PEER REVIEWED LETTER

Cryptogenic Methicillin-Resistant Staphylococcus Aureus Brain Abscess

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We present an unusual case of cryptogenic methicillin-resistant *Staphylococcus aureus* brain abscess in which a patent foramen ovale was found at autopsy.

Clinical Presentation

An immunocompetent 51-year-old Amish male from Southwestern Ontario presented with new onset seizure. He had a history of excessive alcohol use, and a remote history of illicit drug use, but no drug use in the preceeding six months. There was no recent hospitalization or antimicrobial use, and his HIV status is not known. Initial CT neuroimaging with contrast demonstrated areas of low attenuation posteriorly in the left cerebral hemisphere, most consistent with old infarction. He was started on Dilantin and over the following months no further seizures occurred, but his family reported him to be mildly confused and unsteady on his feet. Two months later he developed worsening confusion, right sided weakness, and his level of consciousness deteriorated suddenly. Key findings on physical exam included normal heart and lung sounds, no fever, a supple neck, and right arm and leg weakness. Bloodwork demonstrated a white blood cell count of 14.6 X 10^9/L, normal liver enzymes and an ethanol level of 0.1 mmol/L. No urine toxicology studies were performed.

The CT imaging at this point showed two ring enhancing lesions in the left cerebral hemisphere consistent with abscesses, the largest measuring 3.3 cm, as well as marked white matter edema and 1.1 cm midline shift (Figures 1a & 1b).

The patient was started on IV vancomycin, cefotaxime and metronidazole. The larger abscess was drained of 10 cc through a burr hole and the culture grew methicillin-resistant *Staphylococcus aureus* (MRSA), which was sensitive to vancomycin. The molecular type was MRSA-1028 (CMRSA10). Subsequent blood cultures also grew MRSA, though the patient did not develop sepsis clinically. His neurological status did not improve and neuroimaging demonstrated increasing swelling, mass effect and low attenuation (ischemia) of the posterior fossa. He died on post-operative day two.

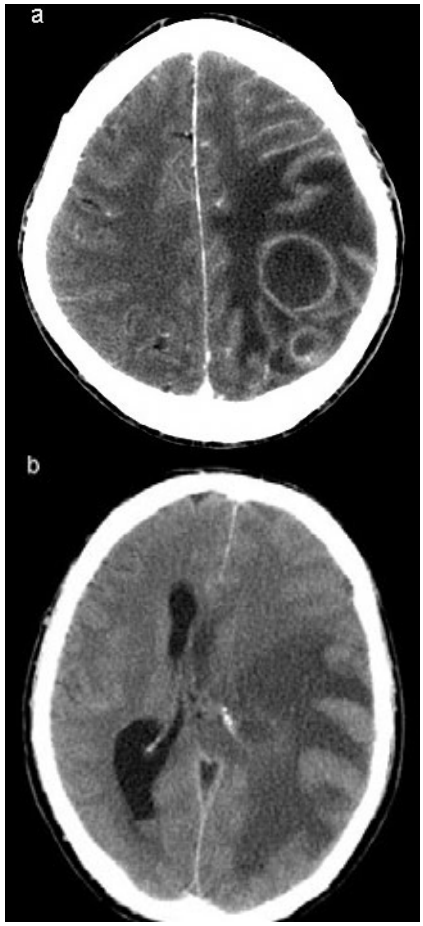

Figure 1. *a – CT head demonstrating two ring enhancing intra-parenchymal brain lesions; b – lesions were associated with surrounding edema and midline shift*

Pathology

No systemic source of infection was found at general autopsy. Notably, there were no skin lesions of an infectious nature or findings suspicious of IV drug use. No pneumonia, endocarditis, or other infectious sources were noted. A 0.2 cm opening was present in the foramen ovale.

The brain was swollen. The basal leptomeninges were purulent and there was right uncal and tonsillar herniation

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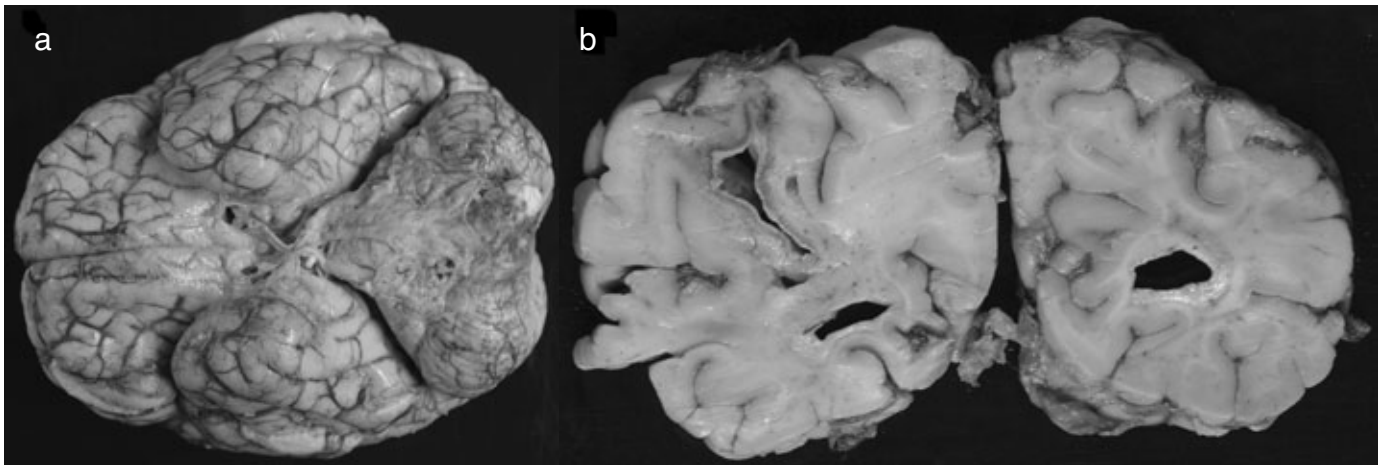

Figure 2. *a – purulent basal leptomeninges and right uncal and tonsillar herniation; b – coronal brain slice through the occipital lobes showing partially encapsulated left intracerebral abscess with rupture into the lateral ventricle*

(Figure 2a). Serial coronal slices confirmed two intra-cerebral abscesses: the larger within the left posterior parieto-occipital region measuring 6 x 3 cm (Figure 2b). The abscesses were partially encapsulated, but a rupture site into the occipital horn of the left lateral ventricle was seen and there was purulent material within the ventricles.

Histology confirmed severe basal meningitis containing gram positive cocci (Figure 3b). The abscess contained four distinct layers (Figure 3a) with partial encapsulation. The rupture site was characterized by a breach in the capsule with adjacent ventriculitis.

Discussion

Presentation, Location and Source of Brain Abscess

The most common presentations of brain abscess are confusion or decreased level of consciousness (59% of cases) and headache (49%), and seizures occur in 25% of cases.[1] The location of a brain abscess depends on the source of infection. According to a review of brain abscesses from Dublin by Roche et al,[2] the most common location is within the frontal lobe (32%), which can be due to local spread from an orbital cellulitis or frontal sinusitis. Similarly, temporal lobe abscesses can result

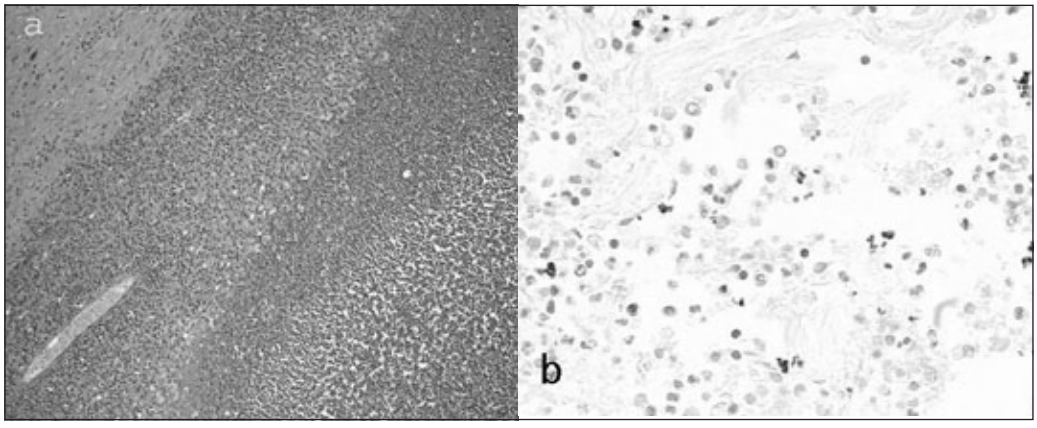

Figure 3. *a – the histology of the abscess showed 4 distinct layers (H&E x 100); b – the innermost layer of the abscess contained a mixed inflammatory infiltrate, necrotic debris and gram positive cocci (Gram's method X 400)*

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from spread from an adjacent mastoiditis.[2] The proportion of brain abscesses due to contiguous spread from the sinuses or mastoiditis may be decreasing, and a recent review by Carpenter reported only 24% of cases had a contiguous focus of infection in the sinus or ear.[3] Hematogenous spread from a peripheral source (such as pneumonia or endocarditis) causes 9.8% of cases. In a subset of cases there is a pre-disposing underlying medical condition such as congenital heart disease, HIV, IV drug use, diabetes or alchoholism.[1,2] In 19% of cases no source of infection can be identified, and these are considered cryptogenic.[2]

Methicillin Resistant Staphylococcus Aureus

Numerous surveillance studies in the United States have confirmed that MRSA is common among *Staphylococcus aureus* isolated in hospitals and more recently in the community. Community-acquired MRSA (CA-MRSA) is isolated from individuals who had no recent exposure to the health care system or from patients who harboured the infection at the time of admission. The SENTRY study reported a steady increase in methicillin resistance among nosocomial and community-acquired *Staphylococcus aureus* isolated in the three year period between January 1, 1997 and December 31, 1999.[3] For nosocomial strains, the rate of methicillin resistance increased from 34% to 45%, while for community acquired strains, it increased from 22% to 28%. In some communities in the United States, up to 75% of community isolates of *Staphylococcus aureus* are methicillin resistant.[4] The prevalence of CA-MRSA in Canada is not known but considered low. The most common infections resulting from CA-MRSA involve the skin and soft tissue, though cases of fatal, invasive CA-MRSA infections have occurred in children.[5]

Patients infected with hospital-acquired MRSA (HA-MRSA) are more likely to be older whereas CA-MRSA is more common among children.[6] In addition, HA-MRSA and CA-MRSA show differences in molecular typing and antimicrobial susceptibility pattern. Further, CA-MRSA are often Panton-Valine leukocidin (PVL) positive.[7] Panton-Valine leukocidin toxin stimulates release of cytokines from leukocytes and causes necrosis and abscess formation. Infection associated with PVL-positive strains tend to occur in children and young adults and are associated with a higher mortality.[8,9] In Canada, based on molecular typing ten major CA-MRSA clusters, CMRSA-1 to CMRSA-10 have been identified.[10] The CMRSA-10 clone (equivalent to USA300) has emerged as the predominant cause of infections in North America and is usually PVL-positive.[11]

A study of the incidence and risk factors for MRSA infection in Southwestern Ontario reported in 2000 stated that the local annual incidence of MRSA infection was 37/100,000, and the most common sites of infection were the urinary tract, surgical wounds, skin ulcers and lower respiratory tract. Only 9.4% of MRSA cases were community acquired, and the most common risk factor for MRSA infection was recent hospitalization.[12]

MRSA and Brain Abscess

Positive microbial cultures are identified in 73% of cases of brain abscess. The majority are caused by gram positive bacteria, notably *Streptococcus* (35%) and *Staphylococcus* (21%). In the Roche et al series, most brain abscesses due to *Staphylococcus* were sensitive to methicillin (17.5%), while the remaining 3.2% were methicillin-resistant.[2] According to a study of microbial resistance in central nervous system (CNS) specimens from across the USA, the proportion of *Staphylococcus aureus* isolates from brain abscesses that were also resistant to oxacillin was 33%.[13]

In a recent retrospective analysis of brain abscesses from London, England, eight out of 49 brain abscesses were due to *Staphylococcus aureus*, all occurred in either a post traumatic or post neurosurgical setting, and two of the eight were resistant to methicillin.[1] There were five brain abscesses caused by MRSA in the Roche et al series, four of which were either post-neurosurgical patients or had sustained recent head trauma. All five cases had what are considered risk factors for MRSA infection, including recent ICU admissions, intubation and ventilation, and/or the placement of central lines.[2] Other reported cases of MRSA brain abscesses are similar, including a Scandinavian case in which MRSA brain abscess developed after resection of a brain tumour.[14]

Outcomes for patients with MRSA brain abscesses has not been thoroughly studied. The overall mortality rate for brain abscesses is decreasing, however rupture of a brain abscess into the ventricular system remains a devastating complication, often resulting in death.[1]

Patent Foramen Ovale (PFO) and Brain Abscess

Autopsy studies have demonstrated a PFO in 20-35% of adults and though they are usually clinically silent, trans-esophageal imaging studies have shown right to left shunting of blood with Valsalva maneuvers.[15] Patent Foramen Ovale has been suggested to be a potential source of embolism leading to cryptogenic stroke.[15] There have been four reported cases describing an association between crytopgenic brain abscess and PFO.[16] Proposed explanations for this association include poor dental hygiene resulting in systemic oral flora who gain access to the arterial system via a PFO. Alternatively, a PFO may be a predisposing factor to hematogenous spread from a primary silent focus.

Conclusions

This case demonstrates that MRSA can be a cause of brain abscess. However, this is the first reported case of an MRSA brain abscess where no source of infection was detected on complete post-mortem examination. It also illustrates that a Patent Foramen Ovale may play a role in some cases of crytogenic brain abscess.

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