Pyogenic ventriculitis complicating *Aggregatibacter aphrophilus* infective endocarditis: A case report and literature review

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Pyogenic ventriculitis (PV) is an uncommon, but frequently fatal infection that results from inflammation of the ventricular ependymal lining associated with a purulent ventricular system. PV has been rarely reported as a secondary complication of infective endocarditis. Prompt diagnosis and treatment with appropriate culture-directed antibiotics with adequate central nervous system penetration is crucial when managing patients who are suspected of having PV. The present study reports on a fatal case of a previously well 42-year-old alcoholic woman with infective endocarditis caused by *Aggregatibacter aphrophilus*, with secondary brain abscess and spontaneous rupture into the ventricles causing PV.

Key Words: Aggregatibacter aphrophilus; *Community-acquired; HACEK;* Haemophilus aphrophilus; *Infective endocarditis; Meningitis*

Une ventriculite pyogène compliquant une endocardite infectieuse à *Aggregatibacter aphrophilus* : Un rapport de cas et une analyse bibliographique

La ventriculite pyogène (VP) est une infection peu courante mais souvent fatale qui découle de l'inflammation du revêtement épendymaire du ventricule et s'associe à un système ventriculaire purulent. Le VP est rarement déclaré à titre d'infection secondaire de l'endocardite infectieuse. Un diagnostic et un traitement rapides à l'aide d'antibiotiques pertinents selon les résultats des cultures et assurant une pénétration suffisante du système nerveux central sont essentiels pour prendre en charge les patients chez qui on présume une VP. La présente étude fait état du cas fatal d'une femme alcoolique de 42 ans auparavant bien, atteinte d'une endocardite infectieuse causée par l'*Aggregatibacter aphrophilus* accompagnée d'un abcès cérébral secondaire et d'une rupture spontanée des ventricules entraînant le VP.

Pyogenic ventriculitis (PV), also called ependymitis, ventricular empyema and pyocephalus, results from inflammation of the ventricular ependymal lining associated with a purulent ventricular system. PV predominately occurs in patients with previous head trauma, or those undergoing prolonged intraventricular surgery and placement of drains and shunts into the ventricular space (1). Less frequent causes include ruptured brain abscesses, extension of dental abscesses and progression of meningitis into the ventricles (2-4). PV has rarely been reported as a complication of infective endocarditis (IE) (3).

CASE PRESENTATION

A 42-year-old Caucasian woman was admitted to hospital after being found at home with a reduced level of consciousness and incontinence of urine. She had been unwell for two months with progressive fatigue and left-sided chest discomfort before the onset of nausea, vomiting and increasing lethargy for three days preceding admission. Her medical history was remarkable only for nicotine and alcohol abuse. Her admission vitals revealed a fever of 40.2°C, respiration rate of 28 breaths/min, heart rate of 140 beats/min and a blood pressure of 138/77 mmHg. Her physical examination was notable for poor oral hygiene with multiple dental caries and broken teeth, reduced level of consciousness with a Glasgow Coma Score of 8 and a new systolic ejection murmur. She lacked peripheral stigmata of IE and had no focalizing neurological signs. She was intubated, ventilated and transferred to the intensive care unit for investigations and management.

Initial investigations revealed a white blood cell count of 23.2×10^9/L (20.6×10^9/L neutrophils), a platelet count of 415×10^9/L and a hemoglobin level of 150 g/L. Blood, urine, cerebral spinal fluid (CSF) and pleural fluid were cultured for microbial pathogens. Serum chemistry was within normal limits, with the exception of hypokalemia of 2.4 mmol/L. Computed tomography (CT) of her head demonstrated several ring-enhancing intraparenchymal cerebral abscesses – the largest in the left occipital lobe with surrounding edema extending into the lateral ventricle (Figure 1). The ventricles were opacified and had a heterogeneous appearance consistent with pyogenic debris, resulting in mild hydrocephalus. Subsequent CSF analysis revealed frank pus, a pleocytosis of $17{,}250\times10^6$/L white blood cells (89% neutrophils), a protein level of 9 g/L and a glucose level of less than 0.5 mmol/L. Chest imaging with an enhanced CT revealed a large pulmonary abscess in the left lower lobe, with an associated empyema (Figure 2). Transesophageal echocardiogram demonstrated a mobile vegetative mass of 0.6 mm on the noncoronary cusp of the aortic valve.

The patient received empirical antibiotic therapy within 2 h of presentation, which consisted of 2 g of intravenous ceftriaxone every 12 h, 500 mg of intravenous metronidazole every 8 h and 1 g of intravenous vancomycin every 12 h. Intravenous dexamethasone (4 mg) every 6 h was added 4 h after presentation following the CT scan, showing cerebral edema secondary to multiple ring-enhancing lesions. Surgical management including intraventricular drains for intrathecal

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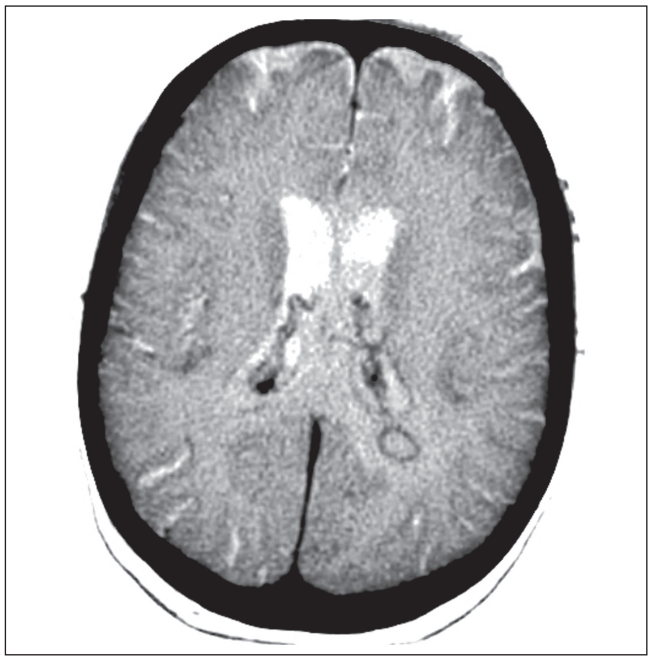

Figure 1) *Contrast-enhanced computed tomography scan revealing bilateral intraventricular debris and enhancement of the posterior aspect of the lateral ventricles, choroid plexus and subependymal regions. The largest of the multiple ring-enhancing lesions, measuring 1.4 cm × 0.8 cm, is also visualized with surrounding edema posteriorly to the left lateral ventricle*

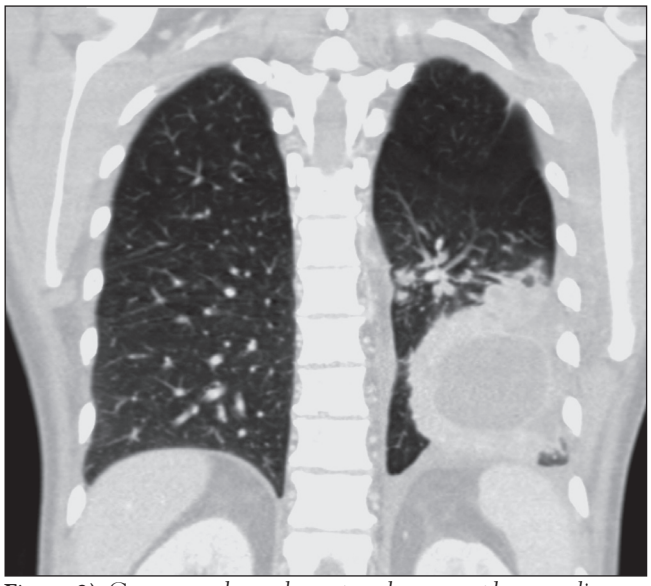

Figure 2) *Contrast-enhanced computed tomography revealing an isolated 6.7 cm × 3.6 cm rim enhancing heterogeneous fluid collection with a small amount of gas in the left lower lobe of the lung*

administration of antibiotics was deferred given her initial tenuous status. Unfortunately, her neurological status failed to improve after 48 h, and subsequent neuroimaging studies demonstrated diffuse vasospasm and bilateral anterior and middle cerebral artery evolving infarcts secondary to further septic emboli. After lengthy discussions with her family, the focus of care was changed to comfort measures, and the patient died seven days following her original presentation. The family declined an autopsy. An initial set of aerobic and anaerobic blood cultures drawn at presentation, before antibiotic administration, failed to grow a pathogen despite four days incubation in BacT/ALERT 2D automated instrument (bioMerieux Canada, Inc), as did daily serial blood cultures following antibiotic administration. CSF cultures collected 12 h following antimicrobial administration were sterile. The only culture that yielded a microbiological diagnosis was that of the pleural fluid drawn 26 h after admission, which grew a Gram-negative coccobacilli confirmed by standard biochemical methods and 16S rDNA polymerase chain reaction to be *Aggregatibacter aphrophilus*, susceptible to ampicillin, cefotaxime, ceftriaxone, gentamicin and chloramphenicol. The patient was presumed to have developed *A aphrophilus* IE (possible endocarditis by modified Duke criteria) and subsequent embolic brain abscesses and pyogenic ventriculitis secondary to an aspiration-induced pulmonary abscess during a period of intoxication. The patient's major underlying risk factor was her poor oral hygiene.

DISCUSSION

Bacterial brain abscesses are a focal suppurative process involving the brain parenchyma that can arise by extension of contiguous infections (such as sinusitis and dental abscess), direct inoculation (penetrating head injury and neurosurgical procedures) or hematogenous spread from distant sources (5). Accordingly, the microbial pathogens causing brain abscesses vary depending on the etiological pathogenesis of the abscess. With the advent of new diagnostic modalities (such as CT and magnetic resonance imaging), improved surgical techniques and newer therapeutics including third-generation cephalosporins, the mortality secondary to bacterial brain abscesses has fallen from 30% to 60% in the 1970s to approximately 10% in the 1990s (6). Factors associated with increased risk of mortality from bacterial brain abscess include deep-seated location of infection, host immune suppression, Glasgow Coma Score lower than 9 on presentation, intraventricular rupture of the abscess and secondary pyogenic ventriculitis (6,7).

Symptoms associated with a ruptured cerebral abscess into a lateral ventricle are nonspecific but may include headache, fever, focal neurological deficits, seizure and nuchal rigidity (6,7). The diagnosis is typically made via a combination of CSF analysis revealing gross purulence and marked abnormalities, and neuroimaging findings. The radiological findings most consistent with a diagnosis of ventriculitis include intraventricular debris (secondary to accumulation of proteinacious material and tissue necrosis [94%]) and hydrocephalus (secondary to blockages of the aqueduct of Sylvius or the foramina of Luschka and Magendie [76%]) (2). Magnetic resonance imaging is more sensitive at identifying periventricular signal abnormalities consistent with ependymal lining inflammation.

Interestingly, despite the varying etiologies of bacterial brain abscess, bacteria that comprise the normal oropharyngeal flora are responsible for a disproportionate burden of disease (8). *A aphrophilus*, formerly *Haemophilus aphrophilus*, is a fastidious Gram-negative organism that is a normal member of the human oropharyngeal flora. While it is not responsible for odontogenic disease, it is a rare cause of invasive disease (sinusitis, pneumonia, empyema, skin and soft tissue infection, and

bone and joint infection) and has infrequently been linked to central nervous system disease (4,9). *A aphrophilus* is most notable for its inclusion in the HACEK (*Haemophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella*) grouping of organisms causing community-acquired IE (10,11). *H aphrophilus*, along with *Haemophilus paraphrophilus* and *A actinomycetemcomitans* have been reclassified within the newly created genus, *Aggregatibacter* (Nørskov-Lauritsen), on the basis of commonality of nucleic acid sequences of housekeeping genes (12). Furthermore, this change recognizes the X factor independence of these organisms, distinguishing them from *Haemophilus* species. *A aphrophilus* is known to be exquisitely sensitive to antimicrobials, and failure to isolate it from sterile fluids, such as blood and CSF, is common following antimicrobial exposure, as illustrated by the present case (11,13).

While HACEK organisms gained notoriety as traditionally difficult-to-culture causes of IE, they are no longer viewed as difficult to identify. With advancing technology, it has been repeatedly demonstrated that the isolation of HACEK organisms may be achieved with modern automated blood-culturing systems after four days of liquid media growth. In fact, HACEK organisms are routinely identified following incubation for a mean of three days and median of 3.4 days (10). Extended incubation of blood cultures to identify HACEK pathogens has been suggested to be unnecessary in routine circumstances. In the present case, a single set of blood cultures before antibiotics failed to identify *A aphrophilus* despite 96 h of incubation. Terminal subcultures on solid media held for five days were similarly negative. Alternatively, the organism was identified from anaerobic cultures of an empyema after 48 h of growth on chocolate agar.

The negative clinical outcome in the present case appears to be associated with the nature of PV rather than the virulence of the organism per se. *Haemophilus/Aggregatibacter* species endocarditis is typically associated with a mild clinical course once diagnosis is made, with a mortality rate of lower than 10% (11,13). This is true even in the case of spread to the central nervous system confined as cerebral abscesses or meningitis (14,15). However, PV is frequently associated with high rates of morbidity and mortality (7). This is particularly true when PV is secondary to ruptured intracerebral abscess relative to contamination of nosocomial ventricular drains (1,7). Factors associated with the development of secondary PV from brain abscesses include embolic spread and deep parenchymal location (7). Kiyan et al (3) described a similarly fatal case of IE complicated by intracerebral abscess and subsequent PV also caused by a relatively benign pathogen, coagulase-negative staphylococci.

Early empirical therapy is critical in the management of PV secondary to ruptured intracerebral abscesses. Broad-spectrum antibiotics that achieve high levels within the CSF will form the cornerstone of therapy (16). Glucocorticosteroids may be used if substantial mass effect exists, and surgical drainage either via craniotomy and open drainage or a stereotactic approach should be considered early in the management of the patient (6). Furthermore, surgically placed intraventricular drains may further enable the direct administration of an intrathecal antibacterial, such as vancomycin, colistin and aminoglycosides, to enhance sterilization. However, even with optimal combined medical and surgical management, intracerebral abscesses complicated by PV are frequently associated with very high case-fatality rates.

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REFERENCES

1. Lyke KE, Obasanjo OO, Williams MA, O'Brien M, Chotani R, Perl TM. Ventriculitis complicating use of intraventricular catheters in adult neurosurgical patients. Clin Infect Dis 2001;33:2028-33.
2. Fukui MB, Williams RL, Mudigonda S. CT and MR imaging features of pyogenic ventriculitis. Am J Neuroradiol 2001;22:1510-6.
3. Kiyan S, Aksay E, Ersel M, Yanturali S. A rare diagnosis in ED: Cerebral pyogenic ventriculitis due to infective endocarditis. Am J Emerg Med 2007;25:120-2.
4. Kao PT, Tseng HK, Su SC, Lee CM. *Haemophilus aphrophilus* brain abscess: A case report. J Microbiol Immunol Infect 2002;35:184-6.
5. Tonon E, Scotton PG, Gallucci M, Vaglia A. Brain abscess: Clinical aspects of 100 patients. Int J Infect Dis 2006;10:103-9.
6. Xiao F, Tseng MY, Teng LJ, Tseng HM, Tsai JC. Brain abscess: Clinical experience and analysis of prognostic factors. Surg Neurol 2005;63:442-50.
7. Takeshita M, Kagawa M, Izawa M, Takakura K. Current treatment strategies and factors influencing outcome in patients with bacterial brain abscess. Acta Neurochir 1998;140:1263-70.
8. Gendron R, Grenier D, Maheu-Robert L. The oral cavity as a reservoir of bacterial pathogens for focal infections. Microbes Infect 2000;2:897-906.
9. Paju S, Carlson P, Jousimies-Somer H, Asikainen S. *Actinobacillus actinomycetemcomitans* and *Haemophilus aphrophilus* in systemic and nonoral infections in Finland. APMIS 2003;111:653-7.
10. Petti CA, Bhally HS, Weinstein MP, Joho K, Wakefield T, Reller LB, Carroll KC. Utility of extended blood culture incubation for isolation of *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* organisms: A retrospective multicenter evaluation. J Clin Microbiol 2006;44:257-9.
11. Das M, Badley AD, Cockerill FR, Steckelberg JM, Wilson WR. Infective endocarditis caused by HACEK microorganisms. Annu Rev Med 1997;48:25-33.
12. Norskov-Lauritsen N, Kilian M. Reclassification of *Actinobacillus actinomycetemcomitans*, *Haemophilus aphrophilus*, *Haemophilus paraphrophilus* and *Haemophilus segnis* as *Aggregatibacter actinomycetemcomitans* gen. nov., comb. nov., *Aggregatibacter aphrophilus* comb. nov. and *Aggregatibacter segnis* comb. nov., and emended description of *Aggregatibacter aphrophilus* to include V factor-dependent and V factor-independent isolates. Int J Syst Evol Microbiol 2006;56:2135-46.
13. Darras-Joly C, Lortholary O, Mainardi JL, Etienne J, Guillevin L, Acar J. Haemophilus endocarditis: Report of 42 cases in adults and review. Clin Infect Dis 1997;24:1087-94.
14. Wolf J, Curtis N. Brain abscess secondary to dental braces. Pediatr Infect Dis J 2008;27:84-5.
15. Adeyemi-Doro FA, Hui AC, Ho FN, Ip M. *Haemophilus aphrophilus* meningitis complicated by hydrocephalus in an immunocompetent adult. Infection 1998;26:405-7.
16. Jansson AK, Enblad P, Sjolin J. Efficacy and safety of cefotaxime in combination with metronidazole for empirical treatment of brain abscess in clinical practice: A retrospective study of 66 consecutive cases. Eur J Clin Microbiol Infect Dis 2004;23:7-14.