Progressive Diaphyseal Dysplasia

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History

A six-year-old boy presented for evaluation of right leg pain of three months’ duration. There was no history of trauma, fever, illness, travel, or unusual exposure to animals. Detailed birth history, growth and development were all unremarkable. Pain awakened him at night consistently, and he had a mild limp. His activities had been only minimally restricted.

Examination revealed a robust young male with marked tenderness along the subcutaneous border of the midshaft right tibia, with easily appreciated warmth along this area. There was measurable, nonpitting soft tissue swelling, without erythema or other skin manifestations of an underlying process. There was no muscle weakness or atrophy appreciated, and range of motion of the adjacent knee and ankle was full and only slightly painful. Neurologic examination of the lower extremities was within normal limits. No abdominal masses were palpable.

Radiographs (Fig. 1) demonstrated an infiltrating, poorly-defined sclerosis in the intramedullary canal with periosteal reaction. Laboratory studies included absence of anemia or leukocytosis, a sedimentation rate of 25 mm per hour, negative VDRL, normal serum chemistries for calcium, phosphorus, alkaline phosphatase, electrolytes, total proteins, albumin, and liver enzymes. Urinalysis and chest radiograph were also normal. A technetium bone scan (Fig. 2) revealed no other lesions in the skeleton. Tomography failed to identify a nidus suggestive of osteoid osteoma.

The initial differential diagnosis was reduced to Ewing’s sarcoma versus osteomyelitis (chronic, Garre’s), though the latter was discounted somewhat due to the diaphyseal location. Incisional biopsy was carried out under fluoroscopic control, with the major findings being absence of purulent or granulation material, thickened periosteum and distinct layers of new bone formation outside of the cortex proper, and a somewhat greyish, fibrotic tissue in the intramedullary canal not at all reminiscent of normal marrow. Pathologic diagnosis was chronic serous osteomyelitis, due to lack of tumor cells present and evidence of chronic inflammatory response histologically combined with periosteal new bone. A fibrous, histiocytic marrow was commented upon, though this was a nonspecific finding. All cultures for acid-fast, fungus, and bacterial organisms were negative.

Fig. 1: Presenting radiographs of the right tibia. An ill-defined intramedullary sclerosis with periosteal reaction is seen at the junction of the middle and distal thirds of the diaphysis.

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The patient was started empirically on antistaphylococcal medication, first intravenously and then orally, placed in a long leg cast, and discharged non-weight-bearing. One month later, the sedimentation rate was 21 mm per hour. Ten weeks postbiopsy, the patient reported pain in the left leg of increasing severity over the previous two to three weeks. Initially, inasmuch as the pain in the left leg had appeared during the time he had been non-weight-bearing on the right (biopsied) leg, it was assumed the pain was due to bearing all weight on the left leg. However, in spite of resuming weight bearing in a walking cast on the right leg at six weeks postbiopsy, symptoms got worse on the left. Radiographs at this time (Fig. 3) revealed the appearance of a similar lesion in the left tibia, and striking thickening of the diaphysis on the right. Repeat bone scan (Fig. 4) now demonstrated uptake in the left tibia, and surprisingly, relatively less in the right, in spite of the biopsy ten weeks earlier. The sedimentation rate was now 33 mm per hour. The diagnosis of progressive diaphyseal dysplasia (Engelmann’s disease) was now entertained. Because of healing at the biopsy site on the right, cast immobilization was discontinued, and antibiotics were stopped.

Fourteen weeks postbiopsy, radiographs confirmed bilateral diaphyseal cortical thickening (Fig. 5). Clinically, the patient was asymptomatic except for mild aching in both legs, relieved by aspirin. Radiographs of the lower extremities of both parents and the only sibling were normal, except for a documented unicameral bone cyst in the brother’s proximal femur.

Discussion

Progressive diaphyseal dysplasia is a rare generalized skeletal dysplasia, characterized by symmetrical, bilateral thickening of the diaphyseal cortex of long bones, with sparing of the epiphyses and metaphyses. Bones of membranous origin have occasionally been noted to be dense on radiograph. Clinically, bone pain, fatigue, muscle atrophy and weakness, leading to gait abnormalities, bowing, and generalized malaise, have been the classical presenting symptoms, with the radiographs being diag-
Fig. 4A: Repeat bone scan demonstrating increased uptake in the left tibia, with scant uptake in the right.

Fig. 4B: Lateral view of bone scan. Greater uptake of isotope on the left is seen, in spite of the healing biopsy site on the right.

Fig. 5: Characteristic diaphyseal sclerosis and thickening of progressive diaphyseal dysplasia.

nastic. However, a significant percentage of cases follow a somewhat milder course, such that the diagnosis is made in adult life when radiographs are made for an unrelated problem, or during a search for affected family members when a symptomatic relative is uncovered.

The first descriptions of patients with progressive diaphyseal dysplasia are contained in the original reports by Cockayne, Camurati, and Englemann. The latter's description in 1929 of a severely affected patient with advanced muscle wasting lent the condition the eponym of Englemann's disease. Most striking was the apparent systemic involvement of these severely affected patients, with severe limb pain, bowing, muscle weakness and wasting, failure to thrive, asthenic habitus, and various neurologic findings including gait abnormalities and reflex changes. Deafness, either of neurologic or bony origin, has also been reported. Inheritance has generally felt
to be autosomal dominant, but with wide variability of phenotypic expression, as more recent studies have uncovered sporadic occurrence in asymptomatic or mildly affected individuals. The diagnosis in such cases, because of typical radiographs demonstrating changes of long duration, has been obvious.

This case demonstrates the presumed clinical course from the outset of the process known as progressive diaphyseal dysplasia. The etiology of this disorder is unknown, but whatever induces the changes in bone to lift the periosteum and cause an inflammatory response in the medullary cavity, followed by permanent thickening of the diaphyseal cortex due to periosteal new bone deposition in the absence of osteoclastic remodelling, the process follows the course documented by the radiographs and isotope scans of this case. First one tibia and then the other were noted to have periosteal reaction combined with an infiltrative, fluffy intramedullary sclerosis, with nonspecific histological evidence of inflammation on biopsy, and clinical evidence of inflammation (pain, warmth, soft tissue swelling) localized to the area of abnormal bony density over the tibiae. With the passage of several weeks, the process passed into a perhaps chronic and more quiescent stage, with the diagnostic symmetrically thickened tibial diaphyses bilaterally. Of interest particularly is the lack of any of the atrophy, weakness, systemic fatigue or asthenia classically described.

The clinical problem presented by this patient, due to his early presentation, was the differential diagnosis of periosteal elevation in the face of an ominous appearing infiltrative sclerosis (Fig. 1) in the medullary canal. Diverse etiologies — including trauma, neoplasia, infection (pyogenic, luetic, tuberculous), rheumatic disease (periarteritis, hypertrophic osteoarthropathy), vitamin disturbance (scurvy, hypervitaminosis A and D, fluorosis), heavy metal toxicity, and miscellaneous bony lesions such as osteoid osteoma, Garre’s sclerosis osteomyelitis, Paget’s disease, osteopetrosis, and melorheostosis — might all have been considered in the differential diagnosis of this lesion. From the history, clinical evaluation and laboratory studies, the main diagnoses considered were limited to Ewing’s sarcoma and osteomyelitis. Results of the biopsy eliminated the former, and the patient was treated empirically for the most likely bacterial osteomyelitis, as the nonspecific microscopic findings gave no guidance toward any other diagnosis. When the symmetrical bilaterality of the lesions became apparent several weeks later, the antibiotic treatment was properly abandoned.

Laboratory studies in patients with progressive diaphyseal dysplasia are usually of little aid in diagnosis. The sedimentation rate is transiently elevated in about one-half of the reported cases. Anemia, increased alkaline phosphatase, and urinary hydroxyproline have also been reported. Histologically, deposition of periosteal woven bone and its compaction into lamellar bone is presumed to be the microscopic process resulting in diaphyseal thickening, though biopsy results have usually been inconsistent in other case reports. Lack of osteoclastic remodelling has been noted in one report, suggesting an unopposed bone deposition as the pathogenesis. Furthermore, treatment with corticosteroids has been reported in a small number of patients, with good symptomatic response and posttreatment biopsy evidence of increased bone resorption, osteon formation and remodelling. One case demonstrated normalization of radiographic bone changes. In the milder cases, simple analgesics such as salicylates have usually controlled symptoms adequately.

The tibia is the most commonly affected bone in the skeleton, being involved in 95% of the patients reviewed by Hundley and Wilson. If it can be assumed that progressive diaphyseal dysplasia is most likely to start in the most frequently affected bone, then this case would appear to elucidate the clinical course of the disease at its outset. Because the process did not present bilaterally at its outset, and the early radiographic appearance was not characteristic, biopsy was performed. Within several weeks of biopsy, the bilaterality of the process and the characteristic diaphyseal sclerosis became apparent. Hence, progressive diaphyseal dysplasia, especially when presenting as a sporadic case with mild involvement, must be considered in the differential diagnosis of periosteal elevation in the diaphysis of a long bone, particularly if the lesion is in the tibia.

References

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