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 cependant 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.

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Received for publication February 22, 1991. Accepted September 4, 1991

STREPTOCOCCI ASSOCIATED WITH LANCEFIELD SEROGROUP C include those classified as *Streptococcus milleri*, *Streptococcus dysgalactiae* (including *Streptococcus equisimilis*), and *Streptococcus equi* (including *Streptococcus zooepidemicus*) (1-4). Streptococci of this serogroup have mainly been described as pathogens in a number of animal species (2,3). *Strep equisimilis* has been reported to cause septic arthritis and septicemia in swine (3). *Strep dysgalactiae* causes mastitis in cattle, while *Strep equi* is the causative agent of strangles, a mucopurulent infection of the upper respiratory tract of horses (1,4). Group C streptococci can be isolated relatively frequently from normal human skin, pharynx and female genital tract (3,4). The use of simplified latex and co-agglutination testing rather than the more time-consuming precipitin reaction originally described by Lancefield – using heat- and acid-extracted cell wall carbohydrate – has allowed routine serotyping of streptococcal isolates (3). This has led to greater awareness of infections caused by nonserogroup A streptococci. Nonserological methods of identification (including hemolysis reactions, antibiotic sensitivity and fermentation reactions) often left group C streptococci unclassified or misclassified as group A streptococci (3). Reports of group C streptococcal infections in humans have usually described invasion of local tissues (1,2,5). Suppurative tonsillitis and pharyngitis, as well as skin, wound and puerperal infections, have been reported (1,2,5). To the authors' knowledge, only 12 cases of meningitis in adults caused by group C streptococci (including no case with pre-mortem clinical manifestations of both endocarditis and meningitis) have been previously reported in the world literature. The present authors report their experience with a patient with *Strep equisimilis* endocarditis whose clinical presentation was that of meningitis, and who died despite apparently adequate antimicrobial therapy.

CASE PRESENTATION

A 67-year-old female known to have rheumatic mitral valvular disease was brought to the hospital because of shortness of breath and altered consciousness. The patient had been previously known to have mitral stenosis associated with chronic atrial fibrillation and had had multiple previous episodes of decompensated congestive heart failure related to atrial fibrillation with a rapid ventricular response. She had previously refused cardiac catheterization and the 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 biochemistry 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

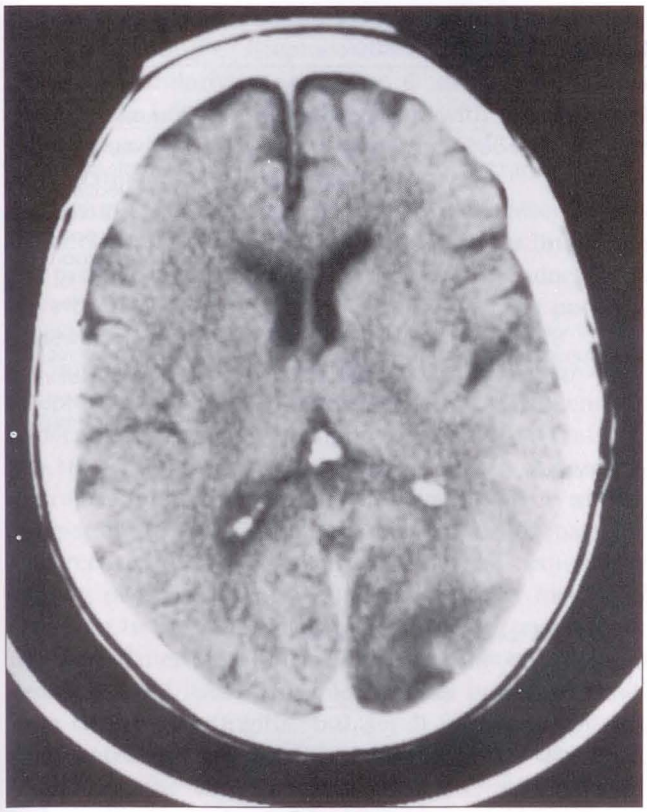

Figure 1) *Computed tomographic scan after infusion of contrast material showing a nonenhancing hypodense area in the left parieto-occipital region in a 69-year-old female presenting with shortness of breath and altered consciousness*

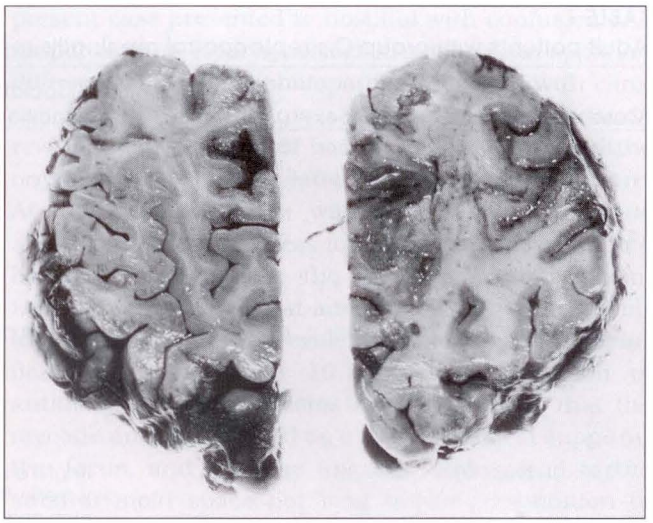

Figure 2) *Gross pathological appearance of recent left parieto-occipital cerebral infarction in a 69-year-old female with Group C streptococcal meningitis and endocarditis*

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 tendinae 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

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

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

occipital infarct in proximity to a large subarachnoid artery with partial necrosis of its wall associated with a dense inflammatory infiltrate. The lumen of this artery contained a red cell thrombus. The lesion was interpreted as an early mycotic aneurysm despite the absence of discernible bacteria. There was no histological evidence of inflammation of the leptomeninges.

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-

tococcal 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 the cases 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 (2,23,24).

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, meningoencephalitis 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 suppurative 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 piperacillin, 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.

ACKNOWLEDGEMENTS: We thank Dr I Huttner, Department of Pathology, Royal Victoria Hospital, and Dr S Carpenter, Department of Neuropathology, Montreal Neurological Hospital, for kind assistance in pathological interpretation and photography.

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