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Case report

Bacterial meningitis due to the *Streptococcus mitis* group in children with cerebrospinal fluid leak

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ABSTRACT

The *Streptococcus mitis* group constitutes a part of the oral flora in humans and has been reported to cause infective endocarditis, brain abscesses, sepsis, pneumonia, and peritonitis. However, the *S. mitis* group rarely causes meningitis in children. We experienced a case of bacterial meningitis due to the *S. mitis* group in a 14-year-old girl with Gorham-Stout disease undergoing treatment with sirolimus for skull base osteolysis and cerebrospinal fluid (CSF) leak. Antibiotic treatment was initiated with linezolid and levofloxacin due to allergies against β-lactam antibiotics. On the third treatment day, antibiotics were switched to penicillin G according to CSF culture results, which were positive for penicillin-susceptible *S. mitis* group. Antibiotic therapy was successfully completed after 14 days without any neurological sequelae. There have apparently been no reports of *S. mitis* meningitis in pediatric patients with skull base osteolysis and CSF leak as in our case. Our findings suggest that clinicians should be aware of the possibility of *S. mitis* meningitis for patients with skull base osteolysis and/or CSF leakage.

Introduction

The *Streptococcus mitis* group is an assemblage of species included among viridans streptococci [1] and constitutes normal flora of the oral cavity, upper respiratory tract, gastrointestinal tract, and skin in humans [2]. The *S. mitis* group may cause infective endocarditis, brain abscesses, sepsis, pneumonia, and peritonitis [3–6].

The *S. mitis* group has been reported as causative organisms of meningitis in children with leukemia or lymphoma [1,2]; however, meningitis caused by the *S. mitis* group in immunocompetent children is extremely rare. Therefore, antibiotic regimens and treatment duration have not been standardized for meningitis due to *S. mitis* in children.

Here we report a pediatric case of *S. mitis* group meningitis. The patient had Gorham-Stout disease (GSD), which is a disease characterized by osteolysis with abnormal lymphangiomatous proliferation. We also conducted a literature review regarding the risks and treatment for meningitis caused by the *S. mitis* group.

Case report

A 14-year-old girl with GSD was referred to our hospital with complaint of fever and neck pain. She has had two previous episodes of bacterial meningitis at the age of 10 and 12; the causative organisms were *Streptococcus pneumoniae* and *Streptococcus agalactiae*, respectively. Detailed studies revealed a massive osteolysis of the skull base accompanied by cerebrospinal fluid (CSF) leakage, leading to the diagnosis of GSD. Sirolimus, an mTOR inhibitor, was initiated at 13 years of age in expectation of suppressing pathological lymphangiogenesis in GSD.

She had fever and neck pain several days before admission, which gradually worsened. She also complained of headaches, vomiting, and jaw pain and visited the emergency department. On examination, she was ill-appearing and febrile to 37.9 °C. Her blood pressure was 112/47 mmHg, pulse rate was 97/min, respiratory rate was 16/min with an O_2 saturation of 100% in room air. Head and neck examination showed mild swelling and tenderness of the right anterior neck. Neither nuchal rigidity nor Kernig's sign were observed; however, jolt accentuation was positive. Her consciousness

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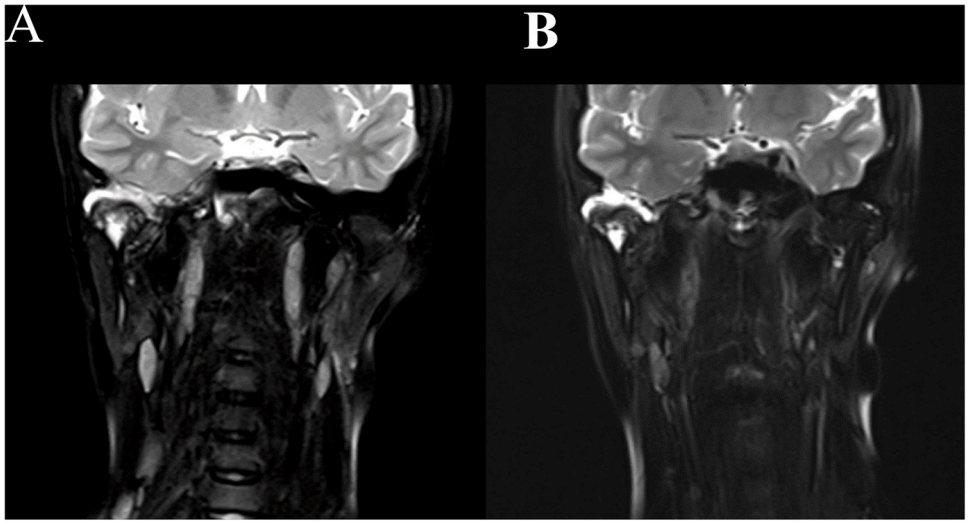

Fig. 1. Magnetic resonance imaging study (T2 study), A. Fourteen month before admission, B. On the seventh day of admission, Right-to-front skull base was destructed with osteolysis and cerebrospinal fluid leakage was observed.

remained clear, and cranial nerve, motor, and sensory examinations were unremarkable. Blood tests exhibited white blood cells of 15,920/μL and C-reactive protein serum level of 3.98 mg/dL. A lumbar puncture was performed for suspected meningitis, showing 44/μL white blood cells (39/μL neutrophils), total protein content of 95.7 mg/dL, and glucose of 61 mg/dL. Gram stain of the CSF was negative.

Bacterial meningitis was suspected clinically, and linezolid (1200 mg/day every 12 h) and levofloxacin (450 mg/day every 24 h) were initiated because of her known allergies to cefotaxime, cefepime, and vancomycin. Both blood and CSF cultures revealed Gram-positive cocci in chains, finally identified as the *S. mitis* group. Because we had previously confirmed that she had no allergy to penicillin G, the antibiotics were switched to penicillin G (16,800,000 units/day every 4 h) according to the susceptibility testing result on the third day of admission. Her condition improved gradually.

Magnetic resonance imaging study on the seventh day of admission showed CSF leakage that continued from the skull base to the right deep neck, appearing as high signal intensity on T2 images, which was almost the same finding compared to the previous study taken at an asymptomatic period in Fig. 1. No intracranial findings including brain abscess were detected. Antibiotic therapy was completed for 14 days without neurological sequelae. Over the next six months, she had no recurrence of meningitis.

Discussion

We experienced a case of bacterial meningitis due to the *S. mitis* group in a 14-year-old girl taking sirolimus for GSD with osteolysis and CSF leakage. Antibiotic treatment was successfully completed after 14 days without any neurological sequelae. The *S. mitis* group is a rare cause of meningitis in children, and reports on its clinical characteristics and outcomes have been limited. We summarized previously reported *S. mitis* meningitis cases in children in Table 1 [1,2,7–9]. These reports included two neonatal cases, four pediatric cases with cancer and neutropenia, and two pediatric cases without immunodeficiency. All patients were initiated on antibiotic therapy empirically, and antibiotics were changed based on the susceptibility results of blood or cerebral fluid cultures. The treatment duration was 2–3 weeks for most cases. One patient with neutropenia died during the treatment but the remaining seven cases survived. The clinical outcomes of the patients that survived were generally fair without any sequelae. However, one case required tracheostomy for long-term mechanical ventilation. There are a few reports of *S. mitis* group meningitis in adult patients with CSF leakage [10,11]; however, apparently no pediatric cases have been reported on *S. mitis* group meningitis with skull base osteolysis or CSF leakage. Therefore, our report may be the first pediatric case to describe *S. mitis* group meningitis with skull base osteolysis and CSF leakage. Although appropriate treatment duration is still unclear, including in our case, 8/9 (89%) of cases recovered under the 2–3 weeks of antibiotic therapy. This fact indicates that at least two weeks of antibiotic therapy might be necessary.

GSD is a rare disorder of uncertain etiology characterized by bone destruction and abnormal proliferation of thin-walled vascular or lymphatic channels within bone [12,13]. Osteolytic lesions of GSD are sometimes located in the skull base, resulting in CSF leakage through the skull base and into the nasal cavity, paranasal sinus, middle ear cavity, or deep neck tissue. An abnormal CSF communication could become an invasive route of a pathological organism. In addition, the abnormal, sponge-like proliferated lymphatic tissue cannot fulfill the actual role of the lymphatic system as a barrier function against pathogens. Therefore, *S. mitis* group organisms inhabiting the oronasal mucosa might have gained entry through the fragile tissue barrier into the meninges. Our findings indicate that CSF leakage may predispose to developing *S. mitis* group meningitis in pediatric patients also, with or without immunocompromised conditions.

Sirolimus is a macrolide antimicrobial agent and suppresses the immune system by binding to and inhibiting the mammalian target of rapamycin (mTOR), an intracellular transduction molecule associated with cell growth and angiogenesis [14]. Recent studies support the efficacy of sirolimus toward complicated vascular anomalies, including GSD [14,15]. In our case, the osteolytic change and CSF leak have shown an improving trend after the initiation of sirolimus. Sirolimus is known to have an immunosuppressive effect, and that it could carry a risk of severe infections, occasionally resulting in death [16]. As the patient had bacterial meningitis twice before sirolimus, we assume that the main reason for developing *S. mitis* meningitis would be the structural abnormality and barrier dysfunction, rather than the immunosuppressive effect of sirolimus, even though it is difficult to interpret causation.

In conclusion, we encountered a pediatric patient with bacterial meningitis due to the *S. mitis* group taking sirolimus for GSD with skull base osteolysis and CSF leak. Further investigation with

Table 1
Reports on treatment and outcome of bacterial meningitis due to the *Streptococcus mitis* group.

Authors [References]	Age	Sex	Background	CSF cell count	CSF glucose level	Antibiotic regimen, dosage, and frequency	Duration and clinical outcome
Hellwege, et al.[7]	2 days	F	GA 37 weeks, normal pregnancy and delivery	1800 granulocytes/μL	0 mg/dL	* ampicillin 200 mg/kg/dose × 1/day and gentamicin 2.5 mg/kg/dose × 2/day for 3 days →penicillin G 500,000 U/kg/dose × 1/day # oral penicillin 300,000 U/kg/dose × 1/day	* 3 weeks →# 2 weeks without any sequelae
Bignardi, et al.[8]	2 days	F	GA 38 weeks, normal delivery, mother had a transient fever and an itchy macular rash one week ago	190 neutrophils/μL and 230 lymphocytes/μL	23 mg/dL	* netilmicin 3.5 mg/kg/dose × 3/day for only 3 days and penicillin G 200,000 U/kg/dose × 2/day # oral penicillin	* 2 weeks →# 1 week without any sequelae
Balkundi, et al.[2]	7 years	F	Burkitt's lymphoma (BM and CNS relapse), neutropenia and mucositis	3 WBCs	46 mg/dL	tobramycin, nafcillin, and ticarcillin → * vancomycin 60 mg/kg/day	* 2 weeks without any sequelae
	6 years	F	ALL (BM and CNS relapse) and neutropenia	no WBC	8 mg/dL	vancomycin 40 mg/kg/day and ceftazidime →vancomycin: intravenous 60 mg/kg/day and intraventricular 5 mg/day	died at day 7
	9 years	M	ALL (BM, testicular and CNS relapse), neutropenia and sinusitis	no WBC	30 mg/dL	vancomycin 40 mg/kg/day and ceftazidime →vancomycin 60 mg/kg/day with G-CSF	2 weeks without any sequelae
Jaing, et al.[1]	6 years	M	ANLL and neutropenia	5 lymphocytes/μL, no neutrophil	79 mg/dL	vancomycin 15 mg/kg/dose × 4/day and ceftriaxone 100 mg/kg/dose × 2/day with G-CSF	3 weeks without any sequelae → tracheostomy due to prolonged intubation
Yiş, et al.[9]	6 years	M	Poor oral hygiene	20 WBCs /μL	76 mg/dL	ceftriaxone 100 mg/kg/day and vancomycin 60 mg/kg/day with IVIG	2 weeks without any sequelae
	8 years	F	Sinusitis 2 weeks ago of onset	150 WBCs /μL	40 mg/dL	ceftriaxone 100 mg/kg/day with dexamethasone	2 weeks without any sequelae

CSF, cerebrospinal fluid; F, female; M, male; GA, gestational age; BM, bone marrow; CNS, central nervous system; WBC, white blood cell; ALL, acute lymphoid leukemia; ANLL, acute nonlymphocytic leukemia; GCS-F, granulocyte-colony stimulating factor; IVIG, intravenous immuno-globulin;

additional cases is required to clarify whether the protective effect of sirolimus against disease progression of GSD could exceed the potential risk of the immunosuppressive effect.

CRediT authorship contribution statement

Haruka Fukayama: Conceptualization, Data curation, Writing – original draft, **Kensuke Shoji**: Conceptualization, Writing – original draft, **Michiko Yoshida**: Data curation, Writing – review & editing, **Hiroyuki Iijima**: Writing – review & editing, **Takanobu Maekawa**: Writing – review & editing, **Akira Ishiguro**: Writing – review & editing, Supervision, **Isao Miyairi**: Writing – review & editing, Supervision.

Authorship statement

HF and KS wrote the first draft of the manuscript. MY, HI, TM, AI, and IM modified and reviewed the manuscript. IM supervised and revised the manuscript. All authors approved the final manuscript.

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Declaration of Competing Interest

All authors do not have any potential, perceived, or real conflicts of interest.

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