

## Case Report

뇌출혈을 동반한 *Rothia mucilaginosa* 인공판막 심내막염송여진<sup>1\*</sup>, 김봉영<sup>1\*</sup>, 김영은<sup>2</sup>, 이양순<sup>2</sup>, 배현주<sup>1\*</sup>한양대학교 의과대학 <sup>1</sup>내과학교실, <sup>2</sup>진단검사의학과학교실A Case of Prosthetic Valve Endocarditis with Cerebral Hemorrhage Caused by *Rothia mucilaginosa*Yeo-Jin Song<sup>1\*</sup>, Bongyoung Kim<sup>1\*</sup>, Young-eun Kim<sup>2</sup>, Yangsoon Lee<sup>2</sup>, Hyunjoo Pai<sup>1\*</sup><sup>1</sup>Department of Internal Medicine, <sup>2</sup>Department of Laboratory Medicine, Hanyang University College of Medicine, Seoul, Korea

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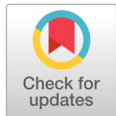
## ABSTRACT

*Rothia* spp. are aerobic, gram-positive cocci belonging to the family *Micrococcaceae*, and are a part of the normal microbial flora of the human oropharynx and upper respiratory tract. We present the first case of the prosthetic valve endocarditis with cerebral hemorrhage caused by *Rothia mucilaginosa* in South Korea. A 65-year-old man with a prosthetic aortic valve visited the outpatient clinic with a complaint of fever. *R. mucilaginosa* was identified in one among four sets of blood culture bottles obtained on the on day 30 of fever onset. Brain magnetic resonance imaging (MRI) showed multiple micro-hemorrhages suggesting septic emboli in both the hemispheres, corticomedullary junctions, and cerebellum. *Rothia* spp. should be considered as a possible pathogen in the cases of infective endocarditis with intracranial hemorrhage.

**Keywords:** Cerebral hemorrhage, Infective endocarditis, Prosthetic valve, *Rothia mucilaginosa*

## INTRODUCTION

*Rothia* spp. are aerobic, gram-positive cocci belonging to the family *Micrococcaceae*, which are part of normal flora of the human oropharynx and upper respiratory tract [1]. They are commonly associated with periodontal diseases and can cause invasive disease very rarely in healthy hosts [1]. However, *Rothia* spp. is increasingly recognized as an opportunistic pathogen mostly for immunocompromised patients [2]. To date, invasive infections caused by *Rothia* spp. have been reported for bacteremia, endocarditis, meningitis, pneumonia, skin and soft tissue infection, bone and joint infection, and endophthalmitis [1-3]. Among them, infective endocarditis was the most common infectious syndrome, and complications such as brain abscess,



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intracranial hemorrhage, and mycotic aneurysm could be accompanied by *Rothia* endocarditis [4]. Invasive infections by *Rothia* spp. have been rarely reported in South Korea [3,5].

Here, we report a case of prosthetic valve endocarditis with cerebral hemorrhage caused by *Rothia mucilaginosa*. To the best of our knowledge, this is the first case of endocarditis complicated with intracranial hemorrhage by *Rothia* spp. in South Korea.

## CASE REPORT

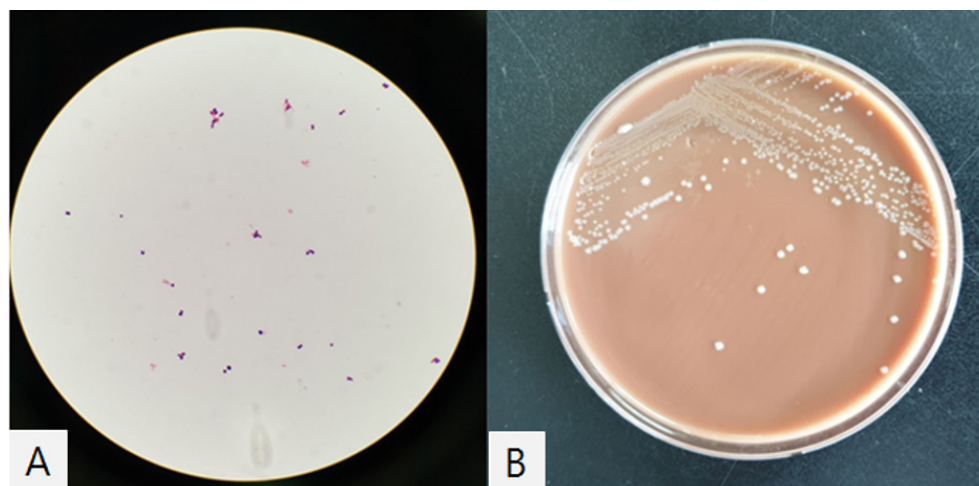
A 65-year-old man presented to an outpatient clinic with persistent fever for a month and newly onset severe headache. The patient underwent aortic valvuloplasty owing to infective endocarditis with aortic stenosis 28 and 22 years ago, respectively. He had admitted to the hospital for three times with prosthetic valve endocarditis during the previous 11 years and the last episode was placed a year ago. The causative pathogens of each episode were *Enterococcus avium*, *Enterococcus faecalis*, and *Streptococcus gallolyticus*, respectively. Besides, he had diabetes mellitus, hypertension, dyslipidemia, and alcoholic liver cirrhosis as underlying diseases.

On admission, his vital signs were as follows: body temperature, 37.7 °C; pulse rate, 72/min; respiration rate, 20/min; and blood pressure, 120/80 mmHg. Petechiae were observed on his trunk but no Janeway lesions or Osler's nodes existed. There was no conjunctival hemorrhage and Roth spot was not detected on ophthalmic examination. Cardiac murmur was not heard on aortic, pulmonary, tricuspid, and mitral area. In addition, neurological deficit including localizing and lateralizing sign was not observed in both upper and lower extremities.

The initial laboratory examination revealed a white blood cell count of 6,600 cells/mm<sup>3</sup>, hemoglobin of 8.2 g/dL, platelet count of 105 × 10<sup>3</sup> cells/mm<sup>3</sup> and C-reactive protein (CRP) level of 5.86 mg/dL. Electrocardiography showed atrial fibrillation with controlled ventricular response and some ventricular premature complexes. Chest and abdomen computed tomography (CT) scans were performed for differential diagnosis of fever, and there was no abnormal finding suggesting infectious syndrome.

On transesophageal echocardiography (TEE), a 1.2 cm sized linear hypermobile structure was found at left ventricular outflow tract. Taking together, these findings with the positive result of blood cultures obtained at the 30 day of fever indicated a diagnosis of prosthetic valve endocarditis; *Rothia mucilaginosa* was reported from one blood culture bottle among 4 sets of blood culture samples which were collected in BacT/ALERT Aerobic and Anaerobic standard bottles (bioMérieux, Durham, NC, USA) through an automated blood culture system (BacT/ALERT 3D; bioMérieux). Gram-stained smears of cultured media revealed gram-positive cocci in small irregular clusters. The colonies on chocolate agar were whitish to grey in color, non-hemolytic, smooth and mucoid (Fig. 1). The colonies did not grow on the blood agar plate. 16S rRNA sequencing confirmed the species as *R. mucilaginosa* with 99% of identity. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS; Bruker Daltonics, Billerica, MA, USA) identified the strain as *R. mucilaginosa* (highest score = 2.092).

At the day of admission, brain magnetic resonance imaging (MRI) was taken for evaluation of headache,



**Fig. 1.** Microbiological examinations. A. *Rothia mucilaginosa* Gram staining ( $\times 1,000$ ) B. Whitish to grey *Rothia mucilaginosa* colonies grown on chocolate agar plate at 35°C and 5% CO<sub>2</sub>.

which showed multiple microhemorrhages suggesting septic emboli on both hemisphere, corticomedullary junction area and cerebellum.

We started vancomycin, rifampin, and ceftriaxone as an empirical therapy accordingly and the clinical response to the antibiotic therapy was good; his body temperature became normalized and CRP level decreased.

Since no Clinical and Laboratory Standards Institute (CLSI) protocols exist for *R. mucilaginosa*, we performed antimicrobial susceptibility test using CLSI criteria for staphylococci (M100-S21), as described previously [6]. The result of antimicrobial susceptibility test was reported on hospital day 7 (Table 1), and we changed antibiotic regimen to ampicillin and rifampin.

**Table 1.** Antibiotic susceptibility of *Rothia mucilaginosa*

Antibiotics	Susceptibility*	Inhibition zone diameter (mm)	Minimal inhibitory concentration (µg/mL)
Penicillin	S	46	-
Ampicillin-sulbactam	S	45	-
Clindamycin	R	11	-
Erythromycin	S	42	-
Rifampin	S	43	-
Tetracycline	S	34	-
Levofloxacin	S	30	-
Trimethoprim-sulfamethoxazole	R	0	-
Tobramycin	R	0	-
Vancomycin	S	-	1

\* The drug susceptibility of *Rothia mucilaginosa* in the present case was determined by using disk diffusion test according to the 2011 Clinical and Laboratory Standards Institute (M100-S21) criteria for staphylococci. The vancomycin susceptibility was determined by E-test because the disk test is not available for differentiating among vancomycin-susceptible, -intermediate, and -resistant isolates of *Staphylococcus* spp.

Abbreviations: S,susceptible; R,resistant.

On hospital day 11, the patient presented gait disturbance with aggravation of headache. Follow-up brain CT and magnetic resonance angiography were performed: newly developed intracranial hemorrhage at left temporal lobe and head of caudate nucleus was observed without vascular malformation such as mycotic aneurysm. Dysphagia and proximal muscle weakness on upper extremities were aggravated gradually and increased size of intracranial hemorrhage was found at follow up brain CT on hospital day 24. After changing antibiotics from ampicillin to vancomycin again, his symptoms were stabilized and there was no progression in neurologic sign.

However, on hospital day 56, the patient's mental status became stuporous and he was transferred to intensive care unit. Follow-up brain CT showed newly developed intracranial hemorrhage at left parietal region, and intraventricular hemorrhage in both lateral ventricles. The antibiotic regimen was maintained with vancomycin and rifampin and his neurologic symptoms and signs showed waxing and waning. On hospital day 67, he was transferred to general ward and finally was transferred to another hospital for his family's request on hospital day 75. Right side motor weakness remained as a sequela to the patient.

## DISCUSSION

Since the first case report of infective endocarditis caused by *Rothia* spp., a total of 39 cases of *Rothia* spp. associated infective endocarditis have been reported. The majority of identified pathogens were *Rothia dentocariosa* (66.7%, 26/39), followed by *Rothia aeria* (17.9%, 7/39) and *R. mucilaginosa* (15.4%, 6/39). One of the most important underlying conditions for acquisition of *Rothia* spp. associated invasive diseases is dental or periodontal diseases [1]. Immunocompromised conditions such as hematological malignancy, severe neutropenia, diabetes mellitus, alcoholism, chronic liver disease and HIV infection are known to be another important risk factor [1].

Among the reported infective endocarditis cases due to *Rothia* spp., 41% (16/39) had intracranial complications, which was higher proportion compared with general infective endocarditis patients; symptomatic neurological complications occur in 15%–30% of patients with infective endocarditis and are mainly the consequence of embolism from vegetations [7]. The exact reason for the higher rate of intracranial complication in *Rothia* spp. associated infective endocarditis is yet to be identified.

The reported cases of infective endocarditis with intracranial complications are summarized in Table 2. The most common presentation was intracranial hemorrhage (37.5%, 6/16), followed by septic emboli (25.0%, 4/16), mycotic aneurysm (25.0%, 4/16), cerebral infarction (18.7%, 3/16), and brain abscess (12.5%, 2/16). Among them, 75% (12/16) of patients had risk factors for *Rothia* spp. associated invasive diseases: 7 with dental or periodontal diseases, 3 with immunocompromised condition, and 8 with cardiac valve diseases.

The optimal antimicrobial treatment of *R. mucilaginosa* infection has not been determined. According to the previous case reports, the organism seems to be susceptible to a variety of antibiotics targeting gram-positive pathogens such as ampicillin, rifampin, and vancomycin [3]. However, the pathogen was frequently resistant to penicillin, clindamycin and aminoglycosides as well as to trimethoprim-sulfamethoxazole

**Table 2.** Reported cases of infective endocarditis with intracranial complications

Author	Year	Age/Sex	Risk factors	Pathogen	Antibiotic therapy	Intracranial complications	Outcome
Issacson et al. [Am J Med 1988; 84: 352-4]	1988	27/F	Bicuspid aortic valve Periodontal abscess	<i>R.dentocariosa</i>	Penicillin + Gentamicin	Brain abscess	Cure (No sequelae)
Shands et al. [Am J Med 1988; 85: 280-1]	1988	41/M	Mitral regurgitation	<i>R.dentocariosa</i>	Vancomycin + Gentamicin, then Penicillin + Gentamicin	Intracranial mycotic aneurysms with cerebral hemorrhage	Cure (No sequelae)
Binder et al. [Infection 1997; 25: 22-6]	1997	70/M	Alcohol abuse Carios teeth Mitral regurgitation Aortic insufficiency	<i>R.dentocariosa</i>	Penicillin + Vancomycin + Netilmicin	Multiple brain abscesses, mitral insufficiency requiring reconstruction and replacement	Cure (No sequelae)
Binder et al. [Infection 1997; 25: 22-6]	1997	50/M	Periodontitis Prosthetic aortic valve	<i>R.dentocariosa</i>	Rifampin + Ceftriaxone	Aortic root abscess, intracerebral hemorrhage attributed to intracranial mycotic aneurysms	Unknown
Ricaurte et al. [South Med J 2001;9 4:438- 40]	2001	49/M	Undefined heart murmur Dental work (root canal)	<i>R.dentocariosa</i>	Cefotaxime, then Vancomycin + Gentamicin	Right frontoparietal hematoma	Cure (No sequelae)
Boudewijns et al. [7]	2002	17/F	Congenital bicuspid valve	<i>R.dentocariosa</i>	Penicillin + Amikacin	Intracranial mycotic aneurysms with subarachnoid hemorrhages, aortic root abscess requiring replacement	Death
Sadhu et al. [Diagn Microbiol Infect Dis 2005; 53: 239-40]	2005	55/M	Diabetes mellitus Liver cirrhosis Dental abscess	<i>R.dentocariosa</i>	Penicillin + Gentamicin	Cerebellar hemorrhages	Cure (No sequelae)
Chowdhary et al. [Am J Med Sci 2015; 350: 239-40]	2015	34/M	Intravenous drug user	<i>R.dentocariosa</i>	Vancomycin + Ceftriaxone + Doxycycline	Septic emboli to right middle cerebral artery	Cure (No sequelae)
Fridman et al. [Tex Heart Inst J 2016; 43: 255-7]	2016	58/M	None	<i>R.dentocariosa</i>	Penicillin, then Vancomycin + Ceftazidime	Cerebral mycotic aneurysm, endogenous endophthalmitis	Cure (No sequelae)
Willner et al. [4]	2018	62/F	None	<i>R.dentocariosa</i>	Vancomycin + Ceftriaxone, then Penicillin	Acute or subacute infarctions	Death
Tarumoto et al. [Intern Med 2012; 51: 3295-9]	2012	40/M	None	<i>R.aeria</i>	Ceftriaxone + Gentamicin	hemorrhagic infarction with left posterior cerebral artery region	Cure (No sequelae)
Hiraiwa et al. [Eur J Intern Med 2013; 24 Suppl 1: e204]	2013	63/M	Kidney transplantation Dental caries	<i>R.aeria</i>	Penicillin	Brain septic emboli	Cure (No sequelae)
Thiyagarajan et al. [BMJ Case Rep 2013. Doi: 10.113 6/bcr-2013-200534]	2013	61/M	Tooth extraction	<i>R.aeria</i>	Penicillin + Rifampicin + Gentamicin	Septic emboli in temporal artery	Cure (No sequelae)
Crowe et al. [Infection 2014; 42: 419-23]	2013	48/M	None	<i>R.aeria</i>	Penicillin + Gentamicin, then Rifampicin + Ciprofloxacin	Brain septic emboli	Cure (No sequelae)
Collarino et al. [New Microbes New Infect 2016; 13: 40-2]	2016	57/M	Severe mitral insufficiency	<i>R.aeria</i>	Amoxicillin + Gentamicin	Left frontal subarachnoid hemorrhage	Cure (No sequelae)
Pinsky et al. [J Clin Microbiol 1989; 27: 215-6]	1989	35/M	Intravenous drug user	<i>R.mucilaginosa</i>	Vancomycin + Gentamicin	Left frontal lobe infarction	Cure (No sequelae)

and ciprofloxacin [1]. Although the antimicrobial susceptibility test showed the organism is susceptible to ampicillin, vancomycin and rifampin, rapid progression of neurologic symptoms and signs with aggravation of cerebral hemorrhage were observed in the present case after changing antibiotic regimen from vancomycin to ampicillin. Interestingly, his neurologic symptoms started to improve after changing antibiotic regimen from ampicillin to vancomycin again. Further studies are necessary to clarify this issue.

In South Korea, one case of infective endocarditis caused by *R. aeria* was reported in the patient taking immunosuppressive medication and the patient was successfully treated without intracranial complications [5]. To the best of our knowledge, this is the first case of infective endocarditis with cerebral hemorrhage caused by *R. mucilaginosa* in South Korea. Clinicians should consider *Rothia* spp. as a possible pathogen in the cases of infective endocarditis with intracranial complications.

## 요약

*Rothia* 종은 호기성 그람양성구균으로 *Micrococcaceae* 과에 속하며, 사람의 구인두 및 상부 호흡기의 정상 세균총이다. *Rothia mucilaginosa*에 의한 뇌출혈을 동반한 인공판막 심내막염 국내 첫 증례가 확인되었기에 보고한다. 인공 대동맥판막 수술력이 있는 65세 남자 환자가 발열을 주소로 본

원 감염내과 외래에 내원하였다. 발열 후 30일째 시행된 혈액배양검사 중 한쌍에서 *R. mucilaginosa* 가 동정되었다. 뇌 자기공명영상검사에서 양쪽 대뇌반구, 피질과 수질의 접합부, 소뇌에서 패혈성 색전증을 시사하는 미세출혈 소견이 확인되었다. 뇌출혈을 동반한 감염성 심내막염에서 *Rothia* 종은 원인균으로 고려되어야 한다.

## CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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