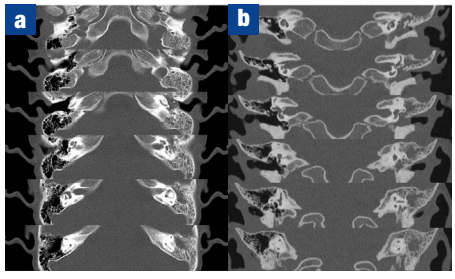
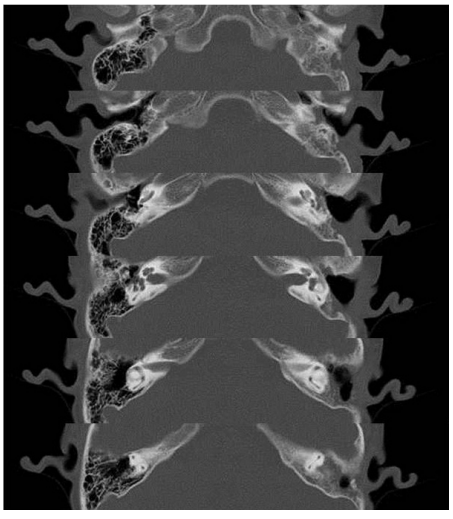


Figure 3. Axial view of the temporal bone computed tomography scan 2 years after the surgery showed no residual lesion and no evidence of recurrence.



The remaining three cytosolic components are p47phox, p67phox and p40phox, encoded by the genes NCF1, NCF2 and NCF4 respectively (Shin and Lee, 2016). Approximately 66% of all cases of chronic granulomatous disease result from mutations in the X-linked gp91phox (CYBB), followed by the autosomal recessive forms of chronic granulomatous disease, with defects in the gene coding for p47phox (NCF1) accounting for 30% of all cases of chronic granulomatous disease. Only 5% of cases are the result of mutations in CYBA (p22phox), NCF2 (p67phox) or NCF4 (p40phox) (Goldblatt, 2014).

The lung, skin, lymph nodes, liver and gastrointestinal tract are the most frequent sites of infection in chronic granulomatous disease. Only a few cases of otomastoiditis have been reported (Blayney and Bunch, 1984; Winkelstein et al, 2000). Wounds and surgical sites heal very slowly in patients with chronic granulomatous disease and may form fistulas. In the authors' hospital, the usual duration for completion of postoperative management after radical mastoidectomy is 2 months. However, it took 5 months to achieve stabilization of this patient's operative site, and prophylactic antibiotics were administered for 6 weeks.

Corticosteroids have been used principally to treat inflammatory complications arising as a result of the treatment of chronic granulomatous disease (Freeman et al, 2011; Shin and Lee, 2016). In this case, the authors did not administer corticosteroids, but instead used interferon-gamma (IFN-γ) and antibiotics postoperatively. This patient had suffered repeated episodes of infections and inflammations. During the treatment of repeated episodes, IFN-γ showed better response to the lesions than corticosteroids without a severe complication in this patient. IFN-γ reduced the number and severity of infections in patients with chronic granulomatous disease in a large, multinational, multicentre, placebo-controlled study (The International Chronic Granulomatous Disease Cooperative Study Group, 1991). IFN-γ was effective for all genetic subtypes of chronic granulomatous disease (Marciano et al, 2004).

Effective management of chronic granulomatous disease is predicated on prophylactic antibiotics, antifungals and IFN-γ, along with management of acute infections as they occur. Prophylactic trimethoprim-sulfamethoxazole reduces the frequency of major infections from approximately once every year to once every 3.5 years, reducing staphylococcal and skin infections (Holland, 2013). This patient was given prophylactic trimethoprim-sulfamethoxazole during the period of surgical wound maturation and remodelling. **BJHM**

LEARNING POINTS

- The possibility of otological manifestation should be considered in patients with chronic granulomatous disease.
- In patients with chronic granulomatous disease, use of antimicrobials and corticosteroids is essential for the treatment of inflammatory complications and infection control.
- Surgical treatment is helpful for management of intractable otomastoiditis in patients with chronic granulomatous disease.

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