Group C streptococcal endocarditis presenting as clinical meningitis: Report of a case and review of the literature

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AR HUANG, DJ BRIEDIS. Group C streptococcal endocarditis presenting as clinical meningitis: Report of a case and review of the literature. Can J Infect Dis 1992;3(5):247-252. Lancefield group C streptococci are known to be pathogenic in a number of animal species, but cause human disease much less commonly than do streptococci of serogroups A or B. Reported cases of bacteremic infection, pneumonia or meningitis in humans have been very severe with a grave prognosis. The authors describe a patient who presented with classic clinical and laboratory evidence of bacterial meningitis which proved to be a complication of endocarditis caused by a group C streptococcus. This is the first reported case in which meningitis was the presenting manifestation of group C streptococcal endocarditis and is only the second case in which group C streptococcal meningitis and endocarditis have been associated in the same patient. A total of 13 cases of group C streptococcal meningitis have now been reported in the medical literature. Five of these patients died, and four others recovered only to be left with neurological sequelae. The current case confirms the seriousness of group C streptococcal infections in humans. Such infections are associated with a poor prognosis despite apparently adequate antimicrobial therapy.

Key Words: Endocarditis, Group C streptococci, Meningitis

Endocardite aux streptocoques du groupe C, accompagnée d’un tableau clinique de méningite: rapport de cas et survol de la littérature

RÉSUMÉ: Les streptocoques Lancefield du groupe C sont connus pour leur pathogénicité chez certaines espèces animales. Ils occasionnent beaucoup moins fréquemment de maladies chez l’homme que les streptocoques des groupes A ou B. Les cas déclarés de bactériémie, de pneumonie ou de méningite chez l’homme ont été très graves et ils s’accompagnaient d’un pronostic sombre. Les auteurs décrivent un patient qui présentait des signes cliniques classiques et des épreuves de laboratoire de méningite bactérienne qui s’est révélée être une complication d’une endocardite à streptocoque du groupe C. Il s’agit du premier cas déclaré de méningite dans le contexte d’une endocardite à streptocoque du groupe C et ce n’est là que le second cas où une méningite et une endocardite à streptocoque du groupe C sont associées chez le même patient. En tout, treize cas de méningite à streptocoque du groupe C ont été rapportés dans la littérature médicale, cinq de ces patients sont décédés, quatre autres ont gardé des séquelles neurologiques. Le cas actuel confirme la gravité des infections aux streptocoques du groupe C chez l’humain. De telles infections sont associées à un pronostic sombre, malgré l’administration d’un traitement antimicrobien apparemment adéquat.
Strep equisimilis

The patient had been well after not having seen her for two days. Immediate authors report their experience with a patient with gynecological or urological procedures. There was no possibility of valve replacement surgery. Medications prior to admission consisted of digoxin, diltiazem, furosemide, warfarin and potassium supplementation. The patient had been well until two days prior to admission. There was no history of recent dental, gynecological or urological procedures. There was no history of exposure to pets or other animals. The patient was found by a neighbour who investigated after not having seen her for two days. Immediate history prior to this point was unavailable. The patient appeared short of breath and confused, and was brought to the hospital.

On examination, the patient was an elderly caucasian female who was stuporous. Pulse was 150 beats/min and irregular, blood pressure 130/90 mmHg, respirations 40/min, and temperature 38.8°C orally. Examination of the head and neck was notable for marked nuchal rigidity. The fundi were unremarkable. The patient’s mouth was edentulous and her throat appeared normal. Examination of the chest revealed only a few scattered wheezes. Examination of the cardiovascular system revealed 8 cm jugular venous distension. The apex beat was not displaced. Heart sounds were present with an opening snap but without discernible murmur or gallop. Neurological examination revealed a stuporous woman who moved all four limbs equally and withdrew well to painful stimulus. No focal neurological deficits or cranial nerve abnormalities were discernible. Visual fields could not be assessed. The remainder of the physical examination was normal, with no peripheral stigmata of endocarditis.

Hematological evaluation was within normal limits except for a peripheral leukocyte count of 18,900 cells/mm$^3$ (89% polymorphonuclear leukocytes) and a prothrombin time of 17.4 s. Initial biochemical revealed a serum glucose of 10.4 mmol/L, creatine kinase of 1144 U/L, alanine aminotransferase of 62 U/L, aspartate aminotransferase of 172 U/L, and lactate dehydrogenase of 590 U/L. Electrocardiography demonstrated atrial fibrillation with a ventricular rate averaging 150 beats/min and no acute ischemic changes. A chest radiograph was interpreted as showing interstitial pulmonary edema. Urinalysis was within normal limits. Lumbar puncture yielded clear cerebrospinal fluid with 50 erythrocytes and 400 leukocytes/mm$^3$ (98% polymorphonuclear), glucose 5.5 mmol/L, and protein 540 g/L. Gram stain of spinal fluid revealed the presence of Gram-positive cocci in chains. Therapy with cefotaxime 6 g/day was begun immediately after lumbar puncture on the first hospital day.

Echocardiography showed thickened and calcified mitral valve leaflets, as well as a dilated left atrium, which was felt to be consistent with moderate mitral stenosis. No vegetation was identifiable. Computed tomography of the head demonstrated a hypodense area in the left parieto-occipital region associated with effacement of the sulci (Figure 1). No enhancement of the region was noted after infusion of contrast material. The lesion was interpreted as being consistent with a cerebral infarction which had occurred within the past week. In addition, a number of lesions were seen in the area of the basal ganglia, which were interpreted as remote lacunar infarcts.

Strep equisimilis was isolated from spinal fluid culture as well as from all six blood cultures taken prior to
Institution of antibiotic therapy. The organism was beta-hemolytic and susceptible by disc sensitivity testing to penicillin, oxacillin, cefazolin, vancomycin, erythromycin and cotrimoxazole. The minimal inhibitory and bactericidal concentrations for penicillin G were equal to or below 0.03 U/mL. Minimal inhibitory and bactericidal concentrations were, respectively, 1.0 and 2.0 µg/mL for gentamicin, 8.0 and 8.0 µg/mL for netilmicin, 6.2 and 6.2 µg/mL for tobramycin, and 4.0 and 16.0 µg/mL for amikacin. Combination therapy with penicillin G 24,000,000 U/day and netilmicin 100 mg every 8 h was substituted when initial culture results became available on the second hospital day. Intubation and inotropic support became necessary on the second hospital day. After four days of therapy with penicillin and netilmicin, repeat blood cultures were negative, and peak and trough serum bactericidal activities were both greater than 1:5096. Despite antibiotic therapy and diuresis, the patient remained febrile and in mild to moderate congestive heart failure. Repeat spinal fluid examination on the eighth hospital day revealed an absence of cellular elements, a glucose concentration of 5 mmol/L, protein 620 g/L, negative Gram stain and negative culture. Repeat computed tomography of the head the same day was unchanged from admission. Antibiotic therapy was not altered. By the 10th hospital day the patient had become more alert and her nuchal rigidity was improved. She remained respirator dependent, however, and on the 16th hospital day sustained a sudden cardiac arrest. Attempts at resuscitation were unsuccessful.

Autopsy revealed the immediate cause of death to be congestive heart failure and multiple pulmonary emboli. The lungs weighed 1450 g, and multiple recent pulmonary emboli were present on a background of pulmonary edema and emphysema. The heart weighed 360 g. There was evidence of severe atherosclerotic changes in the aorta and coronary arteries, but no myocardial infarct was identified. The left atrium was dilated and a left atrial thrombus was present. A severely thickened mitral valve exhibited fusion of the chordae tendineae and superimposed ulceration associated with friable thrombotic material on the valve surfaces. Colonies of Gram-positive cocci were identified in histological sections of the heart valve. There was no evidence of embolization of thrombotic material to the myocardium. Post mortem culture of the valve material was not performed. The spleen weighed 300 g and showed passive congestion. Gross examination of the kidneys showed bilateral nephrosclerosis. Histological examination revealed focal glomerulonephritis with immune complex deposition in addition to foci of peritubular and perivascular inflammatory reaction in varying stages of organization, representing probable embolization.

Gross examination of the brain revealed normal-appearing meninges, a normal circle of Willis, and slight softness of the left inferior occipital lobe. Sectioning of the brain allowed identification of an area of recent infarction in the left occipital lobe (Figure 2). Microscopic examination of the brain disclosed multiple cerebral infarcts of various ages in the right frontal lobe, the left cerebellum, and the right lateral occipital lobe. There was histological confirmation of the new left
TABLE 1
Adult patients with group C streptococcal meningitis reported in the medical literature

<table>
<thead>
<tr>
<th>Case</th>
<th>Year (reference)</th>
<th>Age/Sex</th>
<th>Disease</th>
<th>Associated conditions</th>
<th>Therapy*</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1970 (10)</td>
<td>64/F</td>
<td>Endocarditis (mitral); clinically unsuspected foci of meningitis at autopsy</td>
<td>None</td>
<td>Ampicillin and streptomycin</td>
<td>Died</td>
<td>Mitral vegetation with destruction of anterior leaftlet; early focal areas of meningitis; post mortem meningeal cultures positive for group C streptococci</td>
</tr>
<tr>
<td>2</td>
<td>1978 (11)</td>
<td>59/M</td>
<td>Meningitis</td>
<td>Farm worker</td>
<td>Ampicillin and gentamicin; penicillin G</td>
<td>Recovered</td>
<td>Requeded; sequelae of positional vertigo and incomplete hearing loss</td>
</tr>
<tr>
<td>3</td>
<td>1980 (12)</td>
<td>66/M</td>
<td>Meningitis</td>
<td>Kept 4 dogs which were ill with diarrhea and skin infections but no group C streptococci could be cultured from the animals</td>
<td>Penicillin G</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1980 (13)</td>
<td>24/F</td>
<td>Meningitis</td>
<td>Group C streptococci isolated from pharynx of patient’s pet horse</td>
<td>Chloramphenicol and ampicillin; penicillin G</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1982 (14)</td>
<td>36/F</td>
<td>Pneumonia; bacteremia; meningitis</td>
<td>Pre-existing partial gastrectomy</td>
<td>Cephalothin and gentamicin</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1989 (15)</td>
<td>17/M</td>
<td>Parainflammasis; meningitis</td>
<td>None</td>
<td>Penicillin G and streptomycin</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1989 (2)</td>
<td>45/M</td>
<td>Meningitis</td>
<td>Diabetes; ethanol and IV drug abuse</td>
<td>Penicillin G and cefotaxime; penicillin G</td>
<td>Recovered</td>
<td>Course complicated by subdural hematoma and cerebral herniation</td>
</tr>
<tr>
<td>8</td>
<td>1989 (2)</td>
<td>23/M</td>
<td>Subdural empyema; meningitis</td>
<td>Unknown</td>
<td>Penicillin G and chloramphenicol</td>
<td>Recovered</td>
<td>Gram-negative organism also isolated from CSF; sinus disease not evaluated</td>
</tr>
<tr>
<td>9</td>
<td>1990 (16)</td>
<td>77/F</td>
<td>Otitis; meningitis</td>
<td>Unknown</td>
<td>Penicillin G</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1990 (16)</td>
<td>33/M</td>
<td>Meningitis</td>
<td>None</td>
<td>Ampicillin and gentamicin</td>
<td>Recovered</td>
<td>Sequence of mild hearing loss</td>
</tr>
<tr>
<td>11</td>
<td>1990 (17)</td>
<td>73/M</td>
<td>Meningitis</td>
<td>Alcoholic liver disease</td>
<td>Penicillin G and chloramphenicol</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1990 (18)</td>
<td>24/M</td>
<td>Meningitis</td>
<td>None</td>
<td>Penicillin G</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Present case</td>
<td>67/F</td>
<td>Endocarditis (mitral); mycotic aneurysm; meningitis</td>
<td>Rheumatic heart disease</td>
<td>Cefotaxime; penicillin G and netilmicin</td>
<td>Died</td>
<td>Clinical meningitis at the time of presentation to hospital; course complicated by pulmonary emboli</td>
</tr>
</tbody>
</table>

Initial therapy; subsequent therapy once culture results available; CSF Cerebrospinal fluid

Discussion

Lancefield group C streptococci are important pathogens in a number of animal species (1). These organisms can be isolated from normal human skin, upper respiratory tract and female genital tract. Infection with group C streptococci has been associated with suppurative infection of a number of organ systems with an often protracted clinical course and a high mortality (1,2,5). Clinical infections in humans have most commonly involved limited disease including pharyngitis and tonsillitis, as well as skin, wound and puerperal infections (1,2,5-9). Epidemic outbreaks have occurred involving erysipelas in Baltimore in 1924 (6), puerperal fever in London in 1931-32 (7), and acute cellulitis in London in 1944 (8). Serious human disease caused by beta-hemolytic streptococci of serogroup C is, however, much less common than that caused by serogroups A and B. Among 1107 patients with strep-
Streptococcal bacteremia at the Mayo Clinic between 1968 and 1977, group C streptococci were identified in only eight (5). Similarly, a serogroup C streptococcus was identified in only one of 140 patients with streptococcal bacteremia during a two-year period (1964-66) at the Massachusetts General Hospital (1).

Beginning with a case of endocarditis described by Rosenthal and Stone in 1940 (9), 21 cases (including the present one) of group C streptococcal endocarditis have been described. These cases have been partially reviewed by Salata et al (2).

Only 13 cases (including the present one) of group C streptococcal meningitis in the presence or absence of endocarditis have now been reported in adults (Table 1) (10-18). Five of the 13 died, although an apparently appropriate choice of antibiotic(s) was made in all but one patient (case 5, Table 1). Four of the eight patients who recovered were left with neurological sequelae of varying degrees. Three of these had a history of exposure to animals. Prior to the present report, only one case of meningitis associated with endocarditis had been reported (case 1, Table 1). This patient did not have clinical meningitis, but small foci of meningitis were noted at autopsy. The present case, therefore, represents the first report of group C streptococcal endocarditis complicated by clinical meningitis. Group C streptococci have, in addition, been reported as causative agents in five cases of neonatal meningitis (19-22) and in three cases of intracranial abscess or empyema without meningitis (23,24).

Various neurological complications have been associated with infective endocarditis. The topic has been reviewed by Lerner et al (25). Embolic events, both bland and septic, are most common. More than 90% of large emboli to the brain lodge in the anterior cerebral circulation, mainly in the branches of the middle cerebral artery. The present case showed evidence of embolization in the less common distribution of the posterior cerebral circulation. Additional neurological complications of infective endocarditis include the development of mycotic aneurysms, cerebral abscesses, meningencephalitis and frank meningitis. These may manifest as an acute confusional state with or without focal neurological signs or seizures. The present case presented to hospital with confusion and stupor without focal neurological signs, as an apparent diffuse or 'toxic' encephalopathy associated with clinical signs of meningitis. Spinal fluid examination revealed classic signs of bacterial meningitis, and the organism was easily isolated from spinal fluid culture. At autopsy, evidence was found for a mycotic aneurysm, but no abscess formation was found and no bacteria were seen in the central nervous system. Despite classical clinical and cerebrospinal fluid findings of meningitis, no evidence of leptomeningeal inflammation was seen 16 days after initiation of antibiotic therapy. It seems likely, therefore, that the mycotic aneurysm acted as a parameningeal suppurrative focus, and that the infection had spread to the subarachnoid space not long before presentation to hospital. The clinical course, as well as the absence of leptomeningeal inflammation at autopsy, imply that the death of the patient could not be attributed to either ongoing infection or inadequately aggressive antibiotic therapy.

The clinical presentation of endocarditis as frank meningitis is indeed rare. In a report of 385 patients with bacterial endocarditis diagnosed at the Mayo Clinic (26), 110 patients (29%) were described as having central nervous system complications. Although 66 of the 110 (60%) had neurological signs or symptoms as their initial manifestation, only seven (6.4%) had meningitis. In this series, the presence of neurological complications in cases of endocarditis was associated with an overall mortality of 50% (ranging from 28%, in cases involving viridans streptococci, to approximately 75% in cases involving Staphylococcus aureus or Enterococcus faecalis).

Group C streptococci are very sensitive in vitro to a number of antibiotics including penicillin G, vancomycin, first generation cephalosporins, erythromycin, azlocillin and pipercillin, and newer beta-lactam agents with the exception of moxalactam (27). The present case confirms and adds to the body of literature indicating that, while serious human infections with this serogroup of streptococci are rare, they carry a grave prognosis despite apparently adequate antimicrobial therapy.

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REFERENCES