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Case Report

*Streptococcus gallolyticus* subsp. *pasteurianus* meningitis complicated by venous sinus thrombosis: A case report

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A B S T R A C T

A case of *Streptococcus gallolyticus* subsp. *pasteurianus* meningitis, unusually occurring in a splenectomized patient and complicated by cerebral venous thrombosis, is described. Following presentation with meningism and diagnosis and management of *S. gallolyticus* meningitis, the patient presented again with a further 4 days of fevers and subsequently developed left-sided paresthesias. Cerebral imaging revealed a venous thrombus in the right frontal cortical veins and left sigmoid sinus. The patient recovered following 4 weeks of intravenous ceftriaxone and antiocoagulation with enoxaparin and warfarin. Apart from the splenectomy, no underlying cause was found. The patient was commenced on life-long prophylactic amoxicillin, given appropriate vaccinations, and antiocoagulated with warfarin. After initial difficulties, identification of the causative organism to the subspecies level was confirmed by analysis of short-read whole genome sequencing data. This case demonstrates two features that have not previously been reported for *S. gallolyticus* subsp. *pasteurianus* infections: splenectomy as a potential risk factor and that infection may be complicated by cerebral venous thrombosis. The resolution provided by whole genome sequencing was valuable in accurately identifying the bacterial subspecies.

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Introduction

*Streptococcus gallolyticus*, formerly known as *Streptococcus bovis*, is an uncommon cause of bacterial meningitis (van Samkar et al., 2015). A case of *S. gallolyticus* subsp. *pasteurianus* meningitis, identified using whole bacterial genome sequencing, in which the infection was complicated by cerebral venous thrombosis, is described here.

Case report

A 49-year-old Caucasian woman presented to a metropolitan emergency department in Melbourne, Australia with a 2-day history of fevers, nausea, vomiting, and diarrhoea, and 12 h of worsening frontal-occipital headache, photophobia, and neck stiffness.

Her past medical history included asthma, diverticulosis, and immune thrombocytopenic purpura for which she had undergone a splenectomy 23 years earlier. Her only regular medication was budesonide/formoterol combination inhaler. She had not taken prophylactic antibiotics following her splenectomy. She had documented vaccination for meningococcus, *Haemophilus influenzae* type B, and pneumococcus.

On examination, the patient was febrile at 37.9°C, with a pulse rate of 129 beats/min and a Glasgow coma score of 15. She demonstrated marked neck stiffness and photophobia.
Examinations of her chest, abdomen, legs, and skin were unremarkable. The oropharynx was noted for dry mucosal surfaces but no other abnormalities.

Routine tests on admission revealed leucocytosis with a predominance of neutrophils and a high level of C-reactive protein (137 mg/l). Blood cultures were obtained and a lumbar puncture revealed turbid cerebrospinal fluid (CSF) with glucose 41.4 mg/dl, protein 1.86 g/l, and erythrocytes 2400 × 10^6/l, leucocytes 7200 × 10^6/l, polymorphs 5760 × 10^6/l, and a Gram stain with no organisms detected. Within 24 h, both the blood culture and CSF cultures flagged positive for Gram-positive cocci, with a presumptive identification of *Streptococcus galaloticus* spp via matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF).

A clinical diagnosis of bacterial meningitis was made and the patient was commenced on empiric intravenous (IV) benzylpenicillin 2.4 g every 4 h, IV ceftriaxone 2 g twice daily, IV vancomycin 2 g loading dose, and IV dexamethasone 10 mg four times daily in accordance with the Australian *Therapeutic guidelines: antibiotic*, version 15 (2014). Upon identification of the pathological organism, antibiotics were rationalized to IV ceftriaxone 2 g twice daily and the patient was discharged home 2 days later with a planned 14-day course of outpatient IV ceftriaxone.

Over the next 4 days, the patient experienced ongoing intermittent fevers, approximately two to three episodes per day up to 38.5 °C, and associated diaphoresis. The patient was readmitted to hospital. A transthoracic echocardiogram revealed no valvular lesions or vegetations. Transoesophageal echocardiography was not performed and so infective endocarditis was not definitively excluded.

Two days later the patient experienced episodes of intermittent paresthesias and numbness radiating from her neck to her left hand. Each episode resolved within 5 min. Neurological examination between episodes was unremarkable. A computed tomography (CT) scan of the brain with contrast demonstrated a 20 mm × 11 mm hyper-attenuating lesion in the right frontal lobe with no change in intensity post contrast (image not shown). A multisequential multplanar magnetic resonance imaging (MRI) scan of the brain characterized the right-sided lesion as extra-axial with central intermediate and peripheral hyperintensity on T1 and intermediate hyperintensity on T2, with diffusion restriction and blooming artefact on gradient echo (GRE) sequences, raising the possibility of an acute/subacute haemorrhage and mycotic aneurysm (Figure 1). The patient was commenced on levetiracetam 500 mg twice daily. A CT venogram showed a small linear filling defect within the distal left transverse sinus and extending to a more rounded filling defect at the proximal left sigmoid sinus, representing an acute dural venous sinus thrombosis (image not shown). Further areas of thrombus were demonstrated within the cortical veins overlying the cerebral hemisphere adjacent to the previously identified hypodense lesion, compatible with a thrombosed venous varix.

The patient was therapeutically anticoagulated with bridging enoxaparin and warfarin. In consideration of a possible infected

Figure 1. MRI Brain demonstrating right-sided frontal lobe lesion (arrow) consistent with haemorrhage, mycotic aneurism, or cerebral venous thrombosis. Lesion as appears on a. T2 weighted axial MRI, b. T1 weighted axial MRI, c. T1 weighted coronal MRI, d. Gradient Echo sequence axial.
venous sinus thrombosis, the decision was made to treat for a total of 4 weeks with IV ceftriaxone 2 g twice daily. In consideration of predisposing factors for this unusual bacterial infection, the patient was tested for HIV, human T-lymphotropic virus type 1 (HTLV-1), Strongyloides serology, and faecal assays for Strongyloides, all of which were negative. The paresthesias ceased 5 days after onset. Repeat MRI and magnetic resonance angiography (MRA) at 3 months post presentation demonstrated resolution of the changes and excluded an arteriovenous malformation. The patient was planned for lifelong prophylactic amoxicillin, and subsequent outpatient colonoscopy was unremarkable. She remained seizure-free at 18 months.

Microbiological investigations

Three initial attempts at identification to the subspecies level using MALDI-TOF yielded varying results, with subsp. gallolyticus (91%), gallolyticus (97%), and pasteurianus (99.9%) identified, respectively.

Genomic DNA was extracted from the bacterial cultures isolated from blood samples (accession number AUSMDU00005280) and CSF samples (accession number AUSMDU00005281) for whole genome sequencing (WGS) using the Illumina NextSeq 500 High Output Version 2 kit (300 cycles) following the manufacturer’s protocol. Near-complete 16S rRNA gene sequences were reconstructed using the unassembled short-read data and the Expectation Maximization Iterative Reconstruction of Genes from the Environment (EMIRGE (Miller et al., 2011)) program with the following parameters: the SILVA Small Subunit database was employed as a training reference set; length of reads of 151, insert size of 683, standard deviation of 68, and a phred score of 33 were selected to compute over 10 iterations. EMIRGE reconstructed 1464 bp (V1–V9) of the 16S rRNA gene from sample AUSMDU00005280 and 995 bp (V1–V5/V6) from sample AUSMDU00005281.

The Ribosomal Database Project SeqMatch tool identified Streptococcus gallolyticus as the most probable species-level identification, and a maximum likelihood phylogeny was constructed. Samples AUSMDU00005280 and AUSMDU00005281 clustered within the pasteurianus subspecies clade, in which there were no single nucleotide polymorphisms (SNP) separating the S. gallolyticus subsp. pasteurianus isolates. Therefore, S. gallolyticus subsp. pasteurianus was identified as the most probable organism for samples AUSMDU00005280 and AUSMDU00005281.

Discussion

Streptococcus gallolyticus is a Lancefield group D Streptococcus species, formerly known as S. bovis biotype I (Osawa et al., 1995). The microorganism is a common intestinal commensal present in 10–15% of healthy humans. However, it is a clinically significant organism, as S. gallolyticus/S. bovis bacteraemia has a strong correlation with colonic carcinoma and endocarditis. Community-acquired S. gallolyticus meningitis is a relatively rare phenomenon. A prospective observational cohort study from the Netherlands identified S. gallolyticus as the causative organism in 0.32% of all community-acquired meningitides (van Samkar et al., 2015).

S. gallolyticus has been further categorized into subspecies, including S. gallolyticus subsp. gallolyticus, subsp. pasteurianus, and subsp. macedonicus (Schlegel et al., 2003). The recent classification of these three subspecies of S. gallolyticus means that the clinical significance of each is the subject of ongoing investigation. A recent literature review suggested that subspecies pasteurianus was the causative pathogen in 89% of patients with S. gallolyticus meningitis (van Samkar et al., 2015).

Cerebral venous thrombosis has previously been demonstrated to complicate 10.3% of Streptococcus pneumoniae meningitis (Kastenbauer and Pfister, 2003). Splenectomy or functional hyposplenia has also been reported as an underlying risk factor for pneumococcal meningitis. To the authors’ knowledge there have been no reports of cerebral venous thrombosis complicating S. gallolyticus meningitis, nor has splenectomy been identified as a risk factor for this infection. Thus, the above case report represents the first description of these putative associations. Furthermore, confirmation of the pathogen as S. gallolyticus subsp. pasteurianus via WGS demonstrates the value this method has in clinically relevant microbial identification, especially in light of equivocal results from current routine microbiological diagnostic tests.

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Appendix A. Supplementary data

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