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Case report

Meningitis due to *Enterobacter aerogenes* in the community associated with congenital dermal sinus in a Japanese infant

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ABSTRACT

Congenital dermal sinus is associated with meningitis caused by atypical pathogens. Although nosocomial infections with *Enterobacter aerogenes* in limited settings have been reported, community-acquired infections associated with congenital dermal sinus are rarely observed. We present the first non-neonatal case of a 3-month-old boy with meningitis due to *Enterobacter aerogenes* associated with congenital dermal sinus. The patient visited our hospital with fever and a skin dimple with lumbosacral hemangioma. He was diagnosed with meningitis based on cerebrospinal fluid (CSF) examination, which showed a cell count of 5717/μL. Subsequently, antimicrobial therapy with meropenem, cefotaxime (CTX), and vancomycin was initiated. His fever subsided, and the number of CSF cells decreased. Magnetic resonance imaging was performed for the dimple of the lumbosacral region, revealing the congenital dermal sinus. *Enterobacter aerogenes* was isolated from CSF and stool cultures, and treatment was adjusted to CTX alone based on susceptibility testing. However, the CSF culture remained positive. Although CTX was effective, the response to treatment was partial, and a switch to meropenem was required to achieve negative CSF cultures. In conclusion, *Enterobacter aerogenes*, although atypical, can cause community-acquired meningitis associated with congenital dermal sinus. Consistent with previous reports, in this case, a hemangioma on the back led to the diagnosis of congenital dermal sinus. Hence, systemic examination, including the back, is important. In addition, use of a third-generation cephalosporin (e.g., CTX) may not negate the CSF culture, even if it is effective. Thus, a switch to another drug (e.g., carbapenem) may be required.

Introduction

Most sacral skin dimples are benign; however, some may be associated with spinal dysraphism (e.g., a congenital dermal sinus), which may lead to bacterial meningitis caused by atypical organisms (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Proteus* species, and anaerobes) [1]. The presence of atypical pathogens, rather than typical pathogens such as *Streptococcus pneumoniae* or *Haemophilus influenzae*, suggests the presence of causative complications. *Enterobacter* spp. cause opportunistic and nosocomial infections in the intensive care unit (ICU) [2]. Moreover, pediatric meningitis due to *Enterobacter aerogenes* has been reported in neonates in the neonatal ICU (NICU) [3]. However, community-acquired infections due to *Enterobacter aerogenes* associated with congenital dermal sinus in non-neonates have rarely been reported. We present the case of a 3-month-old boy with meningitis due to *Enterobacter aerogenes* associated with congenital dermal sinus.

Case report

A 3-month-old boy (height: 61.5 cm; weight: 8.0 kg) without any significant medical history, except for a lumbosacral hemangioma, was admitted to our hospital for fever and deteriorating condition. He has received all vaccinations up to the age of 3 months in Japan. He was admitted with body temperature of 38.7 °C, heart rate of 213 beats/min, respiratory rate of 56 breaths/min, and blood pressure of 104/44 mmHg. There was intermittent eye-rolling, he disliked recumbency, and preferred vertical holding, which were suggestive of meningeal irritation. At the center of the lumbosacral hemangioma, a dimple was observed for the first time at admission. His hematological values included a white blood cell count of 13,180/μL (74 % neutrophils),

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hemoglobin levels of 11.2 g/dL, and platelet count of 77.5 × 10^4/μL. Additionally, serology reports revealed C-reactive protein levels of 0.06 mg/dL, and procalcitonin levels < 0.05 ng/mL; urinalysis was normal. Chest X-ray and head computerized tomography did not show abnormalities. CSF examination yielded the following findings: cell count = 5717/μL; protein = 352 mg/dL; glucose < 10 mg/dL; and chloride = 120 mEq/L (Table 1). Therefore, we suspected bacterial meningitis associated with the congenital dermal sinus.

On day 1, we initiated treatment with intravenous meropenem (MEPM) (120 mg/kg/day), cefotaxime (CTX) (300 mg/kg/day), and vancomycin (45 mg/kg/day). Dexamethasone 0.60 mg/kg/day was administered for 2 days. His fever subsided the next day, and ocular deviation was also improved. Other vital signs were gradually normalized thereafter. There was no evidence of immunodeficiency in the patient's past history and blood tests for immunoglobulin and complement.

Blood cultures on admission were negative, whereas *Enterobacter aerogenes* was isolated from CSF and stool cultures. The trend of antimicrobial susceptibility testing of *Enterobacter aerogenes* isolated from CSF is shown in Table 2 (days 1, 3, and 6). On day 3, the CSF cell count decreased to 259/μL, glucose levels were elevated to 53 mg/dL, and Gram staining of the smear was negative. Accordingly, on day 4, we adjusted the treatment to CTX alone based on antimicrobial susceptibility testing of *Enterobacter aerogenes* (minimum inhibitory concentration [MIC]: CTX ≤ 1, susceptible [S]; MEPM ≤ 1, S). On day 6, T2-weighted magnetic resonance imaging (MRI) revealed a congenital dermal sinus communicating with the spinal cord (Fig. 1), which was the probable entry portal for bacteria. *Enterobacter aerogenes* is an enterobacterium, and this organism was isolated from the stool and CSF cultures in the present case. MRI did not show any abnormal findings or malformations including brain abscess. CTX appeared to be effective, leading to improvement in clinical symptoms. Nevertheless, the CSF cell count increased to 395/μL and glucose levels decreased to 34 mg/dL on day 6; the CSF culture on days 3 and 6 remained positive, though Gram staining of the smear was negative. Although the susceptibility to CTX remained unchanged (MIC: CTX ≤ 1, S; MEPM ≤ 1, S, on days 3 and 6), the possibility of in vivo resistance was considered. Therefore, on day 8, we switched treatment to MEPM. On day 9, the CSF cell count further decreased to 120/μL, glucose levels were 34 mg/dL, and the CSF culture became negative for the first time. The patient was transferred to another hospital for surgical management of the sinus.

Table 2
Trend in the antimicrobial susceptibility test for *Enterobacter aerogenes* isolated from cerebrospinal fluid.

Antibiotics	MIC, mg/mL	Susceptibility					
	day1		day3		day6		
ABPC	≧ 32	R	≧ 32	R	≧ 32	R	
ABPC/SBT	≦ 8	R	≦ 8	R	≦ 8	R	
CEZ	≧ 32	R	≧ 32	R	≧ 32	R	
CTM	16	I	8	S	≧ 32	R	
CTX	≦ 1	S	≦ 1	S	≦ 1	S	
CAZ	≦ 4	S	≦ 4	S	≦ 4	S	
CTRX	≦ 1	S	≦ 1	S	≦ 1	S	
CFPM	≦ 2	S	≦ 2	S	≦ 2	S	
CMZ	≧ 64	R	≧ 64	R	≧ 64	R	
AZT	≦ 4	S	≦ 4	S	≦ 4	S	
FMOX	32	I	≦ 8	S	≦ 64	R	
MEPM	≦ 1	S	≦ 1	S	≦ 1	S	
GM	≦ 2	S	≦ 2	S	≦ 2	S	
LVFX	≦ 0.5	S	≦ 0.5	S	≦ 0.5	S	
ST	≦ 38	S	≦ 38	S	≦ 38	S	

MIC: minimum inhibitory concentration.
S: susceptible; I: intermediate; R: resistant.
ABPC: ampicillin; ABPC/SBT: ampicillin/sulbactam; CEZ: cefazolin; CTM: cefotiam; CTX: cefotaxime; CAZ: ceftazidime; CTRX: ceftriaxone; CMZ: cefmetazole; AZT: aztreonam; FMOX, flomoxef; MEPM: meropenem; GM: gentamicin; LVFX: levofloxacin; ST: sulfamethoxazole/trimethoprim

Discussion

The present case of congenital dermal sinus with lumbosacral hemangioma was complicated by bacterial meningitis caused by *Enterobacter aerogenes*, an atypical pathogen. In the course of antibiotic therapy, adjustment of treatment to CTX alone was not able to result in negative CSF culture, although the agent was effective.

Sacral dimples occur in 4.8 % of newborns and are also termed coccygeal pits; in most cases, they are not associated with spinal cord malformations [4]. However, the following findings are suggestive of a high risk of spinal dysraphism: distance > 2.5 cm away from the anus; presence not in the midline; other skin findings (e.g., hirsutism, hemangioma, caudal appendage, deviated gluteal fold); neurological abnormalities; and congenital malformations [4]. Additionally, Guggisberg et al. reported that, among 54 pediatric patients with occult spinal dysraphism (OSD) which contains congenital dermal sinus, 43–95 % had a midline skin lesion. They recommended using spinal MRI for patients at high risk of OSD [5]. Our case had hemangioma in the lumbosacral region located > 2.5 cm away from the anus; notably, the dimple was not noticed during postnatal age, and the patient was considered at high risk for OSD.

Powell et al. assessed 114 children with a congenital dermal sinus and reported meningitis in 59 % of cases [6]. It is important to evaluate the risk of OSD and perform appropriate examinations for the diagnosis of OSD prior to the development of meningitis. Ackerman et al. reported three cases of congenital dermal sinus, all in infants. Two of those had an infected skin lesion, which is a reason for referral, and findings on initial

Table 1
Laboratory findings in blood, urine, and cerebrospinal fluid (CSF) at admission.

■Blood test			■Biochemical test			■CSF examination		
WBC	13180	/μL	TP	6.2	g/dL	Cell count	5717	/μL
Neutrophils	75	%	Alb	4.4	g/dL	Mononuclear leukocyte	10	%
Lymphocyte	17	%	BUN	4.2	mg/dL	Polymorphonuclear leukocyte	90	%
Monocyte	7	%	Cre	0.22	mg/dL	Protein	352	mg/dL
Eosinophils	1	%	AST	47	U/L	Glucose	< 10	mg/dL
RBC	434	× 10^4 /μL	ALT	30	U/L	Cl	120	mEq/L
Hb	11.2	g/dL	LDH	334	U/L			
Plt	77.5	× 10^4 /μL	CK	255	U/L	■Urinalysis		
			Na	136	mEq/L	Protein	(-)	
			Cl	105	mEq/L	Sugar	(-)	
			K	4	mEq/L	Occult blood	(-)	
			Glu	143	mg/dL	Leukocyte esterase	(-)	
			CRP	0.06	mg/dL			
			procalcitonin	< 0.05	ng/mL			

Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; Cl, chlorine; Cre, creatinine; CRP, C-reactive protein; Glu, glucose; Hb, hemoglobin; K, potassium; LDH, lactate dehydrogenase; Plt, platelet; RBC, red blood cells; TP, total protein; WBC, white blood cells.

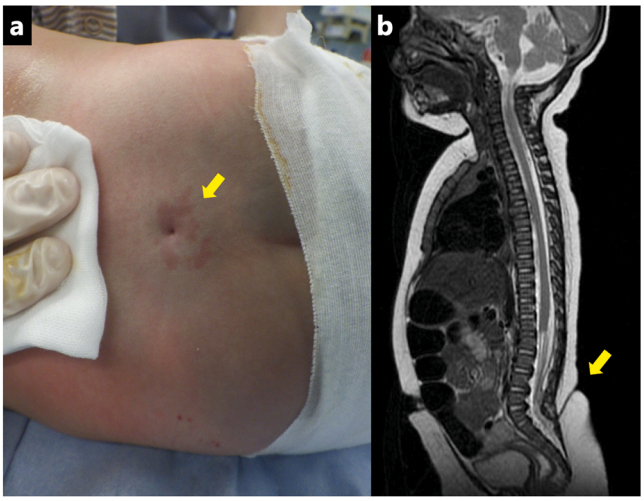

Fig. 1. Images of congenital dermal sinus of the patient. (a) Lumbosacral hemangioma and dimple. (b) Spinal T2-weighted magnetic resonance imaging (MRI) showing a congenital dermal sinus communicating with the spinal cord.

examination [7]. In our case, we also noticed a dimple in the process of examining the source of fever, and found a congenital dermal sinus in the early stage of meningitis. Therefore, in febrile infants, a full physical examination, including back examination, is important. In addition, pediatricians and primary care physicians should consider meningitis as differential diagnosis for febrile infant patients with dimples and other skin findings.

Bacterial meningitis associated with congenial dermal sinus is often caused by atypical bacteria, such as *Staphylococcus aureus*, *Escherichia coli*, *Proteus* species, and anaerobes [1]. A literature review of reports concerning patients with congenital dermal sinus disease who developed abscesses showed similar causative bacteria; however, there were no cases linked to *Enterobacter aerogenes* [8]. Meningitis due to *Enterobacter aerogenes* has been reported only in specific conditions, such as patients undergoing neurosurgical procedures [9–11] and neonates in the NICU [3]. In the present case, we considered that the hematogenous infection was negative, since the blood culture was negative. Therefore, we suspected that the pathogen entered through the congenital dermal sinus due to the detection of *Enterobacter aerogenes* in CSF and stool cultures. In addition, although there have been reports of gut colonization with pathogens preceding and associated with late-onset sepsis in neonates and infants [12], *Enterobacter aerogenes* may have previously colonised the intestine through the maternity hospital or the mother's genital tract. This is a case of meningitis caused by *Enterobacter aerogenes* associated with congenital dermal sinus. It is extremely rare because it occurred in an infant rather than a newborn, and is a community-acquired infection.

Enterobacter aerogenes are dangerous multidrug-resistant bacteria; they are linked to the development of sepsis and a high mortality rate. This pathogen has multiple resistance mechanisms, can produce AmpC β-lactamase and extended-spectrum β-lactamase, and has exhibited resistance to carbapenem [3]. Treatment with a third-generation cephalosporin can also promote the production of AmpC. Foster et al. studied 19 adult patients with meningitis due to *Enterobacter* spp. (34 % of these cases were caused by *Enterobacter aerogenes*). They reported high clinical cure or improvement rates in patients treated with trimethoprim-sulfamethoxazole (83 %) and in those treated with a third-generation cephalosporin (54 %). Of note, several patients developed resistance during treatment with third-generation cephalosporin [13]. Owing to the retrospective design of that study, the investigators were unable to reach a concrete conclusion (i.e., development of resistance versus emergence of a second species). In our case, we also administered CTX from the day of hospitalization, which was effective against the causative organism. Although the treatment reduced the number of CSF cells, the culture remained positive. There was no change in the susceptibility to CTX, suggesting excessive production of AmpC. Switching from CTX to MEMP rapidly changed the culture to negative. Although there are no detailed data other than MIC levels ≤ 1, it is possible that MEPM had a lower MIC than CTX, resulting in better susceptibility. The present case suggests that the administration of a third-generation cephalosporin may not be the optimal option for the treatment of *Enterobacter* meningitis, even if it is effective. Although the susceptibility test suggested that CTX was effective against *Enterobacter aerogenes*, considering the pathogen's ability to produce AmpC and the severity of meningitis, MEPM rather than CTX should have been continued.

To the best of our knowledge, this is the first report of bacterial meningitis due to *Enterobacter aerogenes* in the community with associated congenital dermal sinus in an infant rather than a neonate. Consistent with previous reports, the presence of a hemangioma on the back of the patient led to the discovery of congenital dermal sinus. Therefore, systemic examination, including the back, is important in the assessment of febrile infants. In the presence of skin findings (e.g., lumbosacral hemangioma) in the midback, an OSD (e.g., congenital dermal sinus) should be added to the differential diagnoses. In conclusion, *Enterobacter aerogenes*, an atypical pathogen, can also cause community-acquired infection in meningitis associated with congenital dermal sinus. In addition, in the course of antibiotic therapy for bacterial meningitis caused by *Enterobacter aerogenes*, a third-generation cephalosporin (e.g., CTX) should not be used for severe, life threatening or high inoculum *Enterobacter* infections and as such, carbapenem (e.g., MEPM) should have been the better choice of antimicrobial in this setting.

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Ethical approval

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Consent Statement

Informed consent was obtained from the patient's parent for the publication of this report.

CRediT authorship contribution statement

Y.S., H.S., and T.W. treated the patient and Y.S. drafted the manuscript. Y.W., H.S., T.W., and H.I. contributed to the writing and critical review of the manuscript. All authors have read and approved the manuscript.

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Conflict of interest

None.

Authorship statement

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of

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