Campylobacter Fetus Septic Arthritis: Report of a Case

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We report a case of septic arthritis caused by the fastidious gram-negative rod Campylobacter fetus. We suggest that the organism may be part of the endogenous flora and that the clinical infections tend to occur in compromised hosts. Our patient is the first to be described with multiple myeloma and C. fetus septic arthritis. The documented cases of culture-proven C. fetus septic arthritis reported to date have occurred in three men and one woman, all in the seventh and eighth decades of life, with a mono-articular large joint distribution. The septic arthritis always occurred in previously injured joints and curiously enough need not be associated with a toxic-appearing patient. C. fetus infections are also associated with the signs and symptoms of clinical thrombophlebitis. We stress caution in establishing this diagnosis of phlebitis on clinical evaluation and urge differentiation of true deep vein thrombophlebitis from pseudothrombophlebitis or dissected popliteal synovial cyst. This latter diagnosis may be made non-invasively by ultrasound techniques.

CASE REPORT

A 77-year-old white male of Jewish ancestry entered Yale–New Haven Hospital on December 27, 1977, complaining of an acutely swollen tender right knee.

There was a 20-year history of arthralgias of the proximal and distal interphalangeal joints of the fingers; the knees, ankles, and shoulders were also affected. The erythrocyte sedimentation rate (ESR) was always minimally elevated, but rheumatoid factor was never present. X-rays of the involved joints demonstrated only osteoarthritis. High doses of salicylates were of little benefit. In 1975 the ESR was 60 mm/hr, the rheumatoid factor was still negative, but an ANA was positive to a titer of 1:32. Because of persistent anemia and thrombocytopenia, bone marrow aspirate and biopsy were performed, which revealed sheets of atypical plasma cells. There was $\gamma^G$ kappa monoclonal globulin of 4.5 gm/dl with a moderate amount of free kappa chains in the urine, and the normal serum immunoglobulins were depressed. There were no lytic bone lesions and his serum creatinine was 0.8 mg/dl. A right knee synovial biopsy demonstrated chronic synovitis with a negative Congo red stain for amyloid. Because of the diagnosis of multiple myeloma intermittent melphalan and prednisone were begun. The previously described bone marrow biopsy showed many interesting foamy histiocytes containing PAS-positive material characteristic of...
Gaucher's cells. The acid phosphatase was 13.2 international units/L (normal 1.2–4.5 units/L). The prostatic fraction was normal. The glucocerbroside activity of fresh leukocytes was absent. The spleen, which was nonpalpable, was twice normal size by radioisotope scan.

By November 1977, the IgG kappa was 2.4 gm/dl. The last dose of drugs was taken one month prior to admission. During the five days prior to admission, the right knee spontaneously became progressively more swollen and tender despite increasing prednisone to 30 mg daily. There had been no trauma and he had no contact with farm animals. Fever and chills were conspicuously absent.

**PHYSICAL EXAMINATION UPON ADMISSION**

He was an alert, nontoxic-appearing white male with a blood pressure of 140/94 mm Hg, pulse 76 beats/min, respirations 20 breaths/min, and temperature 98.4°F rectally. Vitiligo was present but there were no splinter hemorrhages, Janeway lesions, Osler's nodes, nor Roth spots. Lymphadenopathy was absent. The chest, cardiovascular system, and abdomen were normal. There were mild flexion contractures of the right and left elbows. Synovial thickening of both wrists and Heberden's nodes were present. The right knee was massively swollen, tender, and warm. The proximal calf was 35 cm in circumference (left 32.5 cm) and also warm and tender.

**Laboratory Data**

The white blood count was 5,200/mm³ with a normal differential. There were 90,000/mm³ platelets, the hematocrit was 28.8 percent, and the ESR 34 mm/hr. The following were also obtained: Whole blood glucose 88 mg/dl, BUN 19 mg/dl, creatinine 0.6 mg/dl, serum uric acid 2.7 mg/dl. The rheumatoid factor was negative but the fluorescent antinuclear antibody was positive to a titer of 1:32. The third component of complement was 108 mg/dl (normal). X-rays of both knees showed vascular calcification, degenerative changes, and a right effusion.

**HOSPITAL COURSE**

An arthrocentesis was performed on the first day. The synovial fluid was serosanguineous, and did not clot. Crystals were not seen microscopically with a polarizing light, nor were organisms seen in the unsedimented fluid gram stain. The cell count was 116,500 erythrocytes/mm³ and 41,000 leukocytes/mm³ (94 percent granulocytes). The fluid protein was 4.3 gm/dl and the glucose 48 mg/dl (simultaneous serum glucose, 127 mg/dl). On the second hospital day, the right calf was more inflamed and a venogram was performed which did not show deep vein thrombophlebitis. On the third hospital day his knee remained inflamed and the patient became febrile for the first time (101°F rectally). A second arthrocentesis was performed which had an identical fluid analysis. Serial longitudinal and transverse sonographic sections through the right knee and calf displayed an area 12 cm in length by 1.8 cm in depth of low-level echos in the posterior portion of the knee and calf compatible with a dissected popliteal synovial cyst (see Fig. 1). Forty mg of prednisolone t-butyl acetate was injected intra-articularly which resulted in some symptomatic improvement. Elevation of the leg and warm soaks were also begun.

On the eighth hospital day, the joint fluid was reported to be growing *C. fetus* and blood cultures were obtained, which were also growing *C. fetus* subspecies intestinalis, three days later. Disc-sensitivities were: sensitive to ampicillin, carbenicillin, cephalosporin, kanamycin, gentamicin, clindamycin, tetracycline, and chloramphenicol. Intermediate to penicillin. Tetracycline therapy was initiated. Over the next three
weeks the inflammation in his right knee and calf gradually subsided. The tetracycline was stopped after four weeks. Repeat blood and synovial fluid cultures after two weeks of therapy and following cessation of tetracycline were sterile.

**DISCUSSION**

Infections with *Campylobacter fetus* have been classically infectious diseases of goats, birds, cattle, and sheep [1,2]. The first report of a human infection with this microaerophilic gram-negative rod did not appear until 1947—Vinzeat et al. [3], and Ward recorded the index case in man for the English literature the following year [4]. In the last 30 years many cases of human infection have been described [3–22], and a recent review summarized 91 cases of bacteremic *C. fetus* infections [23].

Goldenberg et al. collected all of the cases of acute septic arthritis seen at the Boston City Hospital between 1965 and 1972 [24]. They found only thirteen cases caused by gram-negative rods; and none by the unusual pathogen *Campylobacter fetus*. While a 12 percent incidence of “arthritic symptoms and signs” was reported in a literature review of *C. fetus* bacteremia [23], there have been only four cases described of culture-proven purulent *C. fetus* septic arthritis. King and Bronsky reported the first case in 1961 [5]. This index case, like ours, was a septuagenarian (74 years old) who had a previously injured knee, had not been in contact with farm animals, and did not appear septic or acutely ill. The joint fluid was described as serosanguineous with “many” polymorphonuclear cells and erythrocytes. The septic arthritis resolved with chloramphenicol therapy.

The second case was reported four years later by Kilo, Hagemann, and Marzi [6]. They describe a 62-year-old male with a previously injured knee who also had no farm contacts, but was receiving corticosteroid therapy. Both the joint fluid and blood specimens grew *C. fetus*. The synovial fluid was cloudy and purulent and on microscopic exam contained innumerable polymorphonuclear cells and erythrocytes. This patient did have chills and a high fever. The toxic course remitted only after
surgical drainage of the knee and the initial choice of antibiotics (penicillin and streptomycin) was changed to tetracycline.

The third case, of a 74-year-old woman, was reported by Kutner and Arnold [25] and simultaneously by Bokkenhauser [7]. This patient had sustained a fracture of her tibial plateau 26 years earlier. She presented with a large joint acute mono-articular arthritis and \textit{C. fetus} was cultured from the synovial fluid. This arthritis did not respond to immobilization, parenteral penicillin, and streptomycin, necessitating removal of the screw that had been placed in her tibial plateau 26 years earlier. She defervesced and improved after four weeks of ampicillin therapy.

The last and most recent case was described in 1970 by Bokkenhauser [7]. \textit{C. fetus} was recovered from an acutely inflamed knee of a 74-year-old man who had injured his knee years previously. The initial therapy of penicillin and streptomycin was ineffective. Ampicillin resulted in complete resolution of the signs and symptoms.

Four of the \textit{C. fetus} arthritides (including the present case) appeared in men and all of the cases involved previously injured, large joints. While other synovial analyses have not been well described, the fluid from our patient was turbid, bloody, with low viscosity, a poor mucin clot, and had a Group III range of white blood cells (with at least 75 percent polys) characteristic of septic arthritis. Thrombophlebitis was suspected clinically, but, in fact, unproven by venography. These signs and symptoms were demonstrated on ultrasound examination to be the consequence of a ruptured synovial or Baker's cyst. Pseudothrombophlebitis (PTP) is defined as the presence of signs of thrombophlebitis in association with a dissected, ruptured, or large intact synovial cyst [26]. Of Katz's series of 34 patients with PTP, 91 percent had underlying inflammatory joint disease [26]—as did all five of the patients with \textit{C. fetus} septic arthritis. Certainly those with \textit{C. fetus} septic arthritis are at an increased risk to develop the PTP syndrome because of their chronic arthritis.

It is important to point out that clinical thrombophlebitis has been associated with \textit{C. fetus} infections for some time (refer to table 1). Yet, in none of the previously described cases of "phlebitis" have venograms been performed. The normal venogram in our patient with chronic underlying arthritis raised the possibility of a dissected synovial cyst. This diagnosis was made non-invasively by means of ultrasound B-scanning. This technique is well accepted [27-30] and preferable to arthrography in patients with suspected septic arthritis. We need not emphasize the

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\begin{tabular}{|l|c|c|c|c|}
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Author & Total Patients Reported & Clinical Arthritis & Venogram Confirmation & Underlying Arthritis \\
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E.O. King, 1957 [14] & 15 & 1 & Not stated & Not stated \\
Kahler and Sheldon, 1969 [12] & 3 & 3 & No* & 1/3 \\
King and Bronsky, 1961 [5] & 1 & 1 & No & Yes \\
W.W. Spink, 1957 [31] & 1 & 1 & I & \\
Kilo, Hagermann, Marzi, 1965 [6] & 1 & 1 & No & Yes \\
Lee, Ludwig, Geraci, et al., 1970 [16] & 1 & 1 & No & No \\
Laurence, Nibbe, Levin, 1971 [34] & 1 & 1 & No & Yes \\
Franklin and Ulterior, 1974 [18] & 5 & 1 & No & Not stated \\
Present & 1 & 1 & Negative venogram & Yes \\
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*One patient at autopsy showed deep femoral vein containing thrombus.
therapeutic implications in differentiating those patients with true deep vein thrombophlebitis from those with PTP. The former requires chronic anticoagulation, which in this age group is associated with definite risks of hemorrhage, while the latter syndrome responds to intraarticular corticosteroid injections, bed rest, and pressure dressings, considerably safer therapeutic interventions.

The previous literature has stressed the generally high recurring fevers [5,15,31] that characterize this patient population. However, it is important to point out that four of the five patients with septic arthritis did not appear "toxic," e.g., high fevers, chills, headaches, hypotension, and general malaise, so characteristic of gram-negative sepsis. The only woman with septic arthritis was described as acutely ill, moderately dehydrated, and febrile to 39.5°C. In fact, blood cultures were drawn in only three of the five cases. Perhaps the compromised immunologic status of these hosts accounts for their rather benign presentation.

It is endogenous flora that probably account for the overwhelming majority of infections observed in immunocompromised hosts. Guerrant suggested that C. fetus penetrates the intestinal mucosa (like salmonella and Yersinia) resulting in a blood stream infection without the aid of enterotoxin production or epithelial cytotoxicity [23]. Others have emphasized the importance of debilitating disease in patients infected with C. fetus. Our patient is the second with multiple myeloma and C. fetus septicemia to be described. Sampson described, briefly, a 71-year-old male "who was being treated for multiple myeloma" [24]. This patient presented with a fever and blood cultures were positive for C. fetus. Bokkenhauser [7] recovered the organism from the blood stream of single patients with CLL, CML, a hepatoma, and from the pleural fluid of a patient with "lymphosarcoma" following splenectomy. Another patient with lymphosarcoma and a splenectomy died with a febrile illness presumably from this organism, since three sets of blood cultures belatedly grew V. fetus [32]. A third patient with "lymphosarcoma" and C. fetus septicemia, was added later in 1970 [33]. Cooper and Slee reported [17] an interesting patient with "follicular lymphoma" treated with radiotherapy and prednisolone, in whom C. fetus was cultured from blood and feces. C. fetus has been isolated from the cerebral spinal fluid and blood of a second patient with CLL [8], and a patient with Hodgkin's disease [10]. Other than these malignancies, this gram-negative bacillary organism has been responsible for sepsis in patients with agammaglobulinemia [11,34] and a patient with systemic lupus erythematosus being treated with prednisone and azathioprine [35].

The rather sweeping statement has been made [7,22] that fully 25 percent of the reported cases of C. fetus infections have occurred in hosts compromised by chronic alcoholic abuse. None of the four cases of septic arthritis that we have reviewed, nor our patient, were considered abusers of alcohol, but they were all in their seventh or eighth decades of life, two were on chronic corticosteroids, and our patient was certainly compromised by his myelomatosis.

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REFERENCES

1. Carpenter CM, Hubbert WT: Vibrios in diseases transmitted from animals to man. Edited by Thomas G Hull. Springfield, Ill, Charles C Thomas, 1963, p 170
2. Plastridge WN: Adv Vet Sci 2:326, 1955
3. Vinzeat R, Duman J, Picard N: Septicémie grave au cours dela grossesse due à un vibrien aneriment consecutif. Bull Acad Nationale Med (Paris 131:90, 1947
4. Ward BA: Apparent involvement of vibrio fetus in an infection of man. J Bact 55:113, 1948
5. King S, Bronsky D: Vibrio fetus isolated from a patient with localized septic arthritis. JAMA 175:1045, 1961
6. Kilo C, Hagermann PO, Marzi J: Septic arthritis and bactéremie due to Vibrio fetus. Am J Med 38:962, 1965
7. Bakkenhauser V: Vibrio fetus infection in man. Am J Epid 91:400, 1970
8. Collins HS, Blevins A, Benter E: Protracted bacteremia and meningitis due to Vibrio fetus. Arch Int Med 113:361, 1964
9. Hoyt S: Vibrio fetus can cause human infection. Med Lab 2:20, 1968
10. Krutchik AN, Velasquez W: Campylobacter fetus infection in a patient with Hodgkin's disease. JAMA 230:1810, 1977
11. Wyatt RA, Youndszai K, Anuras S, et al: Campylobacter fetus septicemia and hepatitis in a child with agammaglobulinemia. J Pediat 91:441, 1977
12. Kahler RL, Sheldon H: Vibrio fetus, infections in man. NEJM 262:1218, 1969
13. Urman JD, Zurier RB, Rothfield NF: Reiter's syndrome associated with Campylobacter infection. Ann Int Med 86:444, 1977
14. King EO: Human infections with Vibrio fetus and a closely related Vibrio. J Inf Dis 101:119, 1957
15. Lawrence GD, Biggs RD, Woodward TE: Infection caused by Vibrio fetus. Report of two cases. Arch Int Med 120:459, 1967
16. Lee MY, Ludwig J, Geraci JE, et al: Fatal Vibrio fetus endocarditis. Report of one case and review of the literature. Virchows Arch Abt A Path Anat 350:87, 1970
17. Cooper IA, Sree KJ: Human infection by Vibrio fetus. Med J Australia, 1:1263, 1971
18. Franklin B, Ulrior DD: Human infection with Vibrio fetus. West J Med 120:200, 1974
19. Dzau VJ, Schur PH, Weinstein L: Vibrio fetus endocarditis in a patient with systemic lupus erythematosus. Amer J Med Sci 272:331, 1976
20. Targan SR, Chow AW, Guze LB: Campylobacter fetus associated with pulmonary abscess and empyema. Chest 71:105, 1977
21. Gubina M, Zajo-Statler J, Mehe J, et al: Septicemia and meningites with Campylobacter fetus subspecies. Intestinalis Inf 4:115, 1976
22. Targan SR, Chow AW, Guze LB: Spontaneous peritonitis of cirrhosis due to Campylobacter fetus. Gastro 71:311, 1976
23. Guerrant RL, Lahita RG, Winn WC, et al: Campylobacteriosis in man: Pathogenic mechanisms and review of 91 blood stream infections. Amer J Med 65:584, 1978
24. Sampson CC, Smith CD, Deane C: Campylobacter fetus infection in humans. J Nat Med Assoc 67:135, 1975
25. Kutner LJ, Arnold WD: Septic arthritis due to Vibrio fetus. J Bone & Joint Surg 52A:161, 1970
26. Katz RS, Zizzic TH, Arnold WP, et al: The pseudothrombophlebitis syndrome. Medicine 56:151, 1977
27. Silver TS: Gray scale ultrasound evaluation of popliteal artery aneurysms. Am J Roentgenol 129:1003, 1977
28. Carpenter JR, Harrery RR, Hunder GG, et al: Ultrasound evaluation of the popliteal space comparison with arthropathy and physical examination. Mayo Clin Proc 51:598, 1976
29. Moore CP, Sarti DA, Louis JS: Ultrasoundographic demonstration of popliteal cysts in rheumatoid arthritis: A noninvasive technique. Arch & Rheum 18:577, 1977
30. McDonald DJ, Leopold GR: Ultrasound B-scanning in the differentiation of Baker's cyst and thrombophlebitis. Brit J Rad 45:729, 1972
31. Spink WW: Human Vibrosis caused by Vibrio fetus. J Amer Med Asso 163:180, 1957
32. McDonald S, Mautner LS: A case of human Vibrosis. M A J 103:951, 1970
33. Toala P, McDonald A, Kass EH: Septicemia caused by Vibrio fetus. Arch Int Med 126:306, 1970
34. Lawrence R, Nibbe AF, Levin S: Lung abscess secondary to Vibrio fetus, malabsorption syndrome, and acquired agammaglobulinemia. Chest 60:191, 1971
35. Dzau VJ, Schur PG, Weinstein L: Vibrio fetus endocarditis in a patient with septicem lupus erythematosus. Amer J Med Sci 272:331, 1976