STREPTOCOCCUS BOVIS ENDOCARDITIS WITH VERTEBRAL OSTEOMYELITIS, SPONDYLODISCITIS, MENINGITIS AND COLONIC CARCINOMA IN A 72-YEAR-OLD MAN PRESENTING WITH NECK PAIN

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Summary

A 72-year-old man presented with acute neck pain on top of a background of chronic ill health, weakness, intermittent night sweats and progressive weight loss. Vertebral osteomyelitis and spondylodiscitis of the cervical spine as well as meningitis were diagnosed after some delay. Streptococcus bovis endocarditis was later diagnosed as the source of septic emboli to the bones and meninges. Further workup uncovered carcinoma of the colon. He was successfully treated with good functional outcome at one year. The atypical presentation of infective endocarditis in old age and the association between Streptococcus bovis and colonic carcinoma were reviewed and discussed. This is the fourth known case of vertebral osteomyelitis and eighth report of acute spondylodiscitis complicating S. bovis endocarditis. We recommend that patients presenting with new back pain in the absence of previous injury, local spinal tenderness, fever, and heart murmur be evaluated for infective endocarditis and vertebral osteomyelitis/spondylodiscitis. If Streptococcus bovis endocarditis is diagnosed, then a workup for colonic lesion, especially carcinoma, should be done.

Case Report

A 72-year-old man was admitted into the orthopaedics department for severe neck pain for three days. Initial examination revealed tenderness over his lower cervical spine and decreased range of motion of cervical spine, but there was no neurological deficit. X-ray of his cervical spine showed mild spondylolisthesis of C3/4 spine and degenerative changes of lower cervical spine with C5/6 and C6/7 disc spaces narrowed. The diagnosis of cervical spondylosis was made. Low-grade fever was recorded but there was no documentation of any finding on heart murmur. Iron deficiency anaemia (Hb 8.2 g/dl, hypochromic microcytic picture, Fe 15.1 umol/l, TIBC 76.7 umol/l) was also detected. He had no history of non-steroidal anti-inflammatory drug usage. Faecal occult blood test was positive. Oesophagodudoenogastroscopy revealed Helicobacter-associated duodenal ulcer and mild gastritis. Sigmoidoscopy revealed primary piles and no gross lesion was detected up to 20 cm, but the procedure was limited by inadequate bowel preparation so that barium enema was booked for further study. He was given paracetamol for pain relief, *Helicobacter pylori* eradication therapy (omeprazole, clarithromycin and metronidazole), ferrous sulphate, and transfused to a haemoglobin of 12.4 g/dl. He was discharged after eleven days of hospitalisation.

He was readmitted eight days later into our department because of persistent neck pain disturbing his sleep, nausea and vomiting. Further enquiry revealed gradual weight loss for the past eight months, poor appetite, malaise and night sweating for four months. He had no change in bowel habit. He was documented to have a weight loss of 6.5 kg in the past four months. He had a known history of diabetes mellitus, hypertension and right renal stone and his diabetes was all along under satisfactory control by oral hypoglycaemic agents. His body weight on admission was 64 kg. Physical examination revealed marked sweating, mild pallor, regular heart rate of 100/min, a mitral regurgitant murmur and local tenderness over his lower cervical spine. Abdominal and rectal examination revealed no masses. He was observed to have afternoon fever kicks of around 37.5°C - 38°C daily associated with profuse sweating. Initial investigations revealed a high ESR of 97mm/h, polymorphonuclear leukocytosis (white cell count 14.7 x 10^9/l with neutrophils 92.3%) and hypochromic micro-

cytic anaemia (Hb 10.1 g/dl). Serum immunoglobulin pattern revealed mildly elevated immunoglobulin A level at 4.74 g/l (reference range 1.24 - 4.22 g/l) with normal levels of immunoglobulins G & M. Thyroid and renal function tests were normal. X-ray of the cervical spine revealed reduced disc space and probable end plate destruction at C5/6 level. Tuberculin test was negative.

Six days after admission, he developed high fever of 41.5°C with confusion and increased neck pain with marked local tenderness. Infection of the cervical spine was suspected. However, an urgent computerised tomogram of the cervical spine was initially thought to show osteophytes only without evidence of infection in the cervical spine. Lumbar puncture revealed turbid cerebrospinal fluid (CSF) with biochemistry and microscopy compatible with bacterial meningitis (protein 3.02 g/l, glucose 5.2 mmol/l(compared with plasma glucose of 16 mmol/l), raised white cell count of 356/cmm with 90%

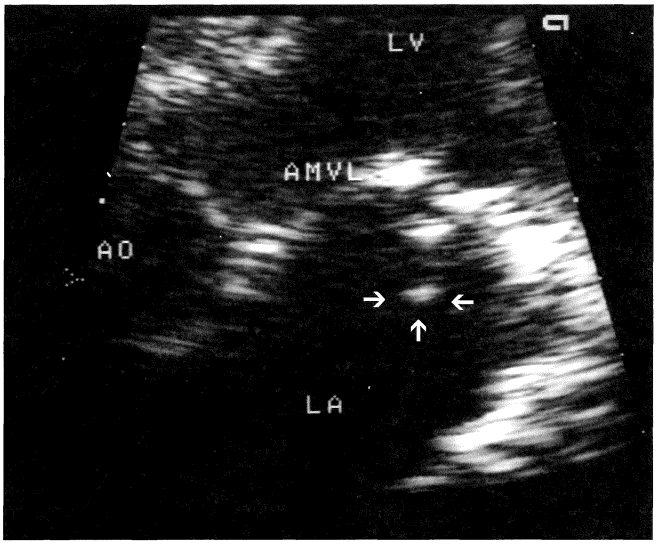


Figure 1. Transthoracic echocardiogram showing a vegetation(arrows) on the atrial aspect of the anterior mitral valve leaflet. (LV=left ventricle, LA=left atrium, AMVL=anterior mitral valve leaflet, AO=aorta)

polymorphs in CSF). He was started on intravenous penicillin, vancomycin, and cefotaxime after blood culture. Echocardiogram (Figure 1) on day 9 revealed vegetation on the atrial side of mitral valve attached to the anterior leaflet, mildly thickened mitral valve and mild mitral regurgitation while the global left ventricular function was good. On the same day, blood culture returned as showing gram positive cocci in chains on microscopy and growing *Streptococcus bovis (S. bovis)* ultrasensitive to penicillin (penicillin minimum inhibitory concentration 0.09 ug/ml). He was thus treated as infective endocarditis with intravenous penicillin G3 mega units every 4 hours and gentamycin 80mg every 12 hours, the latter was stopped after 6 days

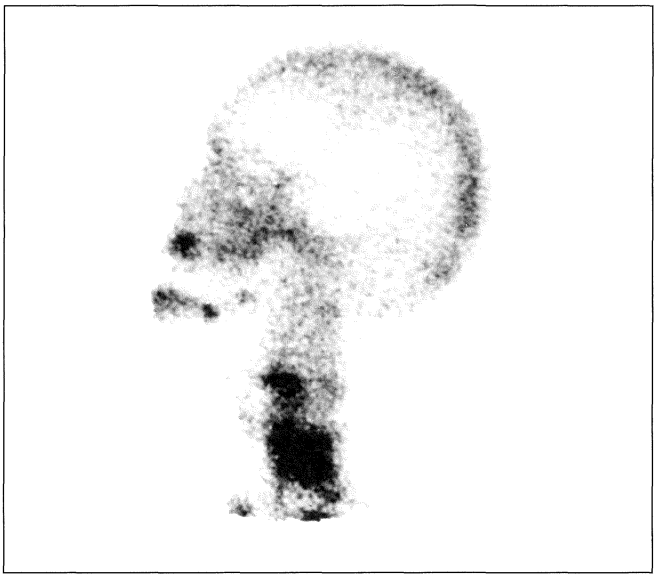


Figure 2. Technetium bone scan showing markedly increased tracer activity in C5 and C6.

because of vertigo. Culture of the CSF was negative, which was likely related to antibiotics received prior to lumbar puncture. Further investigation on his neck pain with MRI of cervical spine on day 25 of hospitalisation was thought to show degenerative changes, narrowing over C5/6 disc and C6/7 disc spaces, and prolapsed intervertebral discs at

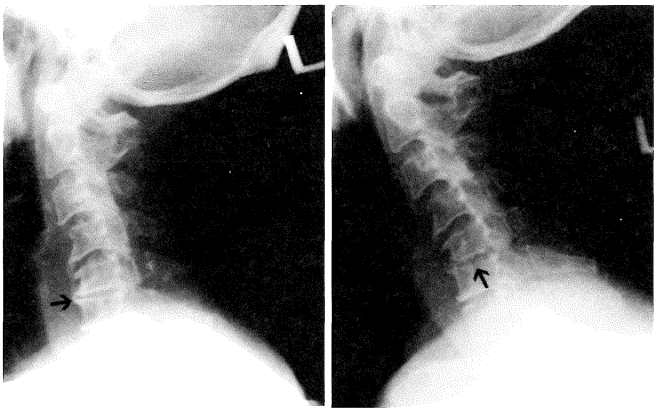


Figure 3. X-ray cervical spine. 3a. First admission(1.10.1996 on day 6 of neck pain): patchy bone loss in C5 vertebra and reduced C5/6 disc space(arrow). 3b. Second admission (17.10.1996): end-plate destruction noted at C5/6 (arrow) in addition to the previous findings.

these levels. Technetium bone scan on day 36 showed markedly increased tracer activities over lower cervical spine (Figure 2) but was thought to

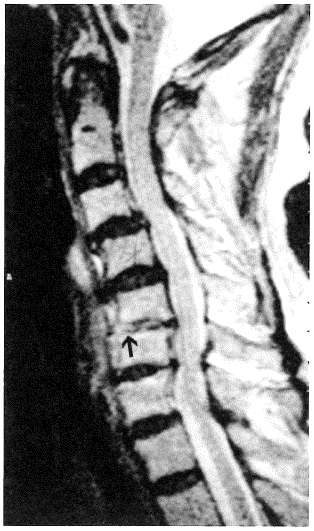
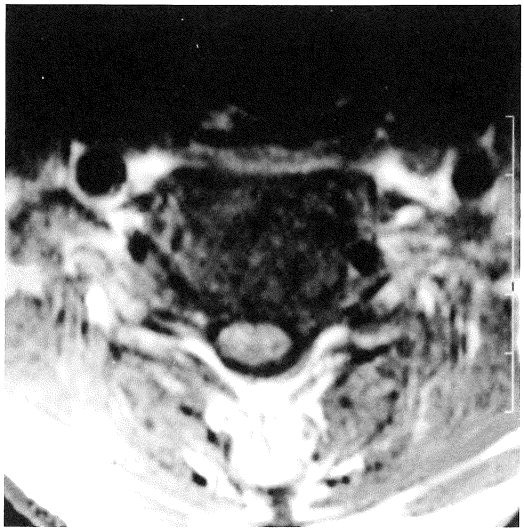


Figure 4a. MRI cervical spine (sagittal view) on 10-11-1996: the intervertebral disc over C5/6 level(arrow) shows hyperintense signal on T2 weighted image compatible with discitis.



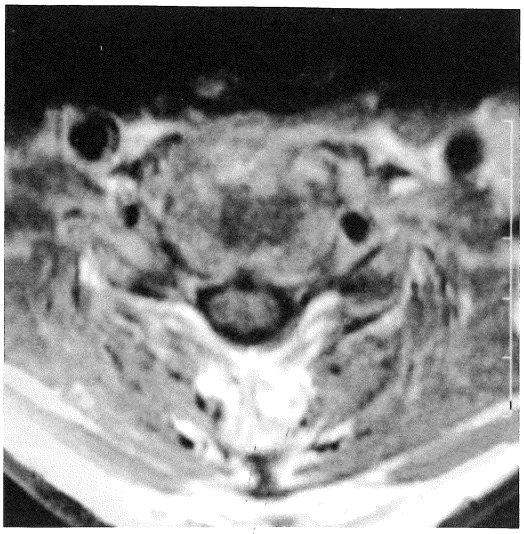


Figure 4b. MRI cervical spine (axial view) on 10-11-1996: C6 vertebra shows hypointense signal on T1 enhanced after contrast compatible with vertebral osteomyelitis.

indicate collapse fracture and degenerative changes rather than infective process. However, detailed review of the cervical spine as imaged by plain radiographs, CT scan and MRI by an experienced radiologist all revealed evidence of C5/6 spondylodiscitis and vertebral oseteomyelitis in addition to degenerative changes (see Figures 3a, 3b, 4a, 4b). A four-week course of penicillin G was completed with good clinical response. His neck pain, fever and night sweating subsided while his mental state, appetite and body weight improved.

However, his haemoglobin continued to decline from 10.1 g/dl on admission to 7.5 g/dl (hypochromic microcytic picture with iron deficiency) one month after admission. Because of the persistence of iron deficiency anaemia and the reported association between *S. bovis* endocarditis and colonic carcinoma, colonoscopy was performed. Colonoscopy with biopsy revealed adenocarcinoma of caecum/ascending colon, adenocarcinoma of sigmoid colon at 25 cm, and multiple colonic polyps due to tubular adenoma with moderate dysplasia. He later received sigmoid colectomy and right hemicolectomy under prophylactic antibiotic cover. He had an uneventful post-operative course and was discharged on day 9 post-operatively.

When followed up in our out-patient clinic, his appetite had improved with gradual weight gain. At 4 months after completion of the antibiotics course, his haemoglobin rose to 16.1 g/dl, ESR fell to 1 mm/hr and his body weight increased to 69 kg (a gain of 5 kg). Five months later, he was hospitalised 12 days for congestive heart failure precipitated by atrial fibrillation with rapid ventricular response, which responded to treatment with digoxin, frusemide and perindopril. One year afterwards, his body weight was maintained, his haemoglobin was 17.8 g/dl, his heart condition was stabilised on digoxin and perindopril, and he could achieve an exercise tolerance of climbing over 100 steps.

Discussion

Atypical presentation of infective endocarditis in old age

Infective endocarditis appears to be increasing among elderly patients[1-6] so that over 50% of patients are now over the age of 65 years[4]. This has been attributed to the decline of rheumatic heart disease in younger subjects, the high frequency of predisposing cardiovascular conditions, the use of prosthetic vascular devices, increased risk for iatrogenic/nosocomial bacteraemia from the use of invasive procedures and immunosuppressants, and the increasing mean age of the general population[1,2,3]. However, it poses a diagnostic and management challenge to physicians as elderly patients usually report fewer symptoms, their presentations may be atypical or nonspecific and they often have underlying chronic diseases[4,6]. They were less likely to report fever and to have tachycardia while anorexia, weight loss, hypotension, confusion and neurologic events such as stroke, seizure were more commonly found in the elderly group[4,7]. As a result

of frequent diagnostic errors, inappropriate antibiotic usage and the co-existence of other serious underlying diseases, the mortality rate, permanent disability and the need for long term care were significantly higher in the elderly population[2,3,4]. A survey by Terpenning, et al, has shown a mortality rate of 45% in patients aged over 60 years compared with 32% of those aged 40 to 60, and 9% of those aged under 40 years[4].

Von Reyn has formulated the clinical diagnostic criteria of infective endocarditis based on the classic triad of infection (fever, positive blood cultures), cardiac disorders (predisposing heart disease, new regurgitant murmur) and embolisation (vascular phenomena)[8]. However, elderly people may not present with this classic triad[6]. The difficulty in diagnosing the disease in elderly people may be due to the attribution of the non-specific symptoms of weakness, anorexia, weight loss, ill health, confusion, joint and back pains to "old age" or to other diseases commonly found in elderly people[2,3,6]. The diagnostic pitfall is illustrated in our patient: neck pain was initially attributed to cervical spondylosis, anaemia ascribed to gastrointestinal diseases alone, while the more chronic constitutional symptoms of weakness, easy fatiguability and ill health were ignored in the first admission.

Fever and heart murmur

Although the combination of fever and heart murmur is the cardinal feature of infective endocarditis, both may be absent in elderly patients[2,3,6]. Some studies have shown that fever was not a presenting symptom in 9 - 20% of elderly patients[8-11]. In elderly people, basal body temperature is generally lower and febrile response may be absent or impaired[6,12], and unless this is taken into consideration, a low grade fever is apt to be missed. However, McAlpine, *et al.* pointed out that inaccuracy of temperature recording may have contributed to the lack of pyrexia reported in some retrospective studies on fever response in infected elderly patients[13]. Prospective studies have revealed that although a febrile response may be delayed it is detectable with careful and effective temperature monitoring in the vast majority of elderly patients with infection[13,14]. Review of the temperature chart of our patient recorded in the first admission actually showed low grade fever kicks (Figure 5a), though partially masked by antibiotics given for Helicobacter eradication therapy and paracetamol given for neck pain. The detection of marked sweating in the second admission alerted us to have a more careful monitor of his temperature, which

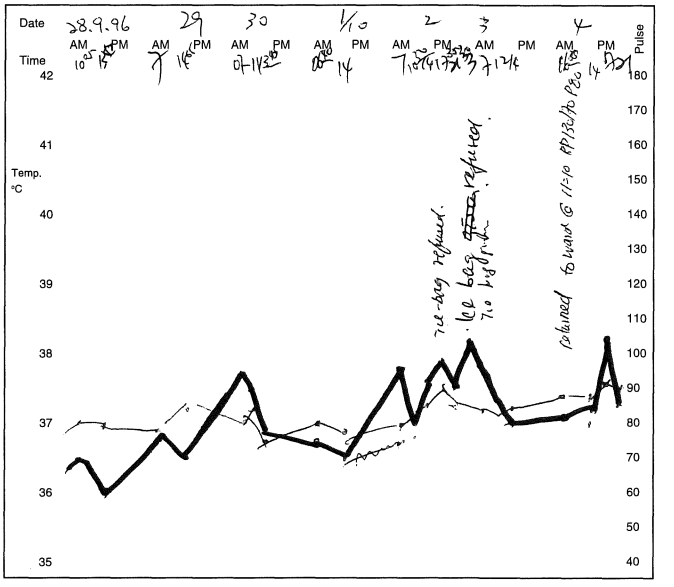


Figure 5a. Temperature chart of first admission: showing low-grade fever kicks.

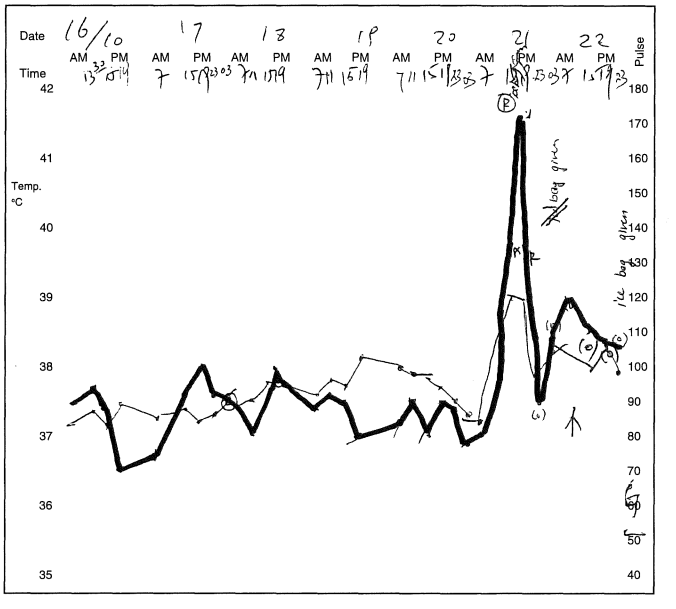


Figure 5b. Temperature chart of second admission showing low-grade fever kicks for the first few days followed by high fever on day 6.

showed low grade fever kicks in the first few days (Figure 5b).

The murmurs are often soft, and by themselves are not likely to arouse suspicion, as such murmurs are common in elderly patients and are frequently attributed to degenerative valve disease or is considered haemodynamically insignificant. Even when fever and a heart murmur are present, the diagnosis can still be missed in 50% of patients[9]. Presumably, the focus of the first admission was on the neck pain as an orthopaedic problem, and

there was no mention of any finding on heart murmur. Though a mitral regurgitant murmur was recorded in our patient on readmission, that the murmur could be a diagnostic clue to infective endocarditis was only retrospectively apparent when the echocardiogram and blood culture results returned.

Musculoskeletal symptomatology, spondylodiscitis and vertebral osteomyelitis

Backache and other musculoskeletal symptoms are common in elderly people and may be readily attributed to degenerative or rheumatic diseases, but the importance of musculoskeletal symptoms as a diagnostic clue in infective endocarditis has been emphasised by various authors[8,15-21]. In an analysis of 192 patients with bacterial endocarditis, musculoskeletal symptomatology was found in up to 44% of patients, was a presenting feature in 27%, and was the only presenting complaint in 15%[15]. Thus patients with infective endocarditis may present initially to orthopaedic surgeons for management [21] as in our present patient. Common manifestations were arthralgias, arthritis, low back pain, neck/scapular pain, diffuse myalgias and leg myalgias[15,19,21]. While most of the musculoskeletal manifestations are thought to be immune-mediated, septic emboli may account for some[15,21].

The association of infective endocarditis with spondylodiscitis and vertebral osteomyelitis were first reported[22,23] in the years 1965 and 1968 respectively. Both are generally thought to be due to septic metastases from the endocardial vegetations. The prognosis is determined by the underlying infective endocarditis[24]. Vertebral osteomyelitis, reported in 2.6% - 3.7% of infective endocarditis[15,19], may be difficult to diagnose in the setting of endocarditis because fever, bone pain and stiffness are common to both illnesses[25]. About 80 cases of spondylodiscitis complicating infective endocarditis have been reported to date[26]. In the 192 cases of infective endocarditis analysed by Chuchill, *et al.*[15], 24 were found to have low back pain and in 5 of these, the low back pain was caused by a lumbar disc space infection. In the 87 patients with infective endocarditis reported by Roberts Thomson, *et al*[21], 13 had severe low back pain and 2 had radiological evidence of septic discitis or vertebral osteomyelitis. Spondylodiscitis in patients with infective endocarditis is predominantly observed in men in the sixth decade and the main clinical findings are back pain (80%) and fever (94%)[26]. Spondylodiscitis is found in lumbar (70%), thoracic(14%), cervical (7%) and bifocal (11%) vertebrae and in 86% of the cases the infectious agent can be isolated[26].

It takes 2 to 8 weeks from the onset of osteomyelitis before there are any obvious abnormalities on a plain radiograph[27]. Even then in 50% of cases of vertebral osteomyelitis the radiographs are normal early on or show changes consistent with degenerative arthritis only, the rest are abnormal and show narrowing of the disc space, sclerosis, erosion of the endplates and destruction of the vertebral bodies[28]. In our patient, the cervical spine radiograph taken in the first admission (Figure 3a) showed narrowed disc space at C5/6 which had been interpreted as due to degenerative change only. Radiograph in the subsequent admission (Figure 3b, taken 23 days from onset of pain) did show some endplate erosion. Computerised tomography may also be normal in the early stages or may disclose a reduction in disc density [28]. Magnetic resonance imaging may reveal abnormalities earlier than either plain radiograph or CT scanning, but is not always available. However radionuclide bone scans with either gallium or technetium are highly sensitive and are the diagnostic procedure of choice if plain radiographs have been unhelpful[25,28,29]. Nevertheless, the common occurrence of degenerative changes in the spine in old age may lead to difficulties in interpretation of any abnormalities detected on imaging and clinical correlation is thus of paramount importance.

Osteo-articular involvement is said to be more common in *S. bovis* infective endocarditis than in other infective endocarditis[21,30]. In one series of 53 *S. bovis* endocarditis[30], 5 had embolic events in the bones (3 spondylitis, 2 sacroileitis). However, to our knowledge, only 3 cases of *S. bovis* endocarditis in association with vertebral osteomyelitis have been previously described[30,32,33] and only 7 cases of *S. bovis* endocarditis presenting as acute spondylodiscitis have been reported[26].

Neuropsychiatric manifestations and meningitis

Neuropsychiatric manifestations are commonly seen in elderly patients with infective endocarditis and may be the presenting symptoms in 33-45% of patients[2,6]. These include confusion, stroke, coma, menigoencephalitis, seizures, depression and paranoia[2,6]. Meningitis may arise as a superficial reaction to a deep-seated inflammation within the brain or as a result of direct infection from septic emboli.

S. bovis infection associated with central nervous system involvement is quite rare. In Ballet's series of 53 cases of *S. bovis* endocarditis, 11 embolic events were localized in the brain. There

have been 2 case reports of *S. bovis* brain abscess related to *S. bovis* endocarditis[34] and colonic villous adenoma[35]. Eleven case reports of *S. bovis* meningitis could be found in the literature review. Unique features included a negative Gram stain of the CSF and a relatively low mortality as compared with patients with meningitis caused by other group D streptococci[36]. More than half of the patients with *S. bovis* meningitis had endocarditis or colonic pathology[36]. Meningitis in our patient may have arisen from septic embolisation from endocardial vegetation or from extension of infection of the spine into the meninges. It is of interest to note the report[23] of a patient presenting with acute back pain, fever and confusion, a lumbar puncture for suspected meningitis led to the drainage of unsuspected vertebral osteomyelitis, and post-mortem revealed infective endocarditis, lumbar vertebral osteomyelitis and spinal pachymeningitis.

Streptococcus bovis endocarditis and colonic neoplasia

Streptococci and staphylococci account for over 90% of cases of infective endocarditis in elderly people [2]. Elderly patients with infective endocarditis have a higher frequency of group D streptococci including both the *Streptococcus bovis* and *Enterococcus faecalis* [6,37]. *S. bovis* endocarditis has a male predominance, occurs almost entirely in the elderly population[2,6,30,38] and is particularly important clinically because of its high association with colorectal disease, especially carcinoma, which have been reported since the mid-1970s[39-42]. *S. bovis*, a Lancefield group D streptococcus, is a commensal organism found in the genitourinary and gastrointestinal tracts. It was found in 10 - 16% of normal healthy people and, for patients with carcinoma of colon, the carriage rate would be up to four to five times higher than that of the normal population[42]. Two biotypes of *S. bovis* can be identified by laboratory testing. *S. bovis* I bacteraemia is highly associated with both colonic neoplasm (71%) and bacterial endocarditis (94%) compared with that of *S. bovis* II bacterameia (17% colonic neoplasm, 18% endocarditis)[43].

The overall rate of patients with *S. bovis* infective endocarditis who had colonic pathology was 42 - 69% as compared with 17% of patients with *S. bovis* bacteraemia[40,44]. Neoplasia was much more frequent in patients with endocarditis than in those with bacteraemia alone. However, the incidence of non-neoplastic colonic conditions such as colitis, diverticulitis or ischaemia were more common in patients with *S. bovis* bacteraemia[44]. A case control study carried out by Hoen, *et al*, further reinforced the evidence that colonic tumours represent a risk factor for the development of *S. bovis* endocarditis. They observed a significant linear trend of increasing risk of endocarditis development with a rising histopathologic grade of the tumour [45]. The tumours were more frequent in the recto-sigmoid region[30].

To explain the strong association between colonic neoplasia and underlying *S. bovis* endocarditis, several mechanisms have been proposed. Ruoff, *et al*, proposed the possibility of specific bacterium-host cell interactions involving *S. bovis* biotype I organism with selective adherence to surface receptors on neoplastic colonic cells or cardiac endothelium[43]. Zarkin, *et al*, thought that there was a change of colonic flora in patients with colonic carcinoma and *S. bovis* may have a specific propensity for both transmucosal invasion and the development of the bacterial endocarditis[44]. Klein, *et al*, believed that focal disruption of the mucosa by the neoplasia with exposure of the underlying blood vessel to the faecal flora is the most likely mechanism[42]. As liver disease and/or dysfunction was documented in 50% of patients with *S. bovis* endocarditis and 53% of patients with bacteraemia, *S. bovis* bacteraemia was an indication of the possibility of underlying colon pathology as well as liver disease, particularly in alcoholics[44,46]. Alterations in hepatic secretion of bile salts or immunoglobulins, porto-systemic shunting in portal hypertension, and a compromised hepatic reticuloendothelial system may promote the overgrowth of *S. bovis* and its translocation into the portal venous system and contribute to the development of *S. bovis* septicaemia and subsequent endocarditis[44].

Vavular lesions

Absence of previous cardiac disease in patients with infective endocarditis was more frequent with *S. bovis* than with other organisms[30,38]. Some series showed a predominance of aortic valve infection in elderly patients[30,38]. This was thought to be related to the high proportion of undiagnosed bicuspid aortic valves[38]. However the study by Terpenning *et. al.* showed that the mitral valve was most frequently involved in elderly patients[4]. This was explained by the underestimation of pre-existing mitral valve prolapse in patients over age 60 because of misleading echocardiographic results as well as the occurrence of calcified mitral annulus fibrosus in old age, another underlying mitral valve lesion predisposing to endocarditis[4].

Treatment and prognosis

Penicillin-sensitive *S. bovis* is effectively treated with high doses of penicillin alone. This is the recommended treatment for patients over 65 years[47]. The alternative short-course regimen of penicillin G and aminoglycoside combination is not preferred for the elderly patient because of the possible increased risk of aminoglycoside toxicity [47]. Vertigo developed in our patient despite serum gentamycin levels not exceeding toxic levels. Serum bactericidal titres were achieved with the dosage of penicillin used. The prognosis of *S. bovis* endocarditis is slightly better than that of infective endocarditis caused by other micro-organisms, but the late mortality rate is above average probably due to the poor prognosis inherent in the underlying colonic disease[30]. Follow-up colonoscopy was suggested as carcinoma of the colon has been reported from 2 to 7 years after an episode of *S. bovis* endocarditis[39,48].

Conclusion

It is likely that our patient had colonic carcinoma 8 months before admission, accounting for his 8-month history of gradual weight loss, and subsequent detection of iron deficiency anaemia and positive faecal occult blood test. Being an elderly man with diabetes mellitus and colonic carcinoma, he has an increased risk of infective endocarditis, in particular that associated with *S. bovis*. The 4-month history of night sweating, malaise and poor appetite can be due to the development of either *S. bovis* bacteraemia or *S. bovis* endocarditis, which further aggravated his weight loss and anaemia. Three days before his first admission, he had severe neck pain due to the development of vertebral osteomyelitis of the cervical spine and 28 days later, he had meningitis, which explained his confusion, high fever and marked neck pain. Although a heart murmur was documented only in the second admission and definite proof of vegetation came 9 days after admission, we think that his vertebral osteomyelitis is more likely secondary to infective endocarditis. This is in concordance with Churchill's study, which showed that, in many instances, back pain(due to disc space infection) preceded other manifestations of endocarditis by months; the mean duration of the symptoms before diagnosis of infective endocarditis being 4.25 months(range 1.5 - 8 months)[15]. On the other hand, one could argue that it all started in the colon. It is possible that both the endocarditis and the osteomyelitis arise directly from the bacterameia secondary to the colonic carcinoma. There has been a case report of *Streptococcus bovis*-infected total hip arthroplasty without infective endocarditis, probably secondary to bacteraemia from an occult premalignant colonic polyp[49]. We don't think that the exact sequence of events can be determined with certainty.

We recommend that patients presenting with new back pain in the absence of previous injury, local spinal tenderness, fever, and heart murmur be evaluated for infective endocarditis and vertebral osteomyelitis/spondylodiscitis. If *Streptococcus bovis* endocarditis is diagnosed, than a workup for colonic lesion, especially carcinoma, should be done.

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