X-linked Agammaglobulinemia Diagnosed Following Bezold's Abscess: A Case Report

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Bezold's abscess is an extracranial complication of otitis media, in which a cervical abscess forms from the mastoid process through an ostial fistula, and is a rare condition in recent years. In this study, we experienced a X-linked agammaglobulinemia, which was discovered due to Bezold's abscess.
Case: A 12-year-old boy suffering from recurrent right suppurative otitis media for three months was treated with tympanostomy and oral antibacterial therapy at a local otorhinolaryngology clinic. The patient visited the clinic due to a recurrence of symptoms. CT showed bony defects in the cortical bone and mastoid process of the lateral side of the right mastoid cell. The patient was referred to our hospital, admitted the same day and underwent emergency surgery. Intraoperative findings led to the diagnosis of acute mastoiditis and Bezold's abscess caused by mastoiditis spreading to the sternocleidomastoid muscle. After drainage and administration of ABPC/SBT, the abscess disappeared, and the patient's general condition improved. Subsequently, a blood typing test performed on admission suggested the influence of low immunoglobulin levels. A close examination by the pediatric department led to a diagnosis of X-linked agammaglobulinemia. As a result, the patient receives regular immunoglobulin therapy and has been free of infection, including Bezold's abscess.
CONCLUSIONS: In the case of recurrent otitis media and rare infections, congenital immune abnormalities should be considered.

Key words: Acute mastoiditis, Recurrent otitis media, immunodeficiency, ABO blood group

INTRODUCTION

Acute mastoiditis is a severe form of suppurative otitis media with an inherent complication risk. Bezold's abscess is an extracranial complication that develops from the mastoid process through an ostial fistula for cervical abscess formation. This condition has become rare in recent years due to widespread use of antimicrobial agents. X-linked agammaglobulinemia (XLA), first described by pediatrician Bruton in 1952, is a specific humoral immunodeficiency disease due to B-cell deficiency [1, 2]. It is caused by mutations in the Bruton's tyrosine kinase (BTK) gene, which is essential for B-cell differentiation and signaling. We report an X-linked anaplastic γ-globulinaemia, identified by an abnormal ABO blood group test following a Bezold's abscess.

MATERIALS AND METHODS

Case Presentation

12-year-old boy (height: 150 cm, weight: 32 kg) presented with swelling in the posterior to lower part of the right ear.

His history of allergic rhinitis and vaccination history: hepatitis B, Hib, pneumococcal, DPT-IPV, MR (measles, rubella), varicella, and mumps.

He had a monthly recurrence of right acute otitis media for three months and was treated with a tympanostomy and oral antibiotic (tosufloxacin; TFLX) at a local otorhinolaryngology clinic. He presented to the clinic with a fever (38.1°C) and swelling from the previous day. A temporal bone CT scan revealed bony defects in the mastoid process and cortical bone lateral to the right mastoid cells. He was referred to our hospital on the same day with a diagnosis of right acute mastoiditis.

Initial findings at our hospital: His right ear was erythematous and swollen in the posterior part, and the right tympanic membrane was erythematous and swollen (Fig. 1). Pure tone audiometry revealed conductive hearing loss of approximately 40 dB in the right ear (Fig. 2). Blood tests showed an elevated white blood cell count (12,900/μL: reference interval 3,800–10,100/μL) and a high CRP (12.6 mg/dL: reference interval 0–1.74 mg/dL); Table 1A. Temporal bone CT showed soft tissue shadows in the right tympanic cavity and mastoid cells and bony defects in the right posterior cranial fossa and lower end of the right mastoid process (Fig. 3). Gadolinium contrast-enhanced MRI showed a pale high-signal area in the right mastoid

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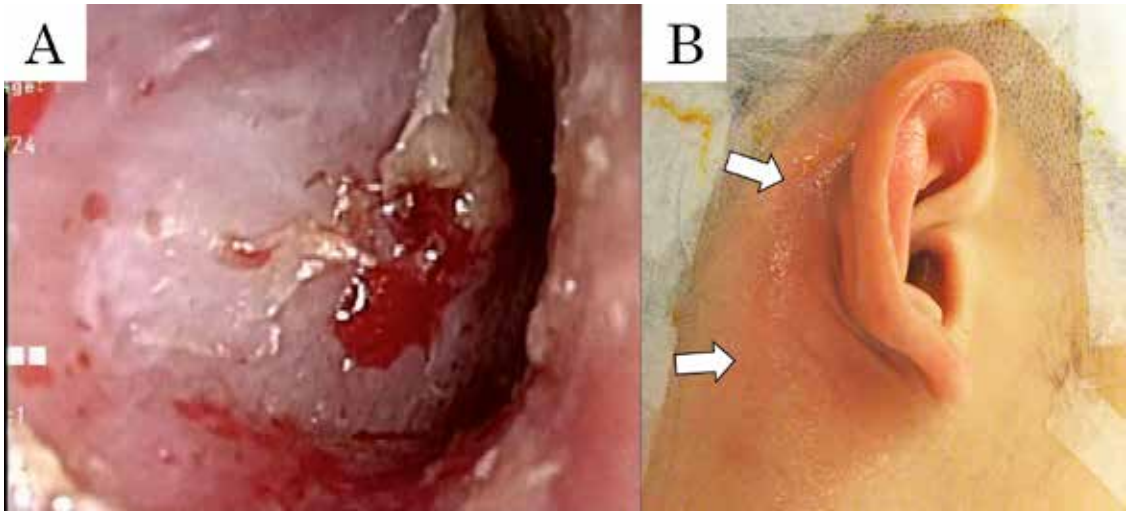

Fig. 1 Findings on hospital arrival.
Redness and swelling of the right tympanic membrane. Redness and swelling (arrows) are seen in the posterior to lower part of the right ear.

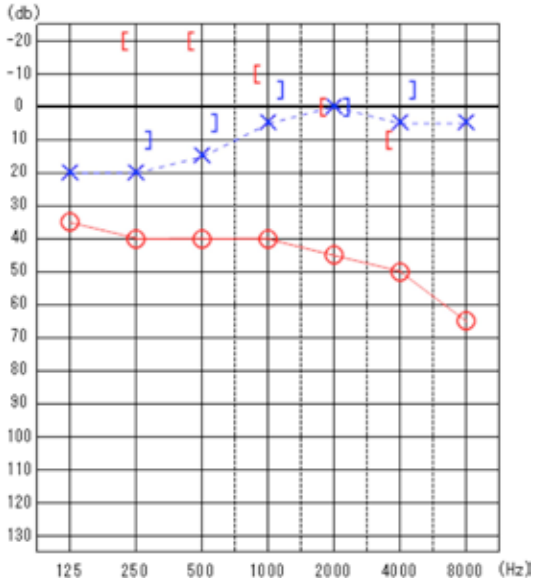

Fig. 2 Pure tone audiometry on hospital arrival.
There was no reduction in bone conductance, and a pneumatic conductance difference of about 40 dB was observed on the right.

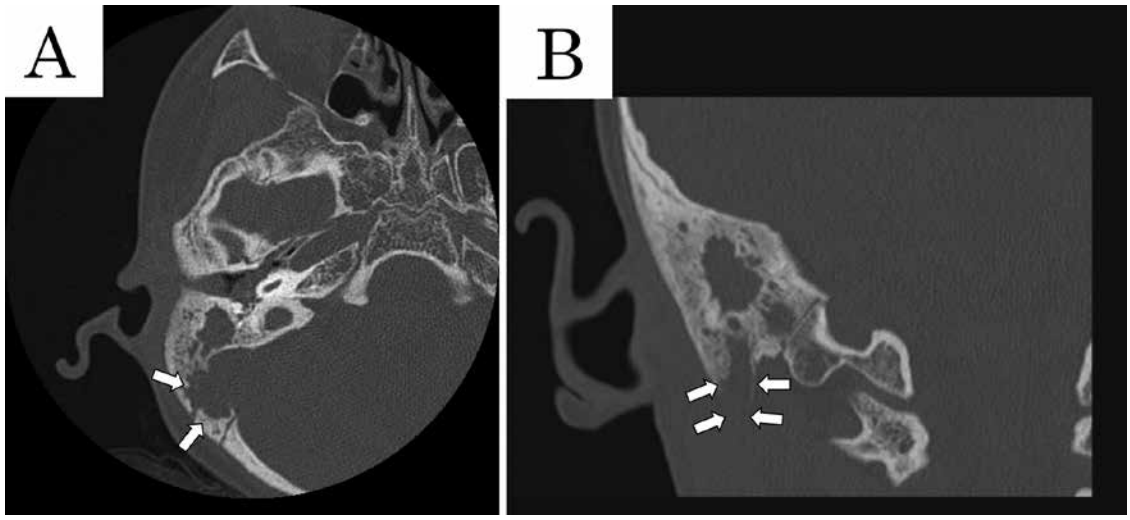

Fig. 3 Computed tomography (CT) scan at the time of hospital arrival.
The mastoid cavity was filled with soft tissue, with bony destruction of the sigmoid sinus and posterior cranial fossa (A) and a bony defect at the mastoid process tip (B).

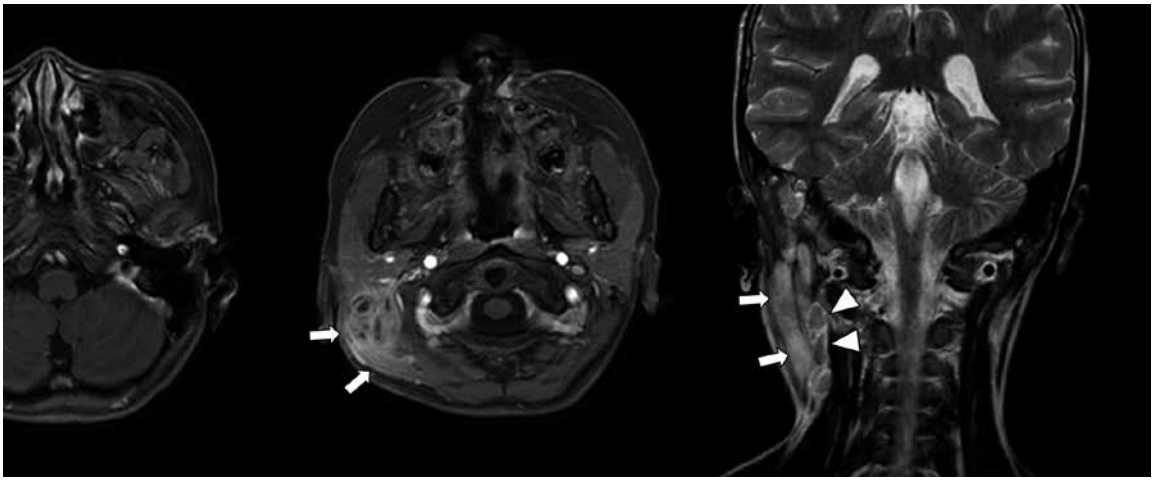

Fig. 4 Magnetic resonance imaging (MRI) (T1-weighted, Gd contrast) on hospital arrival.
Pale high-signal area in the right mastoid cell and contrast effect along the mastoid process to the sternocleidomastoid muscle (arrows). Ring-enhancement lesions are seen in some areas (arrowheads).

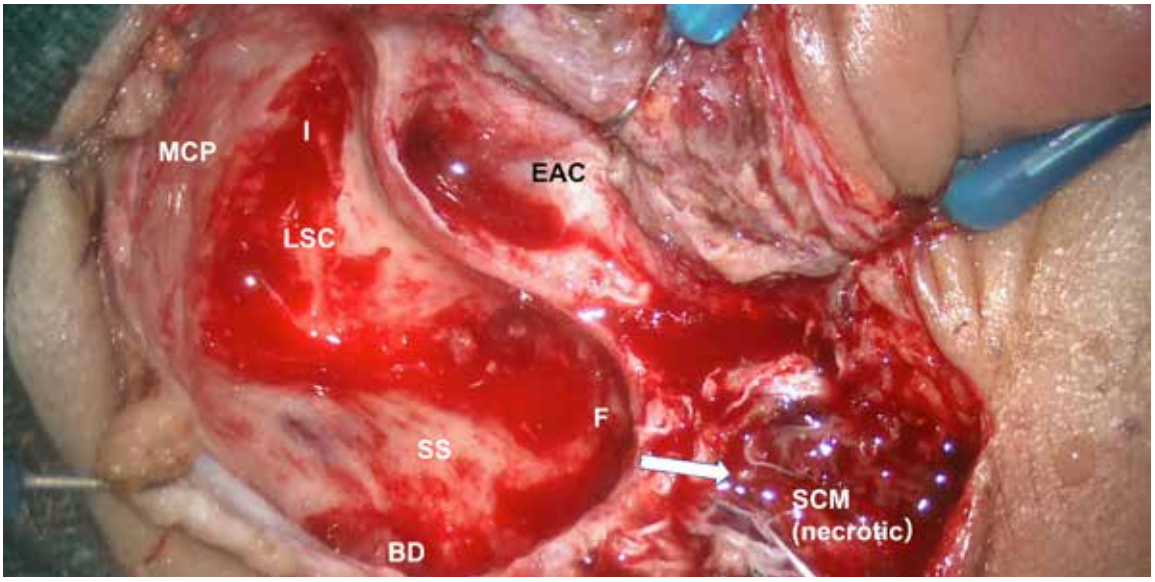

Fig. 5 Intraoperative findings of initial surgery.
A mastoidectomy was performed, and the cervical abscess was opened and drained. Necrosis of the sternocleidomastoid muscle was observed. Arrows indicate fistula and abscess extension from the mastoid process to the sternocleidomastoid muscle.
BD, Bone defect, EAC, ear canal; F, facial nerve; I, incus; LSC, lateral semicircular canal; MCP, middle cranial plate; SCM, sternocleidomastoid; SS, sigmoid sinus;

cavity and contrast effects along the mastoid process to the sternocleidomastoid muscle, with some ring-enhancement lesions (Fig. 4). Therefore, we diagnosed right acute otitis media, right acute mastoiditis, and Bezold's abscess. The patient was hospitalized the same day and underwent emergency surgery.

Mastoidectomy and cervical drainage were performed under general anesthesia. A skin incision was made from the posterior ear to the neck; the neck abscess cavity was opened. A wide mastoidectomy was performed and opened up to the epitympanum. The mastoid cavity was full of inflammatory granulation; the sigmoid sinus was partially exposed but did not suffer hemorrhage. A fistula was observed extending from the tip of the mastoid process to the sternocleidomastoid muscle (Fig. 5). After removing the inflammatory granulation as far as possible, the posterior ear was left open; surgery was completed using a two-stage surgical strategy.

Preoperative ABO blood typing yielded discordant results (major test: blood group O, minor test: blood group AB). This could be due to deficiency of anti-A and anti-B antibodies or anamnestic γ-globulinaemia with a cause on the minor test side; therefore, the pediatric department was asked to investigate further. Peripheral blood tests (Table 1A) showed that red blood cells, white blood cells, and platelets were within reference values. Serum protein fractionation tests revealed low levels of γ-globulin fractions (IgG, IgA, IgM, IgE), and lymphocyte surface marker tests showed a marked decrease in the B-cell system with 98% of the T-cell system and $< 2\%$ of the B-cell system (Table 1B). We did not ascertain a history of immunodeficiency when the mother was initially interviewed; we

Table 1 Results of blood sampling.

A. Blood collection on admission

Blood Cell Count			Biochemistry		
WBC	12900	/μL	Alb	3.5	g/dL
Seg	50	%	CK	27	IU/L
Stab	2	%	AST	16	IU/L
Lympho	45.5	%	ALT	13	IU/L
Mono	2	%	LDH	155	IU/L
Eosino	0.5	%	ALP	142	IU/L
RBC	478	10^4/μL	Cr	0.41	mg/dL
Hb	11.4	g/dL	BUN	14	mg/dL
Ht	36.1	%	Glu	102	mg/dL
MCV	75.5	fL	Na	147	mEq/L
PLT	53	10^4/μL	K	3.6	mEq/L
			Cl	106	mEq/L
			CRP	12.6	mg/dL

B. Additional blood tests on day 7 of hospitalization

Serum Ig level			T/B cell fraction	
		Reference value		
IgG	77 mg/dL	861-1747	T cell	98 %
IgA	<2 mg/dL	93-393	B cell	2 %
IgM	84 mg/dL	33-183		
IgE	<3 mg/dL	< 500		

Blood sampling on admission (A): elevated white blood cell count and high inflammatory response. The leukemic cell fraction showed rod-shaped nucleated cells. Additional blood sampling (B) on the 7th day during a close examination at the pediatric department: gamma globulin fractions (IgG, IgA, IgM, IgE) were below reference values. Lymphocyte surface marker tests showed 98% of the T-cell system and 2% of the B-cell system. Abnormalities in the B cell system were suggested.

reinterviewed her after these results and found that the patient had a history of acute osteomyelitis at three years, pneumonia at age 7, and recurrent otitis media several times per year. Thus, X-linked agammaglobulinemia was diagnosed.

Intravenous ampicillin/sulbactam (ABPC/SBT) was initiated on admission, and the postauricular wound, which was left open, was washed daily with saline solution. Bacterial culture from the cervical abscess on Day 12 of admission revealed *alpha-hemolytic Streptococcus* and *Streptococcus anginosus*, which were sensitive to ABPC/SBT.

After γ-globulin administration (300 mg/kg) on Day 13 of admission, posterior tympanotomy to obtain the drainage route between the auditory tube and mastoid cavity and postauricular wound closure were performed on Day 14. The tympanic cavity was filled with granulation, and the granulation in the mastoid cavity and the tympanic cavity was cleaned again. The chorda tympani nerve was preserved, and the ossicular chain of the ear was left intact, and the operation was terminated with tympanoplasty type I. On Day 21, blood samples showed improvement (white blood cells: 5500/μL, CRP: 0.59 mg/dL); ABPC/SBT was discontinued; the patient was discharged on Day 26 with a favorable general condition. The patient continued to receive monthly γ-globulin infusions on an outpatient basis and has progressed without abscesses, recurrent otitis media, or other serious infections.

Written informed consent was obtained from the patient's guardians for the preparation of this paper.

DISCUSSION

Bezold's abscess is classically associated with acute otitis media. The abscess develops along the deltoid and sternocleidomastoid muscles and descends, presenting as a lateral neck abscess, first reported by Bezold in 1881 [3]. Comparisons with foreign countries are difficult due to differences in antimicrobial agent prevalence and healthcare system; therefore, we examined reports of Bezold's abscess only in Japan. We identified 21 patients since 1960 (Table 2) aged 1-76 (median: 43.5) years; four were children < 15 years. The majority were male (male: 17, female: 4); there were no national reports of X-linked immunodeficiency. Preceding ear diseases included incompletely cured otitis media and masked mastoiditis (8), cholesteatoma (5), ear canal diseases such as stenosis of the external auditory canal (3), chronic otitis media (4), and acute otitis media (1). Recently, the number of cases developing from traditional untreated acute otitis media has decreased, with a shift towards cholesteatoma, chronic otitis media, and masked mastoiditis developing from prolonged inflammation in the mastoid antrum to mastoid tip [4]. Marioni *et al.* [5] summarized 35 cases in Italy since 1967; five cases occurred in patients aged ≤ 5 years and were more common in males (23 cases, 79.3%). In 25 of the 35 cases, mastoidectomy was performed in 22 (88%) and abscess drainage in 16 (64%), and two cases (11%) were treated only with antibacterial agents. The trend was similar in Japan, but no immunodeficiency cases, including X-linked agammaglobulinemia, were reported. In addition, only one case of Bezold's abscess in an immunocompromised patient (HIV) was reported in the English literature [6], but there were no other case reports of X-linked agammaglobulinemia.

Treatment for Bezold's abscess is based on adequate antimicrobial therapy and surgical treatment (mastoidectomy and drainage) [4], although there have been recent reports of symptomatic improvement with cervical drainage alone [7]. Herein, we performed cervical abscess drainage and mastoidectomy simultaneously because the temporal bone CT showed a bony defect in the posterior cranial fossa, and we were concerned about further intracranial otogenic complications, including sigmoid sinus thrombosis. As the sigmoid sinus was partially exposed (Fig. 5), mastoidectomy was considered beneficial in preventing intracranial inflammatory spillover.

Table 2 Literature reports of Bezold's abscess in Japan since 1960.

Age	Sex	Primary auditory disease	Causal Bacteria	Comorbidity	Year of Publication	Author
1	F	Masked mastoiditis	*Staphlococcus aureus*		1960	Kunimoto
38	M	Cholesteatoma	Gram positive cocci		1966	Kamio
69	M	Cholesteatoma	-		1977	Kusumoto
14	M	Masked mastoiditis	*Group A Streptococcus*		1980	Yagi
54	M	Cholesteatoma	*Pepto-Streptococcus*	Alcoholic psychosis	1990	Hiraga
17	M	Masked mastoiditis	-		1991	Aoyanagi
48	M	Cholesteatoma	*Bacteroides, Klebsiella*		1992	Hurukawa
72	M	Traumatic external auditory canal stenosis	*Prevotella, Corynebacterium*	diabetes mellitus	1996	Kobayashi
30	M	Chronic otitis media	Streptococcus anginosus		1996	Hirata
13	M	Masked mastoiditis	Gram-positive anaerobe	Down's syndrome	1997	Wakisaka
76	F	Chronic otitis media	*Bacteroides*	Diabetes mellitus	1999	Konishi
44	M	Cholesteatoma	*Staphlococcus aureus, Proteus mirabilis*		2002	Tanabe
1	M	Masked mastoiditis	penicillin-resistant *Streptococcus pneumoniae*		2003	Matsunaga
73	M	Cholesteatoma	*Staphyrococcus epidermidis, Corynebacterium*	Diabetes mellitus	2004	Komobuchi
67	F	Unknown (no ear symptoms)	-		2007	Yanai
35	M	Masked mastoiditis	-		2007	Yanai
30	F	Masked mastoiditis	penicillin-susceptible *Streptococcus pneumoniae*	Diabetes mellitus, Intellectual Disability	2013	Tateishi
62	M	Chronic otitis externa	*Staphlococcus aureus,* Gram positive cocci		2020	Kusano
55	M	Masked mastoiditis	*Staphlococcus aureus, Streptococcus pneumoniae*		2020	Kobari
43	M	Acute otitis media	*Streptococcus sp*	Schizophrenia, Diabetes mellitus	2021	Takeda

Twenty-one cases were reported in Japan, with only four cases in children under 15 years old.

X-linked aneuploidy is an X-linked latent humoral immunodeficiency disease which typically presents with B-cell deficiency [1]. The BTK gene is essential for B-cell differentiation and signal transduction, and BTK mutations cause impaired differentiation of pro- to pre-B cells, resulting in agammaglobulinemia due to peripheral blood B-cell deficiency. Most cases are diagnosed by the age of five years, approximately 30% of cases are diagnosed after five, and 6% are first diagnosed in adults [2]. The disease is usually identified when bacterial infections such as pneumonia and otitis media recur after four months when maternal transfer antibodies have disappeared. Resistance to viral infection is not usually an issue. Diagnosis is more straightforward if the patient has a family history of the disease, but only about 1/3 of cases have a family history [1]. Therefore, X-linked agammaglobulinemia should be suspected in boys with increased susceptibility to bacterial infection, even without a family history. Serum immunoglobulin levels and peripheral blood B-cell deficiencies should be examined [1]. The prevalence in Japan is estimated to be 1 in 400,000. It is diagnosed by measuring immunoglobulin levels and B-cell counts. Genetic testing may be performed to confirm X-linked agammaglobulinemia, but it is not mandatory [8]. In this case, the parents did not wish to perform testing on the siblings.

Cellular immunity was believed to be preserved as the patient was successfully immunized with live vaccines and had no history of severe viral infections. There was no family history of the disease. The patient was treated at a local otorhinolaryngology clinic for otitis media several times a year since childhood. During the last three months, his acute otitis media had been exacerbating and improving. However, there were no other events suggesting immunodeficiency during this period. The history of hospitalization for acute osteomyelitis at age three and pneumonia at age seven were only discovered after the patient's history was re-interviewed after the immunodeficiency was suspected. We regret that this was due to our inadequate interview at the initial visit. The discrepancy in the preoperative ABO blood typing led to suspicion of low serum gamma globulin, resulting in an X-linked agammaglobulinemia diagnosis. Similarly, Sekine *et al.* [9] reported a 4-year-old child with X-linked agammaglobulinemia diagnosed following preoperative blood typing before tympanostomy tube insertion for repeated otitis media. There was no previous surgical procedure, and blood typing was not performed. This would have likely delayed the diagnosis if no surgical procedure for Bezold's abscess had been planned. Japan's medical system allows free access to pediatrics and/or otorhinolaryngology; osteomyelitis and pneumonia are treated in pediatrics, and recurrent otitis media is treated in otorhinolaryngology. Potentially, definitive diagnosis could have been reached earlier if there had been centralisation of pediatric care management.

Treatment of X-linked agammaglobulinemia involves the administration of adequate doses of appropriate antimicrobials for concomitant bacterial infections, but concurrently, immunoglobulin supplementation is necessary. Immunodeficiency diseases that are easily infectious due to hypogammaglobulinemia should be treated with periodic immunoglobulin replacement therapy. Considering the half-life of serum immunoglobulin (approximately three weeks), generally, 300–500 mg/kg of the intravenous formulation should be administered every 3–4 weeks to maintain the pre-dose IgG level (trough level) ≥ 500 mg/dL [10]. Subsequent monthly treatment was continued on an outpatient basis, and to date, the patient is recurrent severe bacterial infection free.

CONCLUSIONS

We encountered a case of X-linked agammaglobulinemia in which recurrent otitis media developed into a Bezold's abscess. The patient was cured with appropriate surgical treatment and antimicrobial therapy without intracranial complications.

The importance of a detailed history is reiterated; primary immunodeficiency syndrome should also be considered when recurrent otitis media or rare infections are present. Additionally, pediatricians and otolaryngologists need to collaborate closely.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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