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A 76-year-old man with septic arthritis

A 76-YEAR-OLD MAN presents to the hospital with fever, chills, and painful swelling of the left knee. His symptoms began the day before and worsened to the point that he now cannot walk.

His temperature as measured at home was 101.5°F (38.6°C). He has no history of antecedent trauma and says he has no cough, shortness of breath, chest pain, or dysuria.

Medical history

Multiple myeloma of the IgG kappa type was diagnosed 2 years ago and treated with cyclophosphamide. He currently is receiving prednisone 50 mg/day, erythropoietin, and periodic blood transfusions.

His other medications include lisinopril, amlodipine, and doxazosin, as he has a history of hypertension and benign prostatic hypertrophy.

His history also includes degenerative joint disease of the knees, for which he underwent left knee replacement surgery 4 months ago.

He is a retired schoolteacher who lives alone.

Physical examination

The patient is of medium build and is in no apparent distress. His temperature is 99.7°F (37.6°C), blood pressure 140/59 mm Hg, and pulse 91 beats per minute.

His heart sounds are normal with no murmurs. The lungs are clear to auscultation. The abdomen is soft with no palpable masses; the liver and spleen are not palpable.

The left knee joint is swollen, warm, and mildly diffusely tender to palpation, with mild erythema of the overlying skin. A well-healed surgical scar is present on the anterolateral aspect of the left knee. There is a joint effusion. The patient can move the joint through

its full range of motion, but he feels pain at the extremes of flexion and extension. He is unable to walk because of the pain.

All the peripheral pulses are palpable. There are no peripheral stigmata of infective endocarditis, such as petechiae, splinter hemorrhages, Roth spots, or Janeway lesions.

The neurologic examination is normal.

Laboratory findings

Samples for routine laboratory tests and two sets of blood cultures are obtained. The laboratory tests reveal mild pancytopenia:

- White blood cell count $2.4 \times 10^9/L$ (normal 4.0–11.0)
- Hemoglobin concentration 7.2 g/dL (normal 13.5–17.5)
- Hematocrit 22% (normal 40–52)
- Platelet count $88 \times 10^9/L$ (normal 150–400).

There is mild hypoalbuminemia and chronic renal insufficiency, with a creatinine concentration of 1.3 mg/dL (normal 0.7–1.4). Alkaline phosphatase, bilirubin, and transaminase levels are normal, as is the urinalysis.

The chest radiograph is normal.

The patient is admitted to the hospital and evaluated by the orthopedics service for suspected prosthesis infection.

ADDITIONAL DIAGNOSTIC TESTING

1 Which of the following tests is most useful for further evaluation of this patient?

- Knee radiography
- Arthrocentesis
- Surgical exploration of the affected knee

Knee radiography. When a patient with a prosthetic knee joint has pain and inflammatory symptoms, infection needs to be consid-

The patient has full range of motion, but pain at extreme flexion and extension

ered,¹ but also conditions such as mechanical loosening, hemarthrosis, gout, dislocation, metallic debris-induced synovitis, or osteolysis. Plain radiographs are not sensitive or specific enough for the diagnosis of infection, but they may reveal one of the following in about 50% of patients who have an infected prosthetic joint:

- Abnormal lucency (> 2 mm in width) at the bone-cement interface
- Change in position of the prosthetic components
- Cement fracture
- Periosteal reaction
- Motion of components on stress views.¹

Arthrocentesis. The diagnosis of infection depends on isolating the pathogen by aspiration of the joint fluid or by culture of the periprosthetic tissue obtained at arthrotomy. A white blood cell count of more than $25 \times 10^9/L$ or with 75% or more polymorphonuclear leukocytes in the absence of crystals is suspicious for infection.^{2,3} Gram stain is positive in about 25% of cases, so a negative Gram stain does not rule out infection.⁴

Surgical exploration. If the diagnosis remains uncertain after aspiration and culture and the suspicion is high, an open biopsy should be performed.^{2,3}

In our patient, knee radiographs show left knee effusion and the absence of any fractures. Arthrocentesis of the left knee shows the synovial fluid to be purulent and blood-stained, with a white blood cell count of $46 \times 10^9/L$, of which 80% are neutrophils. Synovial fluid cultures are obtained and broad-spectrum antibiotics (vancomycin 1 g/day and ciprofloxacin 500 mg orally twice daily) are started.

■ IDENTIFYING THE PATHOGEN

Patients with multiple myeloma are prone to infections caused by organisms such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, or *Klebsiella pneumoniae* in the lungs and *Escherichia coli* or other gram-negative bacilli in the kidneys. This susceptibility is mainly due to deficiency of normal antibodies and impaired antibody formation after antigenic stimulation.⁵ Other immunologic abnormalities include defective complement function⁶ and neutrophil migration⁷ in

patients with multiple myeloma. Our patient is further susceptible to infections because he is taking a steroid (prednisone).

The patient's blood cultures remain negative after 5 days, but the synovial fluid cultures grow penicillin-sensitive group D streptococci.

Streptococci are gram-positive aerobic bacteria that grow in pairs or chains of varying lengths. They are classified into various Lancefield groups on the basis of antigenic differences in cell wall carbohydrates or teichoic acids. Lancefield's group D streptococci originally included both enterococci and nonenterococcal species, but enterococci are now designated a separate genus.

Among the group D streptococci, *Streptococcus bovis* is one of the most common pathogens, and it is extremely sensitive to penicillin. The infections caused by *S bovis* are mainly bacteremia and endocarditis. An important feature of *S bovis* bacteremia is that 25% to 50% of patients develop endocarditis.⁸

S bovis is identified in the synovial fluid cultures from our patient, so endocarditis is therefore a possibility. However, because of the negative blood cultures, the absence of a heart murmur, and plans for a long course of intravenous antibiotics for prosthetic joint infectious arthritis, echocardiography or similar investigations are not performed.

■ ERADICATING THE INFECTION

2 What is the best strategy for eradicating infection in this patient?

- Antibiotic therapy alone
- Prosthesis removal followed by antibiotic therapy and then prosthesis replacement
- Prosthesis removal and immediate replacement followed by antibiotic therapy

Eradication of infection in a prosthetic joint usually requires both removal of the prosthesis and antibiotic therapy. Antibiotic therapy alone is successful in only 6% to 10% of cases.⁹

An approach that combines prosthesis removal with a subsequent 6-week course of antibiotic therapy and reimplantation is associated with a 97% success rate.^{1,9}

An alternative is to remove the prosthesis and implant a new one during the same procedure. This approach is effective in 50% to

Share of
S bovis
bacteremia
cases associated
with
endocarditis:
25% to 50%



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75% of cases and is often used in elderly or infirm patients to avoid prolonged bedrest and a second major operation.^{1,9}

Case continued

Our patient undergoes left knee synovectomy with debridement of nonviable tissue and replacement of the prosthesis. He is then treated with intravenous penicillin for 6 weeks followed by oral amoxicillin projected to be continued for the rest of his life.

His postoperative course is complicated by left femoral deep venous thrombosis, which is treated with an inferior vena caval filter. He is then discharged home.

■ S BOVIS AND GASTROINTESTINAL DISEASE

3 Which gastrointestinal conditions are associated with *S bovis* infections?

- Colon cancer
- Adenomatous polyps of the colon
- Inflammatory bowel disease
- All of the above

McCoy and Mason¹⁰ first reported a case of enterococcal endocarditis and colon cancer in 1951. It now appears that the causative organism was in fact *S bovis*. In 1977, Klein and associates¹¹ suggested a strong association of *S bovis* bacteremia with colon cancer and found a significantly higher fecal carrier rate of *S bovis* in patients with colon cancer com-

pared with healthy controls and patients with nonmalignant gastrointestinal disease. **TABLE 1** summarizes studies that assessed the prevalence of colon cancer and polyps in patients with *S bovis* bacteremia.^{12–16}

Other gastrointestinal abnormalities have been reported in association with *S bovis* (**TABLE 2**), although less commonly.¹⁷ Despite the presence of gastrointestinal lesions in the patients in these reports, no clear relationship with *S bovis* has been identified except in the case of adenomatous polyps and colon cancer. Notably, *S bovis* infections other than endocarditis have been described in association with colon cancer or adenomatous polyps. These include meningitis, vertebral osteomyelitis, spondylodiscitis, septic arthritis of the hip, splenic abscess, deep neck abscess, and peritonitis.

Only three cases of septic arthritis caused by *S bovis* have previously been reported.^{18–20} These cases presumably originated from clinically inapparent bacteremia. *S bovis* bacteremia is known to occur in association with colonic lesions and, in particular, colon cancer. For this reason, screening for colon cancer is appropriate in our patient.

4 What screening method for colon cancer should be used?

- Flexible sigmoidoscopy and fecal occult blood testing
- Double-contrast barium enema
- Colonoscopy

Our patient underwent synovectomy with debridement and prosthesis replacement

TABLE 2

Gastrointestinal lesions in patients with *S bovis* bacteremia

SITE OF LESION	TYPE OF LESION OR PROCEDURE
Oral cavity	Dental sepsis/procedures, cancer
Esophagus	Mediastinitis, cancer, diverticulum, hiatal hernia, instrumentation
Stomach	Polyps, lymphoma, adenocarcinoma
Duodenum	Diverticulum
Liver	Cirrhosis, metastases, biopsy (carcinoma)
Biliary tree	Cholangitis, cholelithiasis
Peritoneum	Peritonitis/appendicitis, subphrenic abscess, metastases
Spleen	Abscess
Pancreas	Adenocarcinoma
Colon, rectum	Instrumentation/operation, diverticulosis, diverticulitis, inflammatory bowel disease, adenoma, adenocarcinoma, metastases, bleeding, hemorrhoids
Anus	Abscess

ADAPTED WITH PERMISSION FROM BEECHING NJ, CHRISTMAS TI, ELLIS-PEGLER RB, NICHOLSON GI. *STREPTOCOCCUS BOVIS* BACTERAEMIA REQUIRES RIGOROUS EXCLUSION OF COLONIC NEOPLASIA AND ENDOCARDITIS. Q J MED 1985; 56:439–450.

Colonoscopy is the most effective method of colon cancer screening. In a cohort study,²¹ the incidence of colorectal cancer was reduced by 76% to 90% in patients who underwent colonoscopy and polypectomy compared with controls, and none of the colonoscopy recipients died of colorectal cancer during an average follow-up of 5.9 years.

Sigmoidoscopy is not enough: nearly 40% of colorectal cancers arise proximal to the splenic flexure, and flexible sigmoidoscopy will miss these cancers.²²

Double-contrast barium enema (DCBE) missed 26% of adenomas more than 1 cm in size and missed 25% of rectosigmoid cancers in a recent study.²³ Because of this poor sensitivity and the absence of data on barium enema in screening populations, DCBE is not recommended as a primary screening strategy. If colonoscopy is unavailable, incomplete, technically difficult, or refused by the patient, a DCBE should be performed in conjunction with sigmoidoscopy.

Pathogenesis unclear

The pathophysiologic relationship between *S bovis* and colonic lesions remains unresolved. Bacteremia depends on bacterial translocation and bacterial virulence factors.

Bacterial translocation. Three mechanisms contribute to bacterial translocation: bacterial overgrowth, mucosal injury, and immunocompromised state.¹⁴ The fecal carrier rate of *S bovis* is definitely increased in patients with malignant and premalignant colon lesions. For example, Klein et al¹¹ found a 55.5% fecal carrier rate of *S bovis* in patients with colon cancer compared with a 10.4% rate in healthy volunteers. Other studies also have shown a higher fecal carrier rate in colon cancer patients compared with controls.²⁴

Bacterial virulence. There are two biotypes of *S bovis*, and they are distinguished on the basis of dextran production and mannitol fermentation. Type I is more virulent than type II. For instance, one study²⁵ showed type I bacteremia to be associated with cardiac involvement in 94% of patients and with colonic lesions in 71%, whereas type II bacteremia was associated with these respective findings in 18% and 17% of patients. Interestingly, dextran production is one of the factors that contribute to adherence of the bacteria to cardiac valves.

■ CASE CONTINUED: LONG-TERM FOLLOW-UP

Our patient's colonoscopy shows diverticulosis. No polyps or masses are found. The probability of an association between diverticulosis and *S bovis* is difficult to determine from anecdotal reports. Diverticular disease is common in the elderly, and the presence of diverticula in patients with *S bovis* bacteremia may be coincidental.

5 Which colon cancer screening strategy is recommended for this patient?

- No need for further screening
- Continue screening as a high-risk patient (colonoscopy every 5 years)
- Continue screening as an average-risk patient (colonoscopy every 10 years)


Cases of colon cancer have been reported several years after treatment of *S bovis* bac-



teremia—14 years in one case.²⁶ In another case, an invasive cecal carcinoma was reported 28 months after a negative initial screening colonoscopy.²⁷

Colon cancer cases also have been reported in association with infections with enterococci, bacteroides, *Streptococcus agalactiae*, *E coli*, *Klebsiella oxytoca*, *Clostridium septicum*,

Clostridium perfringens, *Streptococcus salivarius*, and *Streptococcus viridans*.^{28,29}

However, no data currently indicate that *S bovis* bacteremia is a risk factor for the future development of colon cancer. So until further data are available, we suggest continued screening of patients such as ours every 10 years, as for average-risk patients, unless other risk factors emerge. 

■ REFERENCES

1. Brause BD. Infections with prostheses in bones and joints. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 5th ed. Philadelphia: Churchill Livingstone; 2000:1196–1199.
2. Insall JN. Infection of total knee arthroplasty. Instr Course Lect 1986; 35:319–324.
3. Friedman RJ, Poss R. Revision total knee arthroplasty in patients with osteoarthritis. Rheum Dis Clin North Am 1988; 14:537–544.
4. Brause BD. Infected total knee replacement—diagnostic, therapeutic, and prophylactic considerations. Orthop Clin North Am 1982; 13:245–249.
5. Paradisi F, Corti G, Cinelli R. Infections in multiple myeloma. Infect Dis Clin North Am 2001; 15:373–384.
6. Kraut EH, Sagone AL Jr. Alternative pathway of complement in multiple myeloma. Am J Hematol 1981; 11:335–345.
7. Spitzer LE, Spath P, Petz L, Cooper N, Fudenberg HH. Phagocytes and C4 in paraproteinemia. Br J Haematol 1975; 29:279–292.
8. Moellering RC Jr. *Enterococcus* species, *Streptococcus bovis*, and *Leuconostoc* species. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 5th ed. Philadelphia: Churchill Livingstone; 2000:2147–2156.
9. Pellegrini VD Jr. Management of the patient with an infected knee arthroplasty. Instr Course Lect 1997; 46:215–219.
10. McCoy WC, Mason JM III. Enterococcal endocarditis associated with carcinoma of the sigmoid: report of a case. J Med Assoc State Ala 1951–1952; 21:162–166.
11. Klein RS, Recco RA, Catalano MT, Edberg SC, Casey JI, Steigbigel NH. Association of *Streptococcus bovis* with carcinoma of the colon. N Engl J Med 1977; 297:800–802.
12. Klein RS, Catalano MT, Edberg SC, Casey JI, Steigbigel NH. *Streptococcus bovis* septicemia and carcinoma of the colon. Ann Intern Med 1979; 91:560–562.
13. Leport J, Leport C, Vilde JL, Cerf M. Endocardites a *Streptococcus bovis* et pathologie colique: a propos de 42 observations. Gastroenterol Clin Biol 1987; 11:25A.
14. Zarkin BA, Lillimoe KD, Cameron JL, Effron PN, Magnuson TH, Pitt HA. The triad of *Streptococcus bovis* bacteremia, colonic pathology, and liver disease. Ann Surg 1990; 211:786–792.
15. Hoen B, Briancon S, Delahaye F, et al. Tumors of the colon increase the risk of developing *Streptococcus bovis* endocarditis: a case-control study. Clin Infect Dis 1994; 19:361–362.
16. Ballet M, Gevigney G, Gare JP, Delahaye F, Etienne J, Delahaye JP. Infective endocarditis due to *Streptococcus bovis*: a report of 53 cases. Eur Heart J 1995; 16:1975–1980.
17. Beeching NJ, Christmas TI, Ellis-Pegler RB, Nicholson GI. *Streptococcus bovis* bacteraemia requires rigorous exclusion of colonic neoplasia and endocarditis. QJM 1985; 56:439–450.
18. Garcia-Porrúa C, Gonzalez-Gay MA, Montenosó JR, Sanchez-Andrade A, Gonzalez-Ramirez A. Septic arthritis due to *Streptococcus bovis* as presenting sign of silent colon carcinoma. Rheumatology 2000; 39:338–339.
19. Grant RJ, Shang WY, Whitehead TR. Isolated septic arthritis due to *Streptococcus bovis*. Clin Infect Dis 1997; 24:1021.
20. Calderon J, Peiro ME, Penalver E. Septic arthritis due to *Streptococcus bovis* [in Spanish]. Med Clin (Barc) 1992; 98:137–138.
21. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993; 329:1977–1981.
22. Rex DK, Chak A, Vasudeva R, et al. Prospective determination of distal colon findings in average-risk patients with proximal colon cancer. Gastrointest Endosc 1999; 49:727–730.
23. Kewenter J, Breringe H, Engaras B, Haglind E. The yield of flexible sigmoidoscopy and double-contrast barium enema in the diagnosis of neoplasms in the large bowel in patients with positive Hemoccult test. Endoscopy 1995; 27:159–163.
24. Burns CA, McCaughey R, Lauter CB. The association of *Streptococcus bovis* fecal carriage and colon neoplasia: possible relationship with polyps and their premalignant potential. Am J Gastroenterol 1985; 80:42–46.
25. Ruoff KL, Miller SI, Garner CV, Ferraro MJ, Calderwood SB. Bacteremia with *Streptococcus bovis* and *Streptococcus salivarius*: clinical correlates of more accurate identification of isolates. J Clin Microbiol 1989; 27:305–308.
26. Honberg PZ, Gutschik E. *Streptococcus bovis* bacteraemia and its association with alimentary-tract neoplasm. Lancet 1987; 1:163–164.
27. Robbins N, Klein RS. Carcinoma of the colon 2 years after endocarditis due to *Streptococcus bovis*. Am J Gastroenterol 1983; 78:162–163.
28. Panwalker AP. Unusual infections associated with colorectal cancer. Rev Infect Dis 1988; 10:347–364.
29. Keusch GT. Opportunistic infections in colon carcinoma. Am J Clin Nutr 1974; 27:1481–1485.

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