—Case Reports—

Acute Focal Bacterial Nephritis in an Infant Referred with Apnea Caused by Mixed Infection with *Enterococcus raffinosus* and *Escherichia coli*

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A 38-day-old infant was referred to our hospital for evaluation of apnea, fever, and pyuria. Invasive bacterial infection, including meningitis, was suspected because of the presence of apnea. A contrast-enhanced CT scan revealed acute localized bacterial nephritis, and meningitis was ruled out. Gram-positive cocci and Gram-negative rods, ie, *Enterococcus raffinosus* and *Escherichia coli*, were isolated from a urine culture at the referring hospital. This case report describes the youngest case of *E. raffinosus* infection. Apnea was the main complaint, but the origin of fever was infant acute focal bacterial nephritis (AFBN) with mixed infection. In infants, bacterial infections, especially invasive bacterial infections, can result in poor outcomes and require careful evaluation and treatment. Furthermore, the possibility of AFBN should not be overlooked, because bacteriuria or leukocyturia may be absent and can flare up if antimicrobials are not administered for an adequate duration. Although ampicillin-susceptible *E. raffinosus* infection in our patient responded well to treatment, there have been reports of vancomycin-resistant enterococci, which highlights the importance of proper use of antimicrobial agents to avoid producing drug-resistant bacteria. (J Nippon Med Sch 2025; 92: 403–408)

Key words: acute focal bacteria nephritis, *Enterococcus raffinosus*, infant, apnea

Introduction

The prevalence of urinary tract infection (UTI) in infants with fever of unknown origin is approximately 5%[1]. UTI in children is a nonspecific symptom and is often severe, especially upper UTIs, which can lead to sepsis and renal scarring. Therefore, in patients with unknown fever and poor general status, urinalysis, urine culture, and blood culture should be performed before antimicrobial therapy is administered[2].

Acute focal bacterial nephritis (AFBN) is a disease concept proposed by Rosenfield et al.[3] and refers to a localized mass lesion without liquefaction in the renal parenchyma. AFBN is caused by a bacterial infection and is considered a disease that is intermediate between acute pyelonephritis and renal abscess and may progress to renal abscess. Early diagnosis, early initiation of treatment, and post-treatment follow-up are essential, as AFBN can sometimes lead to irreversible renal scarring, impaired renal function, and sepsis, which can affect prognosis. However, overdiagnosis may lead to prolonged treatment, so identification of the responsible organism and appropriate antimicrobial therapy are important. The most common symptoms of AFBN are fever and abdominal pain. *E. coli* is the most common pathogen isolated from urine cultures, followed by *Klebsiella* and *Staphylococcus aureus*[4,5]; *Enterococcus faecalis* is reported in fewer than 10% of cases[6]. Furthermore, 20-30% of urinalyses for AFBN patients do not involve bacteriuria or leukocyturia[4].

Enterococcus raffinosus is named for the resolution of raffinose. The natural habitat of *E. raffinosus* is not well understood, but it has been isolated from the oropharyngeal flora of domestic cats and rarely from human clinical specimens[7]. It is implicated as a cause of endocarditis and has been isolated from sources including blood, urine, abscesses, wounds, peritoneal liquid, bile, and spi-

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Table 1 Laboratory results on admission

Complete cell count		Biochemistry		Immunoglobulin	
WBC	9.8×10^9 /L	AST	27 U/L	IgG	458 mg/dL
Neutro	84.0 %	ALT	13 U/L	IgA	11 mg/dL
Lympho	9.7 %	LD	242 U/L	IgM	37 mg/dL
RBC	3.0×10^{12} /L	ALP	363 U/L	**Urinalysis**	
HGB	10.2 g/dL	γGT	105 U/L	specific gravity	1.011
HCT	30.6 %	CK	189 U/L	pH	5.5
MCV	102 fL	AMY	6 U/L	protein	(±)
PLT	399×10^9 /L	T-Bil	4.33 mg/dL	RBC	(±)
Coagulation system		Na	135 mmol/L	WBC	(3+)
PT-INR	1.19	Cl	99 mmol/L	nitrites	(2+)
APTT	37.4 sec	K	4.4 mmol/L	**Cerebrospinal fluid examination**	
FIB	306 mg/dL	Ca	7.7 mmol/L	cell count	6 /μL
D-dimer	1.7 μg/mL	UA	4.5 mg/dL	protein	82 mg/dL
Venous blood gas		BUN	13.2 mg/dL	glucose	68 mg/dL
pH	7.29	Cre	0.26 mg/dL	Cl	118 mEq/L
pCO_2	55.7 mmHg	TP	5.5 g/dL	LDH	27 U/L
pO_2	43.9 mmHg	Alb	3.6 g/dL		
HCO_3^-	26.1 mmol/L	CRP	8.76 mg/dL		
BE	–0.6 mmol/L	Glu	116 mg/dL		
		PCT	24.6 ng/mL		

WBC: white blood cells, Neutro: neutrophils, Lympho: lymphocytes, RBC: red blood cells, HGB: hemoglobin, MCT: hematocrit, MCV: mean corpuscular volume, PLT: platelets, PT-INR: prothrombin time international normalized ratio, APTT: activated partial thromboplastin time, FIB: fibrinogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, ALP: alkaline phosphatase, γGT: γ-glutamyl transpeptidase, CK: creatine kinase, AMY: amylase, T-Bil: total bilirubin, UA: uric acid, BUN: blood urea nitrogen, Cre: creatinine, TP: total protein, Alb: albumin, CRP: C-reactive protein, Glu: glucose, PCT: procalcitonin

nal bone marrow[7,8]. *E. raffinosus* isolates, like *E. faecium*, are frequently resistant to ampicillin (ABPC) and penicillin[7,9]. Clinical and microbiological information on the pathogenicity of this species is insufficient, but clonal spread of *E. raffinosus* has been reported[10]. It is not intrinsically resistant to glycopeptides or high concentrations of aminoglycosides but may acquire resistance genes such as the vanA gene cluster and the ace (6′)-aph (2″) gene, which are easily acquired by *E. faecium* and *E. faecalis*. *E. raffinosus* can spread and cause outbreaks[11], and in fact, resistant strains have been reported in many cases[9,11–13].

Here, we report isolation of *E. raffinosus* from a very young infant. To our knowledge, successful treatment of such a case has not been reported.

Case Description

A 38-day-old boy was referred to our hospital for evaluation of poor feeding and apnea. He was born by induced labor at a gestational age of 35 weeks 4 days with a birth weight of 1,940 g and was diagnosed as having an atrial septal defect on the third day after birth. There was no apparent primary immunodeficiency disease before he was admitted to hospital. He had been evaluated at another hospital for fever, and blood and urine examinations were performed. UTI was suspected because of the presence of pyuria. After collecting specimens of blood and urine cultures, he was started on ABPC and cefotaxime (CTX) but was transferred to our hospital because frequent apnea was observed the day before.

His anterior fontanel was flat and soft, with no rash, but periodic retractive breathing and apnea were reported. His vital signs were temperature 37.6°C, systolic blood pressure 64 mm Hg, heart rate 176 beats/min, respiratory rate 78 breaths/min, and SpO_2 96-98% (in room air). Initial laboratory findings showed a markedly elevated C-reactive protein level of 8.76 mg/dL and a procalcitonin level of 24.6 ng/mL. His white blood cell count was 9,800/μL of which 84.0% were neutrophils. Urinalysis showed leukocytes 3+ and nitrite 2+. Examination of cerebrospinal fluid revealed a cell count of 6/μL. (**Table 1**). Renal ultrasonography was performed; however, no obvious renal pelvis enlargement, ureteral dilation, or blood flow deficit were detected by color Doppler.

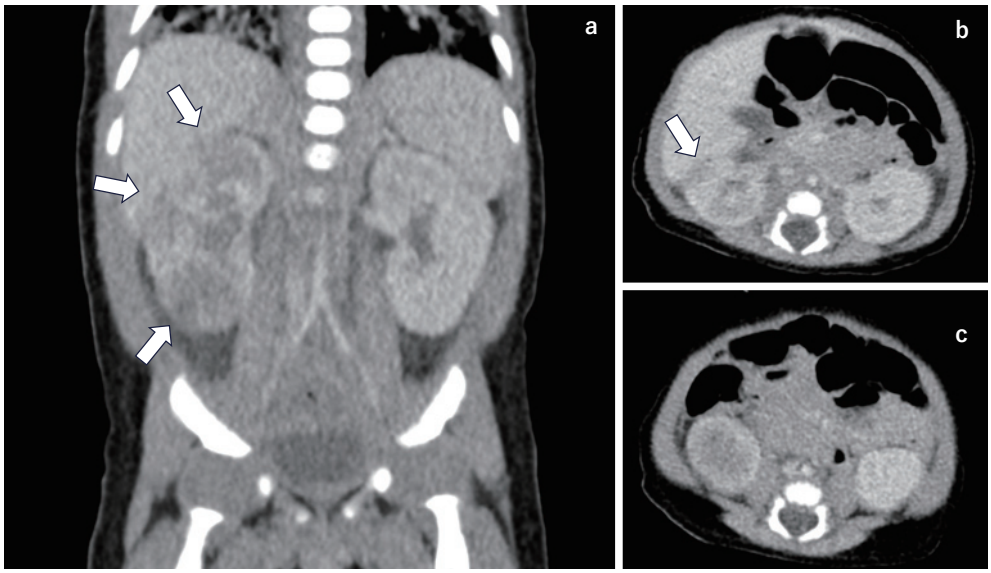

Fig. 1 Contrast-enhanced CT image of the abdomen
a: Coronal section image; **b**: Axial section from the upper kidney; **c**: Axial section from the lower kidney.
Scattered areas of poor enhancement (arrows) in the right kidney are consistent with acute focal bacterial nephritis. There is no evidence of significant hydronephrosis.

ABPC and CTX were administered as empiric therapy after admission to treat suspected meningitis, bacteremia, and UTI. A high flow nasal cannula (HFNC) with 7 L flow, FiO_2 26% was indicated for apnea. On the second day of admission, his body temperature remained high and C-reactive protein (CRP) level was higher. He was therefore switched from ABPC to meropenem (MEPM), and immunoglobulin was administered.

Fever persisted until the third day of hospitalization. Urine culture specimens taken by catheter with aseptic technique at the referral hospital reported growth of Gram-positive cocci and Gram-negative rods, with possible *enterococci* and *E. coli*. In general, *E. faecalis* increases susceptibility to ABPC, but *E. faecium* is intrinsically resistant to ABPC. Because the fever did not decrease after ABPC administration, and considering the severity of his condition, the possibility of *E. faecium* could not be ruled out. The patient was therefore switched to vancomycin (VCM). The CT scan with contrast-enhanced imaging showed acute localized bacterial nephritis (AFBN) in the right kidney (**Fig. 1a**).

On the fourth day, his fever resolved and peripheral blood tests showed decreased CRP. The HFNC was terminated because apnea had resolved.

On the fifth day, quantitative urine culture findings were reported: *E. raffinosus* and *E. coli* concentrations were 10^4 cfu/mL and were considered pathogens. On the seventh day, we received a laboratory report indicating that the *E. raffinosus* was susceptible to all susceptible kits containing ABPC except erythromycin and minocycline, whereas *E. coli* was resistant to ABPC, piperacillin, gentamicin, levofloxacin, and sulfa/trimethoprim but susceptible to CTX and MEPM. Therefore, VCM was changed to ABPC and MEPM to CTX. After 14 days of intravenous antimicrobial infusion, he was discharged in time to switch to oral amoxicillin (**Fig. 2**).

Twelve days after discharge, retrograde voiding cystourethrography (VCUG) was performed as an outpatient procedure (**Fig. 3a**). AFBN was identified in the right kidney on a contrast-enhanced CT scan, and Grade IV vesicoureteral reflux (VUR) was observed on the right side on VCUG. After confirming VUR, the patient has been followed up with prophylactic oral administration of trimethoprim-sulfamethoxazole. A year later, mild atrophy of the right kidney and diffuse, moderate uptake reduction were confirmed on ^{99m}Tc-DMSA scintigraphy. Multiple small, wedge-shaped uptake defects suggestive of renal scars were consistent with a diagnosis of AFBN (**Fig. 3b**). There has been no recurrence or onset of other infections as of this writing.

The patient's guardians provided oral permission for the submission and publication of this case report (including the clinical data and images).

Discussion

In general, when an infant develops fever of unknown

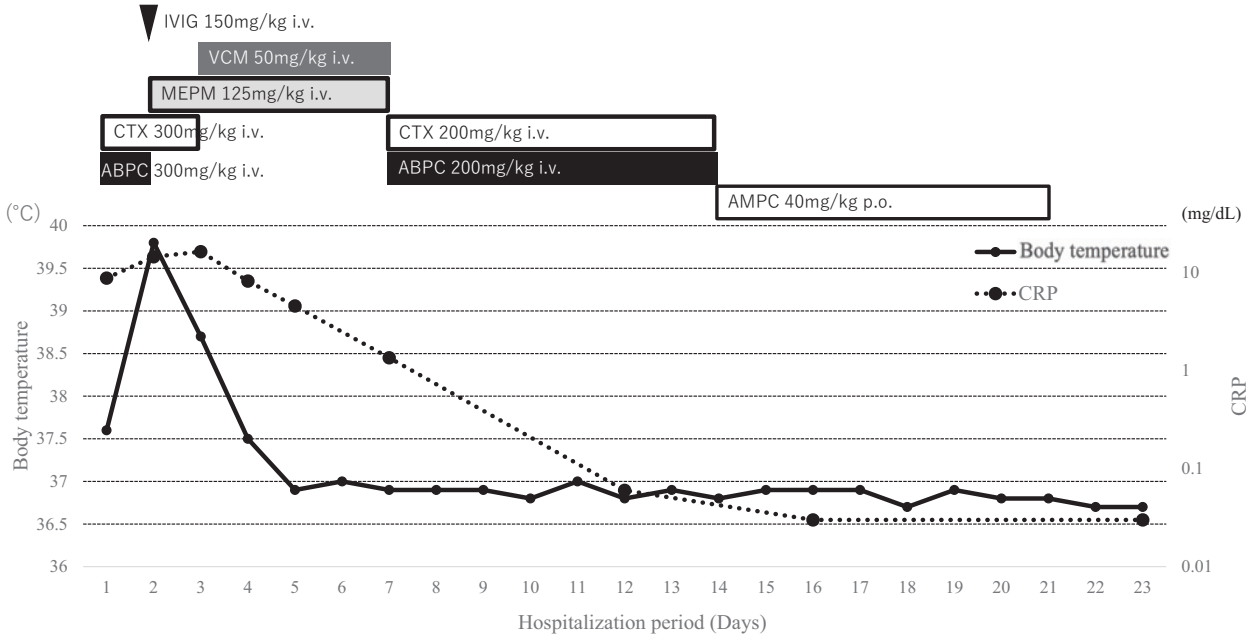

Fig. 2 The clinical course of the patient

ABPC: ampicillin, CTX: cefotaxime, MEPM: meropenem, VCM: vancomycin, AMPC: amoxicillin, IVIG: intravenous injection of immunoglobulin

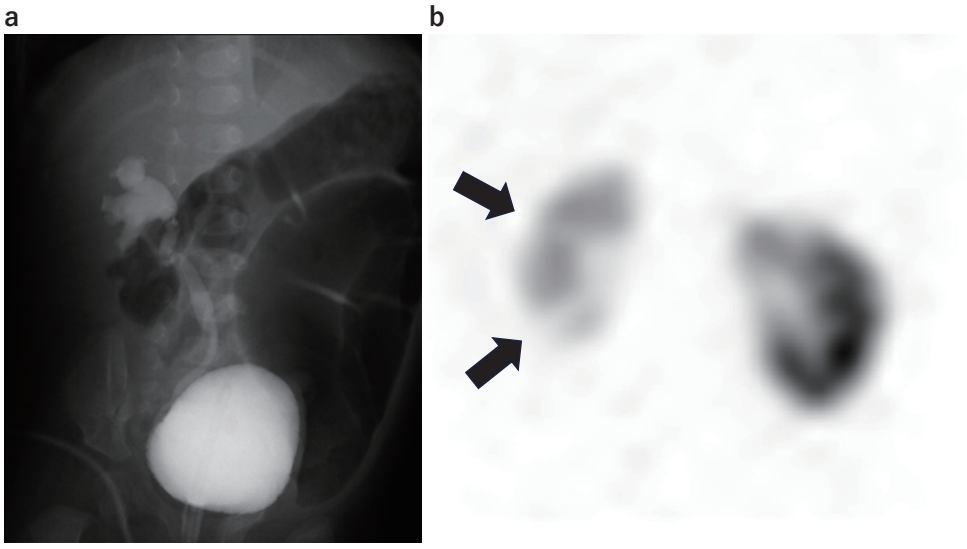

Fig. 3 Voiding cystourethrography and ^{99m}Tc-DMSA renal scintigraphy showing vesicoureteral reflux and cortical defects

a: Voiding cystourethrography (VCUG) revealed grade IV vesicoureteral reflux on the right side.

b: Mild atrophy of the right kidney and diffuse moderate uptake reduction were confirmed on ^{99m}Tc-DMSA scintigraphy. The presence of multiple small, wedge-shaped uptake defects (arrows) suggested renal scarring, consistent with a diagnosis of AFBN.

origin, the possibility of meningitis, bacteriemia, and UTI should be carefully considered as a cause of fever, because the immune system is immature. Our patient's general condition deteriorated quickly, with poor vitality, poor oral intake, and apnea, and blood examinations showed marked increases in CRP and PCT, so the referring physician suspected an invasive bacterial infection, such as bacteremia and meningitis. We also strongly suspected invasive bacterial infection and performed spinal fluid analysis, blood culture, and urinalysis, in addition to general blood examinations.

On the third day of hospitalization, a contrast-

enhanced CT scan revealed AFBN in the right kidney. AFBN is typically established hematogenously and/or retrogradely; however, in this case, no pathogens were isolated in blood cultures. However, only one set of blood cultures was collected in this case. Reports indicate that bacteremia in children often presents with a higher bacteria count than in adults, and although the optimal number of blood culture sets is debatable, collecting multiple sets is believed to improve diagnostic accuracy[14,15].

In this case, *E. raffinosus* and *E. coli* were isolated from a urine culture specimen. Previously, it was believed that infections were rarely caused by multiple pathogens, but with advances in multiplex PCR and other diagnostic methods, mixed infections are now recognized as more frequent than previously assumed[16]. Recently, it has been suggested that the urinary tract is not sterile, and that reflux caused by urinary malformations could lead to an imbalance in the urinary microbiome, thereby increasing the risk of UTIs caused by atypical microorganisms[17,18]. In our case, the presence of grade 4 VUR and immunological immaturity at age 1 month may well have contributed to a UTI caused by multiple organisms.

Additionally, the bacterial count in the catheter-collected specimen was 10^4 CFU/mL, which is consistent with the primary infecting organism. Ultimately, we diagnosed retrograde AFBN caused by mixed infection with *E. raffinosus* and *E. coli.*

Although AFBN is classified as a UTI, respiratory disturbances such as tachypnea and apnea led to the patient's transfer to our hospital. Tachypnea was believed to be caused by increased tissue oxygen consumption from inflammatory cytokines, leading to an elevated respiratory rate. Apnea was attributed to respiratory muscle fatigue from central immaturity and respiratory muscle immaturity[19,20].

Clinical and microbiological information on the pathogenicity of this species is limited, but several reports suggest the spread of *E. raffinosus*[10]. Furthermore, although it is originally not resistant to glycopeptides or high doses of aminoglycosides, it can acquire resistance genes more commonly possessed by *E. faecium* and *E. faecalis*, such as the vanA gene cluster and the aac (6')-aph (2'') gene, and is therefore thought to have the potential to spread in hospital environments and cause outbreaks. It is thought that the spread of *E. faecium* and *E. faecalis* in the hospital environment can cause outbreaks of healthcare-associated infection[11], and resistant strains have indeed been reported in many patients.

If the pathogen had been vancomycin-resistant enterococci in our case, it would have been difficult to treat and may have led to renal sequelae. However, because the pathogen was *E. raffinosus*, which is susceptible to ABPC, the patient responded well to treatment and was cured without complications.

This report's limitations include our inability to confirm whether the two bacterial species identified caused a mixed or mono-species infection. This uncertainty arises from challenges inherent to distinguishing between colony formation and infection. To confirm the pathogen, culture specimens would need to be directly obtained from the lesion. However, collecting specimens of renal lesions from a 1-month-old infant carries significant risks and ethical concerns. Therefore, obtaining direct evidence was challenging in this case.

Nevertheless, the presence of a substantial quantity of bacteria isolated from catheter urine specimens, using sterile techniques, along with the complication of grade 4 VUR and the immunological immaturity of the 1-month-old infant, strongly suggest a mixed infection. Despite the limitations and challenges in confirming this, the combination of clinical and microbiological factors in this cased supports the hypothesis of mixed infection.

E. raffinosus infections occur mostly in older adults, and we are aware of no reports of isolates from UTIs, including AFBN, in infants. *E. raffinosus* has been reported frequently in multidrug-resistant strains, and antibiotics should be chosen carefully to prevent future emergence of multidrug-resistant organisms.

Conclusion

A 38-day-old boy was admitted to our hospital for evaluation of fever, pyuria, and apnea. AFBN from mixed infection with *E. raffinosus* and *E. coli* was diagnosed and, to our knowledge, this is the youngest such patient to be reported. In the case of infantile apnea, it is important to always consider the possibility of invasive infection, including AFBN, as urinary findings are sometimes lacking, and to search for the cause. In addition, it is important to bear in mind the proper use of antimicrobial agents, since many cases of antimicrobial resistance have been reported in *Enterococcus*, *E. coli*, and other organisms.

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