Fusobacterium nucleatum Osteomyelitis in 3 Previously Healthy Children: A Case Series and Review of the Literature

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Fusobacterium nucleatum is a rare cause of monomicrobial osteomyelitis in children. We describe the cases of 3 children with F. nucleatum osteomyelitis of the distal femoral epiphysis with concurrent septic arthritis and review 6 other cases reported in the literature. Our report emphasizes the importance of maintaining a high index of suspicion for anaerobic osteomyelitis, given its atypical presentation and the unique growth requirements of anaerobic bacteria.

Key words. anaerobic osteomyelitis; epiphyseal lesion; pediatric.

Acute hematogenous osteomyelitis is the most common type of osteomyelitis in children and classically involves the metaphysis of long bones. Most cases are caused by Staphylococcus aureus and present acutely [1]. Anaerobic bacteria are an uncommon cause of bone and joint infections in children but may arise from a contiguous focus related to trauma, surgery, or local vascular disease, and in such settings may be polymicrobial in nature [2, 3]. Monomicrobial infection is less commonly reported and while hematogenous seeding may arise from a distant focus of infection, in many cases the source of disease may not be defined. In this article, we present the cases of 3 previously healthy children with anaerobic osteomyelitis of the distal femoral epiphysis caused by Fusobacterium nucleatum and review six other monomicrobial cases of osteomyelitis in children caused by this microbe.

CASE 1

A 6-year-old boy presented to the emergency department with 4 days of severe, intermittent left knee pain without fever or antecedent trauma. Examination revealed an uncomfortable boy with his left knee flexed to 80 degrees. There was no swelling of the knee joint, but he had pain with left leg extension and was non-weight-bearing. White blood cell count was 10.7 x 10⁹/L (normal range: 3.4–9.5 x 10⁹/L), erythrocyte sedimentation rate (ESR) was 9 mm/h (normal: <10 mm/h), and C-reactive protein (CRP) was <0.3 mg/dL (normal: <0.8 mg/dL). Radiographs showed a small left knee effusion and edema in the infrapatellar fat pad, without bone lesions. Arthrocentesis yielded bloody fluid with 5408 total nucleated cells/μL (45% neutrophils, 49% monocytes, 6% lymphocytes). Gram stain was negative. Aerobic and anaerobic blood cultures were collected and synovial fluid was sent for aerobic culture performed following institutional standards. Following arthrocentesis, the patient’s knee pain improved, and he was able to bear weight. He was discharged home with instructions for outpatient magnetic resonance imaging (MRI).

MRI with and without gadolinium was performed the following day and revealed a well-defined T2-intense area in the posterolateral aspect of the medial femoral condylar epiphysis (Figure 1A and B); the metaphysis appeared normal. Computed tomography (CT)–guided biopsy of the left medial femoral epiphysis demonstrated changes consistent with acute osteomyelitis. Biopsy specimens were sent for both aerobic and anaerobic culture, given the patient’s atypical presentation. The following day, the patient developed severe knee swelling and a fever of 38.3°C.

Repeat arthrocentesis yielded cloudy fluid with 91,775 total nucleated cells/μL (86% neutrophils, 11%...
monocytes, and 3% lymphocytes). Fluid was again sent for aerobic and anaerobic culture given the lack of growth on previous cultures. The same day, arthrotomy with irrigation and debridement demonstrated thick debris and purulent tissue with intact joint cartilage. Intravenous vancomycin was initiated out of concern for possible methicillin-resistant *S. aureus* infection. The following day, anaerobic cultures of both bone tissue and synovial fluid obtained during the CT-guided biopsy grew a gram-negative bacillus, and the patient’s medication was changed from vancomycin to piperacillin–tazobactam.

One week after initiation of piperacillin–tazobactam, the patient developed spiking fevers and increased pain and swelling of his left knee. Repeat MRI with and without gadolinium showed an increase in the loculated fluid collection within the posterior aspect of the medial femoral condylar epiphysis with possible extension into the knee joint (Figure 1C, 1D). Repeat irrigation and debridement of the knee joint was performed, and the distal medial femoral epiphysis was drilled and curetted percutaneously under fluoroscopic visualization to decompress the epiphyseal osteomyelitis.

During this time, multiple anaerobic cultures of bone tissue and synovial fluid grew *F. nucleatum* susceptible to penicillin, clindamycin, and metronidazole. No other organisms were isolated. Intravenous metronidazole was substituted for piperacillin–tazobactam and continued for 4 weeks. Due to nausea, metronidazole was discontinued.
and oral amoxicillin–clavulanate was prescribed for 2 additional weeks. At follow-up, the patient was symptom free and without functional limitation.

CASE 2
A 7-year-old boy with a 4-week history of left knee pain was admitted to the hospital with 48 hours of worsened pain and new medial knee swelling. There was no history of trauma or fever. Examination showed the pain to be predominantly popliteal. Palpation and movement of the knee joint elicited pain. Laboratory studies revealed a white blood cell (WBC) count of 10.9 × 10⁹/L (normal range: 3.4–9.5 × 10⁹/L), ESR of 18 mm/h (normal: <10 mm/h), and CRP of 2.6 mg/dL (normal: <0.8 mg/dL). MRI with and without gadolinium showed a cystic lesion of the posterior medial femoral epiphysis continuous with the joint space. Arthroscopy was performed with irrigation and debridement of a Brodie’s abscess in the medial femoral condyle. Blood culture and both aerobic and anaerobic synovial fluid cultures were collected. Intravenous cefazolin was initiated, and after 72 hours, the patient’s pain improved. Therapy was changed to high-dose oral cephalexin, and the patient was discharged home.

Forty-eight hours later, the patient was readmitted to the hospital with a fever of 39°C and increased knee pain and swelling. Vancomycin was administered. A repeat MRI showed residual synovitis but no drainable abscess. Five days after arthroscopy, a gram-negative rod grew in the anatomic tract of healthy persons [4, 5]. Of the different Fusobacterium species, F. nucleatum is most commonly isolated from clinical specimens [5]. It is associated with a variety of infections, including otitis media, mastoiditis, sinusitis, dental and gingival infections, peritonsillar and retropharyngeal abscesses, pneumonia, meningitis, peritonsillar, Lemierre disease (septic thrombophlebitis of the jugular vein), and osteomyelitis [4]. Frequently, these infections are polymicrobial with growth of aerobic, anaerobic, and facultative organisms [2, 4].

DISCUSSION
Fusobacterium species are anaerobic, non-spore-forming, gram-negative bacilli that are commonly found in the soil and in the respiratory tracts of animals. Fusobacteria have been isolated from the oropharynx and gastrointestinal tract of healthy persons [4, 5]. Of the different Fusobacterium species, F. nucleatum is most commonly isolated from clinical specimens [5]. It is associated with a variety of infections, including otitis media, mastoiditis, sinusitis, dental and gingival infections, peritonsillar and retropharyngeal abscesses, pneumonia, meningitis, peritonsillar, Lemierre disease (septic thrombophlebitis of the jugular vein), and osteomyelitis [4]. Frequently, these infections are polymicrobial with growth of aerobic, anaerobic, and facultative organisms [2, 4].

Fusobacterium osteomyelitis in children most commonly occurs in the skull and facial bones. These infections have been associated with concurrent otitis media, mastoiditis, sinusitis, trauma, and dental infection [2, 3, 6, 7]. Other cases of Fusobacterium osteomyelitis in children involving the ilium, hip, hand, foot, and long bones have been reported [6, 8–11]. Polymicrobial infection and coinfection with aerobic bacteria are poor prognostic factors [6].
The 3 patients we report all developed monomicrobial osteomyelitis of the distal femoral epiphysis with subsequent septic arthritis requiring irrigation and debridement. All 3 of our patients had epiphyseal involvement, which is unusual for acute hematogenous osteomyelitis. Whether this represents a true predilection is unknown. None of the patients had predisposing conditions such as recent dental work, contiguous infections, or a history of recent gastrointestinal or pharyngeal symptoms. There were no findings compatible with Lemierre disease and no evidence of involvement of the blood vessels supplying the affected bones. There was no history of local trauma. We postulate hematogenous spread, although none of our patients had documented bacteremia.

We identified 6 additional cases of monomicrobial pediatric osteomyelitis caused by *F. nucleatum* (Table 1) in the literature [4, 8–10, 12, 13]. Including the cases we report, all patients were males between the ages of 4 and 10 years. One patient had sickle cell disease and another had a recent history of untreated pharyngitis but no other predisposing risk factors were reported. The duration of symptoms before diagnosis ranged from 4 days to 1 month. Four patients had significant delays in diagnosis and initiation of appropriate antimicrobial therapy. We believe this to be secondary to the subacute presentation of these patients as well as the slow growth of *F. nucleatum* in culture. Two of the patients we describe likely had a delay in diagnosis and treatment because initial synovial fluid samples were not sent for anaerobic culture. Unlike previously reported cases, the ESR at presentation was not significantly elevated in 2 of our cases. Similar to other reported cases, the patients we describe did not have a significantly elevated WBC or documented bacteremia. Of interest, Budd et al. [12] describe the case of a 7-year-old boy with *F. nucleatum* osteomyelitis of the left medial femoral condyle. Involvement of the epiphysis is suggested, although not clearly stated. This again raises the question of whether *F. nucleatum* has an affinity for the distal femoral epiphysis or this is simply another chance finding.

Treatment of *Fusobacterium* osteomyelitis includes antimicrobial therapy and surgical intervention when appropriate. The most commonly used antibiotics for *Fusobacterium* infections include β-lactam agents, clindamycin, and metronidazole. Penicillin remains an effective agent but β-lactamase production is increasingly reported. One study found penicillin resistance among 9% of *Fusobacterium* species [14]. *Fusobacterium* isolates with a positive β-lactamase test should be considered resistant to penicillin and ampicillin, but a negative test does not necessarily predict susceptibility to these drugs as other

### Table 1. Pediatric Cases of Monomicrobial Osteomyelitis Caused by *Fusobacterium nucleatum*

<table>
<thead>
<tr>
<th>Cases</th>
<th>Gender</th>
<th>Age (Y)</th>
<th>Risk Factors</th>
<th>Duration of Symptoms</th>
<th>Location</th>
<th>Septic Arthritis</th>
<th>Positive Culture Specimens</th>
<th>Diagnostic Test</th>
<th>Irrigation and Debridement</th>
<th>Antibiotic Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gregory et al.</td>
<td>M</td>
<td>6</td>
<td>None</td>
<td>4 d</td>
<td>Left medial femoral condylar epiphysis</td>
<td>Yes</td>
<td>Bone tissue</td>
<td>Synovial fluid</td>
<td>Yes</td>
<td>Penicillin, metronidazole, clindamycin</td>
</tr>
<tr>
<td>Murray et al. [8]</td>
<td>M</td>
<td>7</td>
<td>None</td>
<td>4 wks</td>
<td>Proximal left ribs</td>
<td>No</td>
<td>Bone tissue</td>
<td>Synovial fluid</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Kroon et al. [8]</td>
<td>M</td>
<td>10</td>
<td>None</td>
<td>10 d</td>
<td>Right ileum</td>
<td>Yes</td>
<td>Bone tissue</td>
<td>Synovial fluid</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Broome et al. [10]</td>
<td>M</td>
<td>6</td>
<td>None</td>
<td>10 d</td>
<td>Lumbar vertebra</td>
<td>No</td>
<td>Bone tissue</td>
<td>Synovial fluid</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Beuchamp et al. [11]</td>
<td>M</td>
<td>7</td>
<td>None</td>
<td>4 wks</td>
<td>Temporal bone</td>
<td>No</td>
<td>Bone tissue</td>
<td>Synovial fluid</td>
<td>No</td>
<td>None</td>
</tr>
<tr>
<td>Budd et al. [12]</td>
<td>M</td>
<td>7</td>
<td>None</td>
<td>4 d</td>
<td>Left medial femoral condyle</td>
<td>Yes</td>
<td>Bone tissue</td>
<td>Synovial fluid</td>
<td>No</td>
<td>Penicillin, clindamycin</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; PCR, polymerase chain reaction.
mechanisms of β-lactam resistance exist [15]. β-Lactam-β-lactamase inhibitor combinations (such as piperacillin–tazobactam) are likely to be active against Fusobacterium species as well as other anaerobic bacteria and mixed aerobic–anaerobic infections. Likewise, the carbapenems provide excellent coverage, and resistance has not been reported to our knowledge. For patients allergic to β-lactam agents, clindamycin or metronidazole are options. Clindamycin susceptibility should be documented, as up to 9% of Fusobacterium isolates are resistant. Resistance to metronidazole is rare [14], but its use in children may be limited by nausea as evidenced by our first case.

The diagnosis of Fusobacterium osteomyelitis is hampered by difficulty in isolating the organism [16]. Many physicians do not routinely order anaerobic cultures of bone or synovial fluid. In all 3 cases we report, F. nucleatum was only isolated from bone tissue and fluid samples when utilizing anaerobic conditions. At a minimum, we recommend that anaerobic cultures of bone tissue and joint fluid be submitted for children with symptoms of osteomyelitis or septic arthritis when the clinical response is refractory to initial therapy or there is a history of trauma, surgery, or local vascular disease of the affected bone or joint. Treatment for confirmed Fusobacterium osteomyelitis frequently requires surgical debridement in addition to a prolonged course of antimicrobial therapy based on susceptibility testing. The exact duration of therapy depends on severity of illness, clinical response, and normalization of inflammatory markers.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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References