Clinical Medicine & Research
Volume 10, Number 1: 15-25

clinmedres.org

Clinical and Laboratory Features of *Streptococcus salivarius* Meningitis: A Case Report and Literature Review

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Streptococcus salivarius is a normal member of the human oral microbiome that is an uncommon cause of invasive infections. Meningitis is a rare but increasingly reported infection caused by *S. salivarius*. Despite the growing number of reported cases, a comprehensive review of the literature on *S. salivarius* meningitis is lacking. We sought to gain a better understanding of the clinical presentation, evaluation, management, and outcome of *S. salivarius* meningitis by analyzing previously reported cases. In addition to a single case reported here, 64 previously published cases of meningitis were identified for this review. The collected data confirm that most patients presented with classical signs and symptoms of bacterial meningitis with a predominance of neutrophils in the cerebrospinal fluid (CSF) and hypoglycorrhachia. The majority of cases followed iatrogenic or traumatic CSF contamination. Most cases were diagnosed by CSF culture within one day of symptom onset. There was no clear evidence of predisposing co-morbid conditions in patients with meningitis, although in most case reports, limited information was given on the medical history of each patient. Outcomes were generally favorable with antibiotic management. Clinicians should suspect *S. salivarius* meningitis in patients presenting acutely after medical or surgical procedures involving the meninges.

Keywords: *Streptococcus salivarius*, Meningitis, Sinusitis, Viridans Streptococci, Cerebrospinal fluid, Hypoglycorrhachia

Acute bacterial meningitis remains an important cause of morbidity and mortality worldwide, despite advances in prophylactic vaccination and pharmacotherapy. While *Haemophilus influenzae* was previously the most frequent cause of acute bacterial meningitis in the United States, widespread vaccination against this pathogen has resulted in *Streptococcus pneumoniae* supplanting *H. influenzae* as the leading cause of bacterial meningitis.[1] Vaccination against *S. pneumoniae* is now reducing the incidence of central nervous system infections caused by this bacterium.[2]

As the burden of pneumococcal meningitis wanes, a relative increase in the proportion of cases caused by other streptococci emerges. An important example is *Streptococcus salivarius*, a viridans group streptococcus that is prone to causing nosocomial or iatrogenic central nervous system infections.[3] As recently underscored by the Centers for Disease Control and Prevention, *S. salivarius* and other viridans group streptococci are the most frequent causes of bacterial meningitis following spinal procedures such as anesthesia, accounting for up to 60% of cases.[4-6] Several case reports describe *S. salivarius* meningitis also complicating upper respiratory infections, endocarditis, post-traumatic

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Received: February 27, 2011
Revised: April 26, 2011
Accepted: May 11, 2011

doi:10.3121/cmr.2011.1001

cerebrospinal fluid (CSF) leaks, and neurosurgical procedures.[7] Despite the growing number of reported cases, a comprehensive review of the literature on *S. salivarius* meningitis is lacking.

We recently diagnosed a case of spontaneous *S. salivarius* meningitis associated with a CSF leak that likely resulted from chronic sinus infections. Interestingly, this case was associated with a false-positive urine rapid immunochromatographic test (ICT) for *S. pneumoniae*, although *in vitro* testing failed to identify an ICT cross-reaction between *S. salivarius* and *S. pneumoniae*. We sought to report this interesting clinical occurrence and provide a comprehensive overview of previous cases of *S. salivarius* meningitis that summarize key features of this infection.

Methods

The *S. salivarius* reference strain ATCC13419 was obtained from the American Tissue Type Collection (Manassas, VA). The case was approved by the University of Michigan's Institutional Review Board following written informed consent from the patient.

Literature review

A review of the literature identified 64 reported cases of *S. salivarius* meningitis, which are detailed further in table 1. The review was performed for indexed English- and non-English-language articles using MEDLINE (National Library of Medicine, Bethesda, MD) for the search terms "meningitis" and "*Streptococcus salivarius*". Additional references were identified within bibliographies provided by MEDLINE-cited studies. Literature was reviewed through April 2011.

Literature analysis

Case reports were included in this analysis if they documented evidence of *S. salivarius* meningitis. Cases were assessed to characterize demographic features, signs and symptoms of infection, potential sources of infection, method of diagnosis, antimicrobial treatment regimens, and outcomes. Not all data were available from each report. Results were expressed as the total number of cases from which information was available among a total of 65 identified reports of *S. salivarius* meningitis (including the case presented here).

Polymerase chain reaction

The identity of *S. salivarius* from our patient was confirmed by sequencing the 16S rRNA gene. Briefly, conserved primers were used to amplify the 16S rRNA gene with high-fidelity taq polymerase (AmpliTaq Gold, Applied Biosystems, Inc).[8] Amplicons were purified (QIAquick PCR Purification Kit, Qiagen, Inc) and sequenced at 2X coverage (Forward and Reverse directions) using standard Sanger-style sequencing (ABI 3730XL). Raw sequences were trimmed and aligned to a reference sequence from a *S. salivarius* strain (ATCC7073) as well as 20 additional reference 16S rRNA sequences from various *Streptococcus* species. No differences were found between sequences from the strain in question and the *S. salivarius* reference strain.

BinaxNOW ICT

BinaxNOW ICT assays to detect *S. pneumoniae* antigen were conducted according to the manufacturer's instructions using the patient's urine. This test was also performed using CSF directly or broth cultures of the patient's *S. salivarius* CSF isolate or the ATCC reference strain 13419. The broth culture ICT tests were performed by culturing single colonies overnight in brain-heart infusion broth, wetting the ICT test strip with broth and then following the manufacturer's instructions.

Case Report

A 49-year-old obese woman with diabetes mellitus and hemodialysis-dependent end-stage renal disease presented with acute abdominal pain, nausea, vomiting, diarrhea, and headache. The morning of presentation, she developed a mild headache that progressively worsened throughout the day, along with neck stiffness. The patient noted low grade fevers, clear rhinorrhea, and a nonproductive cough for two weeks prior to presentation. She also complained of mild right ear pain for two to three days prior to hospitalization. There was no recent history of dental procedures, oral surgery, or spinal anesthesia.

The patient's medical history included hypertension, diabetic nephropathy, obesity, hyperthyroidism, and gout. Medications included calcium acetate, cinacalcet, glipizide, lovastatin, allopurinol, and methimazole. On initial examination the patient was in moderate distress from neck and head pain. She was afebrile; blood pressure was 143/70 mmHg, heart rate 105 beats/min, respiratory rate 18 breaths/min, and the room air, transcutaneous, arterial oxygen saturation was 99%. The right tympanic membrane was dull with a small purulent air-fluid level. She had clear rhinorrhea and meningismus with neck flexion. There were decreased breath sounds in the lung bases bilaterally, with no adventitious sounds. Cardiovascular examination was normal without murmurs. The abdomen was soft with active bowel sounds and diffuse tenderness to palpation. Her neurological examination was nonfocal with intact cranial nerves, normal reflexes, strength, and sensation to light touch. She was alert and oriented. No rash was present.

Laboratory testing revealed an initial white blood cell count (WBC) of 24.4 x 10^3/uL (normal range, 4.0–10.0 x 10^3/uL) with a differential of 93.6% neutrophils (36.0%–75.0%), normal hemoglobin of 12.2 g/dL (12.0–16 g/dL) and a platelet count of 225 x 10^3/uL (150–450 x 10^3/uL). An initial chest radiograph revealed low lung volumes with hypoventilatory changes and a right middle lobe and retrocardiac opacities consistent with either atelectasis or pneumonia. Concern for pneumonia resulted in empiric treatment with a single intravenous (IV) dose of levofloxacin.

After hospital admission the patient developed worsening headache, neck stiffness and pain exacerbated by neck flexion, an altered mental status with a decreased level of

Table 1. Clinical features of previously reported *S. salivarius* meningitis cases.

Reference	Age (yrs)	Sex	Exposure (Source)	Presenting signs/symptoms	*S. salivarius* Identification Method	CSF gram stain	Blood culture	Treatment (Duration)	Outcome	Complications
Majka 1956[9]	68	NR	Pneumoencephalogram (I)	H, N, V, NucRig	CSF culture	Pos	NR	PCN, Streptomycin, Sulfadiazine (7d)	Survived	None
	26	NR	Pneumoencephalogram (I)	Muscle twitches, N, V	CSF culture	Pos	NR	PCN, Streptomycin, Sulfadiazine (7d)	Survived	None
Lerner 1975[10]	31	M	Dural defect from prior gun shot wound with CSF leak (CL)	NR	CSF culture	Pos	Neg	Cephaloridine (14d)	Survived	NR
	56	M	Alcoholic cirrhosis and variceal bleed (T)	NR	CSF culture	Pos	Neg	PCN (13-17d)	Survived	None
Schlesinger 1982[11]	36	NR	Myelography (I)	Fvr, H, AMS, NucRig	CSF and Blood culture	Pos	Pos	Nafcillin, PCN	Survived	NR
	68	NR	Pneumoencephalography (I)	H, AMS, NucRig	CSF culture	Pos	NR	PCN, Streptomycin, Sulfadiazine	Survived	NR
	26	NR	Pneumoencephalography (I)	H, AMS, NucRig	CSF culture	Pos	NR	PCN, Streptomycin, Sulfadiazine	Survived	NR
Nachamkin 1983[12]	0-1 (3c); 1-25 (1c); 25+ (3c)	NR	NR (various)	Fvr, AMS	CSF culture	Pos in 1/7 cases	Neg	NR	NR	NR
Legier 1991[13]	73	F	Metastatic colonic adenocarcinoma (T)	Aggitation, Fvr, H, Incoherent speech, L, AMS	CSF culture	Pos	NR	Chloramphen ocol, PCN (10d)	Survived	NR
Carley 1992[14]	60	M	EGD with cautery leading to bacteremia and meningitis (T)	Fvr, Obtundation within 48hrs	CSF and Blood culture	NR	Pos	Amp, Gent (10d)	Survived	NR
De Jong 1992[15]	47	M	Lumbar myelography for herniated discs (I)	NR	CSF culture	Neg	NR	Cefotaxime, Flucloxacillin, Rifampin then PCN	Survived	NR
	68	F	Lumbar myelography for herniated discs (I)	NR	CSF culture	Neg	NR	Cefotaxime, Flucloxacillin, PCN then PCN alone	Survived	NR
Watanakunakorn 1992[16]	50	M	Lumbar myelography and epidural nerve block for back pain (I)	Fvr, H, AMS, NucRig, V	CSF and Blood culture	Neg	Pos	Ceftazidime, Vanc then PCN (14d)	Survived	None

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Torres 1993[17]	48	F	Diagnostic lumbar puncture (I)	Fvr, L, NucRig, Obtundation, Shock	CSF and Blood culture	NR	Pos	Cefotaxime, Vanc (15d)	Survived	NR
Newton 1994[18]	23	F	Spinal anesthesia for labor (I)	Fvr, H, L, AMS, NucRig, Photo	CSF and Blood culture	Neg	Pos	Amp, Ceftr, Vanc then Amp (14d)	Survived	None
Verniga 1995[19]	64	M	Myelography for back pain (I)	Fvr, H, L, NucRig	CSF culture	NR	NR	Ceftr, Flucloxacillin then PCN	Survived	NR
de la Fuente 1996[20]	48	M	CSF Fistula following acoustic neuroma resection (CL)	Fvr, H, NucRig	CSF culture	NR	NR	Amikacin, Cefotaxime, Vanc then Vanc (14d)	Survived	None
Schneeberger 1996[21]	27	M	Spinal anesthesia for striping varicose veins (I)	Fvr, H, L, AMS, NucRig	CSF culture	Neg	Neg	Flucloxacillin then Amox (11d)	Survived	NR
Enting 1997[22]	41	F	Liquorrhoea and dural defect (CL)	Fvr, H, NucRig	CSF culture	NR	NR	Amox (17d)	Survived	None
	70	M	Endoscopic sclerotherapy for esophageal varices (T)	Fvr, H, NucRig	CSF culture	NR	Neg	Amox, PCN (24d)	Survived	None
	62	F	Coagulation of gasserian ganglion (I)	Fvr, H, NucRig	CSF culture	NR	Neg	Amox (14d)	Survived	None
Kaiser 1997[23]	50	F	Spinal anesthesia for hysteroscopy (I)	Back pain, Fvr, H, L, NucRig, V	CSF culture	Pos	Neg	Amikacin, Cefotaxime, Vanc then Cefotaxim (8d) then Cefixime (7d)	Survived	NR
Bouhemad 1998[24]	33	F	Spinal epidural anesthesia for labor (I)	Fvr, H, L, NucRig, Photo	CSF culture	Pos	Neg	Amox, Cefotaxime, Fosfamycin then Amox (15d)	Survived	None
Laurila 1998[25]	16	M	Spinal anesthesia for arthroscopic knee surgery (I)	H, L, AMS, N, V	CSF culture	Pos	Pos	Ceftr, Dex	Survived	None
Cabellos 1999[7]	65	F	Cranial trauma (CL)	Fvr, H, AMS, NucRig, V	CSF culture	NR	Neg	Ceftr (10d)	Survived	NR
	53	M	Epidural anesthesia (I)	Fvr, H, AMS, NucRig, V	CSF culture	NR	Neg	Cefotaxime (10d)	Survived	NR
	56	M	Cranial trauma (CL)	Fvr, H, AMS, NucRig, V	CSF and Blood culture	NR	Pos	Ceftr (10d)	Survived	NR
	20	M	Brain abscess secondary to sinusitis (Inf)	Fvr, H, AMS, NucRig, V	CSF and /or Blood culture	NR	NR	Ceftr, Metronidazole (45d)	Survived	NR
Yaniv 2000[5]	52	M	Spinal anestheia for lithotripsy (I)	Fvr, H, L, NucRig, Somnolent	CSF culture	Pos	Neg	Ceftr, Vanc (14d), Dex	Survived	ICU, Resp failure, Cerebral edema, ARF, *C. difficle* colitis

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Megarbane 2000[27]	48	F	Fistula with CSF leak and petro-mastoiditis after resection of left trigeminal neurinoma (CL)	Fvr, H, L, AMS, NucRig, Photo, V	CSF culture	Pos	Neg	Ceftr, Vanc then Amox (21d), Gent (5d)	Survived	None
Idigoras 2001[28]	84	M	Partial bowel obstruction due to rectal adenocarcinoma (T)	Fvr, NucRig	CSF culture	NR	Pos	Amp, Ceftazidime, Vanc then Amp, Gent	Survived	None
	65	F	Epidural anesthesia for meniscectomy (I)	Fvr, H, V	CSF culture	NR	NR	Tobramycin, Vanc then Clindamycin, Vanc	Survived	None
Guerrero-Peral 2002[29]	70	F	Spontaneous fistula (CL)	Fvr, L, AMS, NucRig	CSF and Blood culture	NR	Pos	Ceftr, Vanc then Vanc (10d)	Survived	None
Léautez 2002[30]	50	F	Chronic sinusitis and otitis with CSF leak (CL)	Fvr, H, AMS, V	CSF and Blood culture	Pos	Pos	Ceftr, Vanc then Amp (10d)	Survived	Recurrent CSF leak and meningitis with *Enterococcus*
Maeda 2002[31]	3	F	Oral trauma with skewer (T)	Fvr, Lethary, Lymphadenopathy, L, AMS, NucRig	CSF culture	Neg	Neg	Cefalexin then Panipenem betaminprom (7d), Dex (8 doses)	Survived	Abnormal EEG with no obvious sequele
Trautmann 2002[32]	23	F	Spinal anesthesia for arthroscopic knee surgery (I)	Fvr, N, NucRig	CSF culture	Pos	NR	Ceftr, Gent (14d)	Survived	None
	43	M	Spinal anesthesia for arthroscopic knee surgery (I)	H, N, NucRig	CSF culture	Pos	NR	Ceftr, Fosfomycin, Gent (14d)	Survived	None
Couzigou 2003[3]	NR	NR	Spinal anesthesia for arthroscopic knee surgery (I)	Fvr, H, Photo, V	CSF culture	Pos	NR	*Beta lactam	Survived	None
	NR	NR	Spinal anesthesia for meniscal knee surgery (I)	Fvr, H, Photo, V	CSF culture	Pos	NR	*Beta lactam	Survived	None
Conangla 2004[33]	57	M	Spinal anesthesia (I)	Fvr, H, Hyperreflexia, L, N, V, NucRig, Photo	CSF culture and 16S rRNA sequencing	Neg	Neg	Cefotaxime, Vanc then PCN (15d)	Survived	None
Conte 2006[34]	49	F	CSF fistula due to sphenoid mucocele with rhinorrhea (CL)	Fvr, H, AMS, NucRig	CSF culture	Neg	Neg	Amp, Ceftr	Survived	None
Arif Aladag 2007[35]	7	M	Blunt head trauma due to fall with rhinorrhea due to CSF leak (CL)	Fvr, Lethargy, L, AMS, NucRig	CSF culture	Pos	Neg	Ceftr, Dex, Vanc then chloramphenicol, PCN (14d)	Survived	None
Halaby 2007[36]	37	M	Spinal anesthesia for debriment of toe ulcer (I)	Fvr, L, Generalized seizure, Hypotension, Resp failure	CSF culture	NR	Neg	Bactrim, Flucloxacillin, Metronidazole then NR	Death	Hemolysis, ARF, DIC, Rhabdomyolysis, *C. difficile* colitits

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Rubin 2007[37]	27	M	Spinal anesthesia for arthroscopic surgery (I)	Fvr, H, NucRig, V	Neg CSF culture - organism not ID	NR	NR	Meropenem, Vanc	Survived	None
	NR	NR	Spinal anesthesia for arthroscopic surgery (I)	NR	CSF culture	NR	NR	NR	NR	NR
	70	M	Spinal anesthesia for arthroscopic surgery (I)	H, L, AMS, N	CSF culture Neg, 16s rRNA sequencing	Neg	NR	Meropenem, Vanc (14d)	Survived	None
	59	M	Spinal anesthesia for lithotripsy (I)	Fvr, NucRig, Obtundation	CSF culture Neg, 16s rRNA sequencing	Neg	Neg	NR	Survived	None
	25	M	Spinal anesthesia for arthroscopic surgery (I)	Fvr, AMS, N, V	CSF and Blood culture Neg	Neg	Neg	NR	Survived	None
	58	F	Spinal anesthesia for varicose vein stripping (I)	Fvr, NucRig, Obtundation	CSF culture Neg	Neg	Neg	NR	Survived	None
Franzen 2008[38]	35	F	Spinal anesthesia (I)	Fvr, H, NucRig, Restlessness, Tinnitus, Visual hallucinations	CSF culture	Pos	Neg	Ceftr, Dex, PCN (10d)	Survived	Tiredness and decreased concentration
Shin 2009[39]	20	M	Skull base fracture with CSF leak (CL)	Fvr, NucRig, V	CSF culture and 16S rRNA sequencing	Pos	Neg	Ceftr, Vanc (14d)	Survived	None
CDC MMWR 2010[4]	24	F	Spinal epidural anesthesia (I)	Back pain, H, L, AMS, N, V, Rigors	16s rDNA sequencing	NR	Neg	NR	Survived	None
	31	F	Spinal epidural anesthesia (I)	Back and neck pain, H, L, N	16s rDNA sequencing and culture were both Negative	NR	Neg	NR	Survived	None
	37	F	Spinal epidural anesthesia (I)	H, Lethargy, L, AMS, Seizure	CSF culture	NR	Neg	NR	Survived	None
	25/26	F	Spinal epidural anesthesia (I)	Fvr, H, Lethargy, L, N, Obtundation	CSF and Blood cultures	NR	Pos	NR	Survived	None
	30	F	Spinal epidural anesthesia (I)	Fvr, H, Lethargy, L, AMS	Autopsy CSF culture	NR	Pos	NR	Death within 26hrs	
Martinez 2010[40]	59	F	Spinal anesthesia for arthroscopic knee surgery (I)	Fvr, H, L, AMS, NucRig, V	CSF culture	NR	Neg	Cefotaxime then Cefepime, Vanc then Vanc (16d)	Survived	None
Reif 2009[41]	52	M	Epidural Nerve Block (I)	Fvr, H, V, AMS, NucRig	CSF and Blood Culture	Neg	Pos	Vanc, Cefepime then Ceftr (14d)	Survived	None
Wilson 2010	49	F	Sponataneous CSF fistula (CL)	Abdominal pain, Fvr, H, L, AMS, N, V, NucRig	CSF culture and 16s rRNA sequencing	Pos	Neg	Ceftr, Vanc, Dex (4d) then Vanc, Cefepime (14d)	Survived	None

Amgl, Aminoglycoside; Amox, Amoxicillin; Amp, Ampicillin; AMS, altered mental status; ARF, acute renal failure; c, cases; Ceftr, ceftriaxone; Ceph, cephalosporin (not otherwise specified); CL, cerebrospinal fluid leak; CSF, cerebrospinal fluid; d, days; Dex, dexamethasone; DIC, disseminated intravascular coagulation; F, female; Fvr ,fever; Gent, gentamicin; H, headache; I, iatrogenic; ID, identified; Inf, infection; L, leukocytosis; M, male; N, nausea; Neg, negative; NR, not reported; NucRig, nuchal rigidity; PCN, penicillin; Photo, photophobia; Pos, positive; Resp, respiratory; T, translocation from mouth or gastrointestinal tract; Vanc, vancomycin; V, vomiting; Yrs, years.

*Beta lactam antibiotic of unspecified type

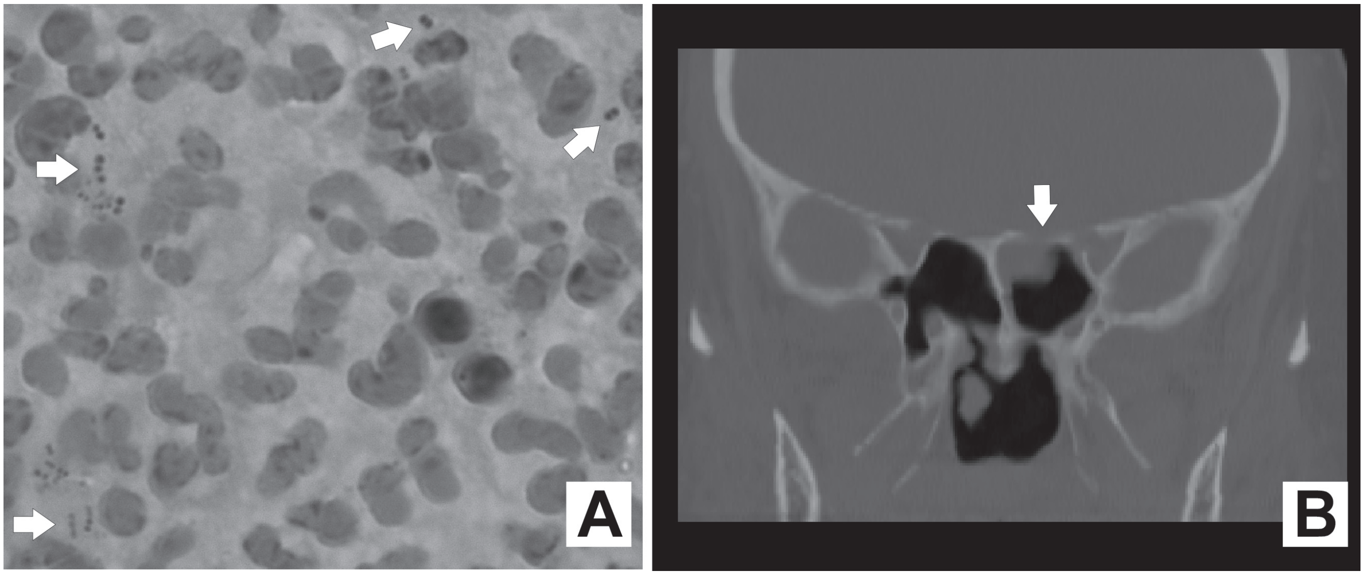

Figure 1. (A) Gram stain of cerebrospinal fluid demonstrated numerous polymorphonuclear leukocytes and Gram positive cocci in pairs and chains (arrows). (B) Coronal computed tomography scan image revealed a defect in the left planum sphenoidale with associated polypoid mucosal thickening in the sphenoid sinus (arrow).

consciousness, and emesis. Nuchal rigidity and pain with neck flexion were noted on exam (though Kernig and Brudzinski signs were absent). The patient's neurological status declined, with loss of orientation, recall, and concentration. The remainder of her neurological examination was unchanged. A non-contrasted computed tomography (CT) scan of the head demonstrated patchy opacification of the left mastoid air cells and a near complete opacification of the left sphenoid sinus. A lumbar puncture was performed approximately four hours after empiric antibiotics. The CSF was cloudy with 16,800 WBCs/mm^3 (87% polymorphonuclear leukocytes, 2% lymphocytes, and 11% histiocytes). The CSF glucose was 83 mg/dL (50–70 mg/dL), while circulating blood glucose was 467 mg/dL (73–110 mg/dL). The CSF protein was 322 mg/dL (15–45mg/dL). Gram stain of the CSF revealed gram positive cocci in pairs and short chains (figure 1A). Testing for cryptococcal antigen and enteroviruses, herpes simplex viruses 1 and 2, and adenoviruses by polymerase chain reaction (PCR) were negative. The CSF was screened for *S. pneumoniae* using a commercially-available ICT, the BinaxNOW Urinary Antigen Test (Binax, Portland, ME), and was negative. Culture of the CSF yielded gram-positive cocci in pairs and chains later identified as *S. salivarius*. The identity was confirmed by sequencing the 16S rRNA gene.

Unexpectedly, urine obtained from the patient was positive for *S. pneumoniae* antigen using the BinaxNOW ICT. In light of this positive urine test for *S. pneumoniae*, the patient's *S. salivarius* isolate was assayed *in vitro* for cross-reactivity with the BinaxNOW ICT, as noted in the methods section. This test was negative, as was a test using the ATCC laboratory reference strain of *S. salivarius*, ATCC 13419. There was low clinical suspicion that the patient had a concomitant *S. pneumoniae* infection because she lacked clinical symptoms of pneumonia, and her obesity was thought to be a source of hypoventalitory changes both on physical examination and chest radiograph.

Initial empiric therapy included vancomycin (1 g IV after dialysis), ceftriaxone (2 g IV every 12 hours) and dexamethasone (15 mg IV every 6 hours for 4 days). Within 12 hours of starting therapy the patient's mental status returned to baseline, and over the next 48 hours her headache and neck stiffness resolved. After the culture results returned, she was treated with cefepime 2 g IV and vancomycin 1 g IV (both after dialysis, three times per week) for 14 days. Broad spectrum antibiotics were maintained pending identification of the streptococcal species. There was complete neurological improvement, and no relapse since therapy was discontinued.

Following discharge, the patient had persistent intermittent occipital headaches and left-sided clear rhinorrhea. Drainage was exacerbated with leaning forward. She was evaluated with a non-contrast maxillofacial CT scan, which showed continued opacification of the left sphenoid sinus and left mastoid. Clinically, the left-sided rhinorrhea was suggestive of a CSF leak, and the drainage tested positive for β2 transferrin by immunofixation. The patient also had a left-sided middle ear effusion that appeared to be consistent with retrograde filling of the middle ear space with CSF via the eustachian tube. A Stealth protocol thin cut maxillofacial CT was obtained, and on close inspection, a defect in the left planum sphenoidale was found. No tegmen tympani defects were noted (figure 1B). She underwent operative endoscopic evaluation, and two defects were found. A defect in the planum sphenoidale measured approximately 3 mm and was

Table 2: Major *Streptococcus* Viridans Groups

S. mutans
S. salivarius
S. anginosus
S. mitis
S. sanguinus

repaired using a free mucosal graft. Another large linear defect was noted in the left cribiform overlying the olfactory tube, measuring about 1 cm by 3 mm. This was adjacent to the septum, in a location that is classically difficult to repair. This was repaired with a vascularized pedicled nasal septal flap (Hadad-Bassagasteguy flap). Since the operation, there has been no further CSF leakage or other neurologic symptoms. Endoscopic evaluation shows complete coverage of the defects. The middle ear effusion persisted and was treated with myringotomy, although fluid was not cultured at the time of tube placement. The middle ear effusion has not recurred.

Results of Literature Review

*Demographics/Predisposing Condition*s

In addition to the case presented here, 64 published cases of *S. salivarius* meningitis were identified in the peer-reviewed literature.[3-5,7,9-41] *S. salivarius* meningitis occurred equally among men and women, with approximately 50% of cases in each gender (50 total cases reporting data). The age distribution of cases was broad, with the most common age deciles being 20 to 29 years of age and 50 to 59 years of age (figure 2). There was no clear evidence of predisposing co-morbid conditions in patients with meningitis, although in most case reports limited information was given on the medical history of each patient.

Exposure/Inoculation

The majority of cases of *S. salivarius* meningitis (39 of 58 cases, 67%) were associated with iatrogenic causes, usually following epidural anesthesia or spinal myelography (table 1). In addition to the case reported here, there were 11 cases related to a leak of CSF. Of these leak-related cases, five developed following head trauma,[7,10,35,39] two cases were complications from a neurosurgical procedure,[20,27] two were due to spontaneous dural defects,[22,29] one was due to a sphenoid mucocele,[34] and a single case was associated with chronic sinusitis and otitis media (like our patient).[30] The remaining cases (5 of 57) were associated with possible translocation from the gastrointestinal tract.[10,13,14,22,28] There was a single case report of translocation from the mouth from trauma,[31] and one report associated with a sinus infection.[7]

Signs and Symptoms

Streptococcus salivarius meningitis typically presented with classic findings of bacterial meningitis. The most commonly reported signs and symptoms were fever in 44 patients, headache in 40 patients, nuchal rigidity in 38 patients, altered mental status in 29 patients, nausea and vomiting in 27 patients (table 1). Leukocytosis was reported in 23 patients who had a median WBC count of 21.2 x 10^3/uL (with a range of 12.1–34.8 x 10^3/uL) (table 1). Other less common presenting features included lethargy, obtundation, photophobia, seizures, sepsis, back pain, rigors, tinnitus, hyper-reflexia, and visual hallucinations.

Duration of Symptoms

A total of 50 reports of meningitis included data regarding the duration of symptoms prior to diagnosis. Of these, 45 cases (90%) presented within one day of symptom onset. Thirty-nine of the 50 cases (78%) were iatrogenic. There was a non-significant trend for iatrogenic cases to get diagnosed sooner following the onset of symptoms than non-iatrogenic cases (22.3 ± 2.7 hours vs. 39.6 hours to diagnosis) (P=0.16 by Student t-test).

Microbiology and CSF Characteristics of Infection

All reported cases were diagnosed on the basis of positive cultures or PCR from a lumbar puncture. Key biochemical and cellular characteristics of CSF obtained from case patients are represented in figure 3. The CSF glucose was typically low, with a mean of 28.1 mg/dL, median of 22 mg/dL, and a range of 1-83 mg/dL. Notably, five case reports indicated glucose levels <10 mg/dL, although specific values were not provided.[4,18,28,38] The CSF protein was typically elevated with a mean of 499.2 mg/dL, median of 434 mg/dL, and a range of 34–1270 mg/dL, with nine case reports indicating protein levels >70 mg/dL.[10,12,18,22,30,40,41] The median CSF WBC count was 5200 cells/mm^3 (mean of 7509 cells/mm^3, range 40–29,500 cells/mm^3). This was always a neutrophil-predominant CSF, as the percentage of neutrophils ranged from 80% to 99% (median 95%). The CSF gram stain was positive in 23 of 36 cases where results were reported. Blood cultures were positive in 13 of 40 cases (32.5%) where data were available; however, data were not presented in these reports regarding the presence or absence of endocarditis.

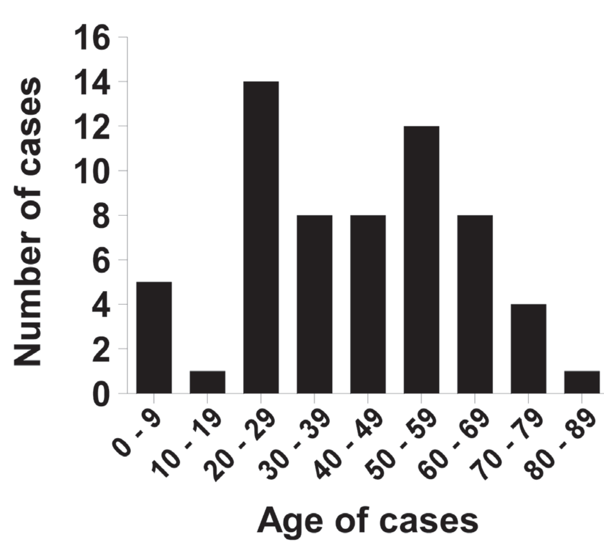

Figure 2. Age distribution of reported patients with *S. salivarius* meningitis (n=60 cases).

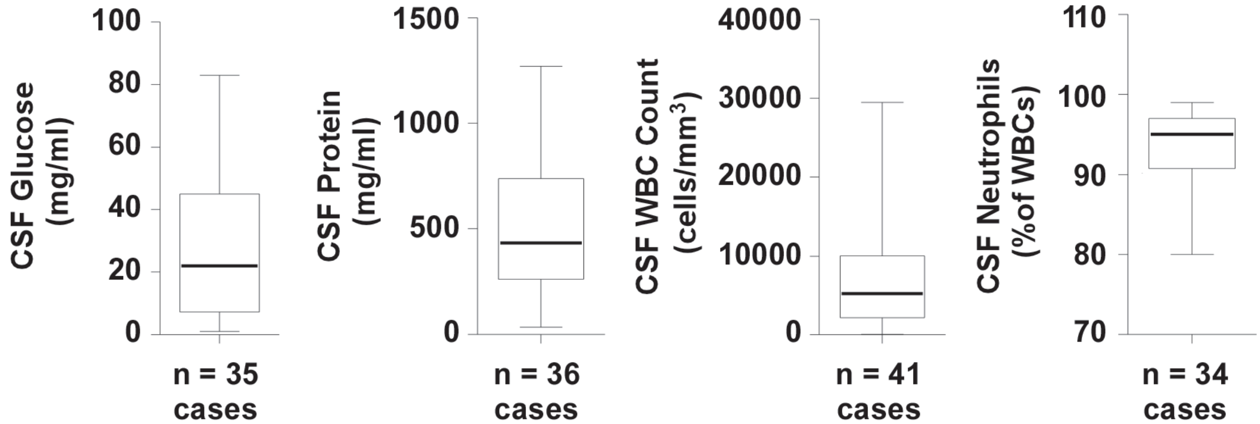

Figure 3. Cellular and biochemical features of cerebrospinal fluid obtained from patients with *S. salivarius* meningitis. Box and whisker plots demonstrate the median values (thick band near the middle of each box), the 25th and 75th percentile values (bottom and top of each box), and the range of reported values (the ends of the whiskers). WBC, white blood cells.

The majority of cases were determined to be *S. salivarius* based on positive CSF cultures in 62 of 65 cases (95.3%). Only three cases had negative CSF cultures, and the bacterial pathogen was identified using alternative methods such as PCR of the 16S rRNA gene.[4,37]

Treatments

The reported treatments of *S. salivarius* meningitis typically included a beta lactam antibiotic, most often either a penicillin or cephalosporin. The next most common medication was vancomycin. Dexamethasone was given in five cases, as well as in the present case described herein.[5,25,31,35,38] The average duration of treatment was 14 days; although, duration was only reported in 33 of the 65 cases (50%).

Outcome and Follow-up

In most cases of *S. salivarius* meningitis, patients survived without major sequelae of the infection, with 55 of 57 patients surviving and only 2 deaths (of those reporting outcome).[4,36] Complications occurred in five patients, one of whom died. These complications included fatigue and decreased concentration in a 35-year-old female who sustained *S. salivarius* meningitis from epidural anesthesia.[38] One patient with a petrous apex cholesteatoma developed a CSF leak and *S. salivarius* meningitis and then developed a recurrence of the leak leading to enterococcal meningitis.[30] A 3-year-old girl who developed *S. salivarius* meningitis after oral penetrating trauma from a wooden skewer had an abnormal electroencephalogram but had no clinical sequelae.[31] One patient required admission to the intensive care unit due to development of cerebral edema, respiratory failure, and acute renal failure. The patient survived the infection, and there was no mention of further sequel after discharge.[5]

Discussion

S. salivarius is a normal inhabitant of the human oral microbiome,[42,43] and it is an uncommon human pathogen.[44] In fact, recent attention has been placed on using this organism as a probiotic because of its ability to prevent colonization and proliferation of pathogenic streptococci and its capacity to suppress inflammatory responses from underlying host cells.[43] However, as the present case and review of the literature suggest, this bacterium can cause life-threatening infections of the central nervous system. These are usually a complication of neurosurgical or anesthesia procedures, but can occur as a non-iatrogenic infection. To our knowledge, this is the largest review of previously published cases of *S. salivarius* meningitis to date.

Meningitis cases caused by viridans streptococci such as *S. salivarius* (table 2) have been increasingly reported since the mid-20th century.[45] The increase in invasive procedures including neurosurgical procedures, spinal anesthesia, and prosthetic devices may account for the greater number of events. Given the probability of continued growth in the total number of invasive central nervous system procedures performed, this problem is unlikely to abate.

Our literature review identified 65 cases, including the present report, of bacterial meningitis secondary to *S. salivarius*. This review associated *S. salivarius* meningitis with CSF leaks (eg, head trauma, neurosurgical procedures, spontaneous leak) in 21% (12 of 58 cases reporting on the occurrence of leaks). Probable gastrointestinal translocation (including the mouth) occurred in 10% (6 of 58) of patients for whom a source was identified, and there were iatrogenic causes in 67% (39 of 58) of cases. A source was not identified in only seven cases. The most common interventions associated with infection in the iatrogenic group were epidural anesthesia, spinal anesthesia, and myelography. *S. salivarius* is a commensal member of the oral mucosa, and many cases have been tracked to the oral microbiome of a healthcare provider performing a procedure on the case patient.[19,32,36] This suggests that droplet transmission or contamination of sterile equipment by the operator is an important mechanism for inoculation. Thus, strict practices of aseptic technique during these procedures and use of a facemask in accordance with guidelines as published by the Healthcare Infection Control Practices Advisory Committee and American Society of Regional Anesthesia and Pain Medicine will be important to limiting the incidence of these events.[4,46]

Microbiological diagnoses were established in most patients by CSF culture, blood culture, or CSF PCR when no pathogen was identified. In the case presented here, the CSF culture was used to identify *S. salivarius*, and PCR with gene sequencing analysis was used to confirm its identity. Interestingly, our patient's urine pneumococcal antigen ICT test was positive. However, neither a pure culture of her CSF isolate nor a reference ATCC strain of *S. salivarius* cross-reacted *in vitro* with this test. While cross-reactions have been noted with the structurally-similar *S. oralis* and *S. mitis*,[47,48] *S. salivarius* should not be added to the list of organisms that cause a false-positive ICT for pneumococcus. It is unlikely that the false positive ICT result adversely affected our patient's care, as her isolate of *S. salivarius* was relatively antibiotic-susceptible (MIC to ceftriaxone=0.5 µg/ml).

To the best of our knowledge, only two cases of antibiotic resistant *S. salivarius* meningitis have been reported to date.[5,40] However according to a study by van Doern et al,[49] 20% of *S. salivarius* were resistant to ceftriaxone and 17% had high resistance to penicillin. These rates of resistance should be of concern to clinicians, leading to aggressive attempts to establish a microbiological diagnosis that allows for appropriately "directed" therapy.

Although the present review was intended to provide a comprehensive overview of the state of knowledge about *S. salivarius* meningitis, it has several limitations. For example, because many of the cases are single reports, reporting bias may affect our findings. In addition, there was not a complete set of data for each case. Although we identified the most common presenting symptoms, causes, and treatment algorithms for many cases, some important data were not reported, including descriptions of the physical examination or rationales to justify antibiotic choices. Most data suggest that *S. salivarius* meningitis presents with classic findings of bacterial meningitis.

In summary, *S. salivarius* is an important cause of iatrogenic meningitis. Strict use of aseptic techniques including a facemask during diagnostic and surgical procedures may limit the incidence of this infectious complication. Thorough investigation of potential cases should be performed in order to prevent potential outbreaks from a single source. When a patient develops *S. salivarius* meningitis without a predisposing iatrogenic or traumatic event, a search for a CSF leak may be helpful. Most patients who develop infection with *S. salivarius* meningitis can safely be treated with a penicillin, third generation cephalosporin, or vancomycin with a good clinical outcome and cure.

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