Immune Deficiency, Thrombocytopenia and Osteomyelitis in Pediatric Patients

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Surgical decompression of osteomyelitis in pediatric patients should be an essential part of therapy in most cases. The initial deferral of prompt decompression in two patients because of underlying chronic, hemorrhagic (thrombocytopenic) disorders—one with Wiskott-Aldrich syndrome and one with Gaucher's disease—resulted in more serious and prolonged courses of the infectious processes. The complications might have been ameliorated by earlier drainage in each case. Based upon the experience gained from these two patients, we recommend early drainage, with appropriate treatment of the hemorrhagic disorder, to prevent more widespread dissemination or prolongation of osseous infection in similarly affected children.

Osteomyelitis poses a special problem in the pediatric patient with an acute or chronic hemorrhagic disorder. In particular, there may be hesitancy to proceed with the needed surgical decompressive procedures because of the patient's inherent risk of bleeding. However, delay in the initiation of appropriate surgical decompression, with resultant bone, cartilage, and soft tissue destruction, may lead to permanent disability, or even death from overwhelming sepsis. This paper discusses the problems posed by associated bleeding disorders and osteomyelitis in children, one with Wiskott-Aldrich syndrome and one with Gaucher's disease.

CASE REPORTS

Case 1: This two-year, seven-month-old white male with Wiskott-Aldrich syndrome, had been receiving transfer factor since two months of age. An "older" brother, also with Wiskott-Aldrich syndrome, died at age nine months. The patient presented with a three-day history of right hip and abdominal pain, chills, and fever. Approximately one week prior to admission he had developed a pustule on one finger, but this had spontaneously drained. Otherwise, he had been progressing well since his most recent prior hospitalization for a fracture of the left femur.

On admission he had a temperature of 40° C. Pertinent physical findings included several petechiae and ecchymoses of the skin. Abdominal examination revealed mild distension, voluntary guarding and slightly decreased bowel sounds. The extremities showed tenderness and decreased range of motion of the right hip and right ankle. Admission laboratory findings included a white blood count of 13,000/mm³ (59 segs, 11 bands), hematocrit of 27.7%, erythrocyte sedimentation rate of 40 mm/hr and

platelet count of 16,000/mm³. The stool guaiac test was negative. Abdominal, right hip, and ankle roentgenograms were negative. Blood cultures were obtained.

On the following day, the patient's fever persisted and he was noted to have further diminished bowel sounds. An intravenous pyelogram was negative. Blood cultures were growing Staphylococcus aureus, sensitive to oxacillin, and he was started on an intravenous dose of 200/mg/kg/day in four doses. His febrile course continued, and he was noted to have swelling, increased tenderness, warmth, erythema and decreased range of motion of the right ankle. The joint was aspirated and approximately 2 cc of purulent material were obtained. Cultures of this material were subsequently positive for Staphylococcus aureus. A Technetium methylene-diphosphanate (MD) bone scan was negative. Repeated joint aspirations, rather than open surgical drainage, were undertaken because of the severe hemorrhagic risk and platelet deficiency, as well as the fact that the patient was sensitized to platelet transfusions (HL-A matched platelets were not available for general use at the time). A gallium scan performed nine days after admission revealed increased activity in the right distal tibia and fibula. Again, recommended surgical drainage was deferred because of the patient's coagulopathy. Twelve days later the patient complained of pain in the left femur. Roentgenograms were consistent with proximal femoral osteomyelitis. A Technetium-MDP bone scan the following day revealed increased activity in the left clavicle, left proximal humerus, right fifth rib anteriorly, entire left femur, right proximal femur and right distal tibia and fibula, as well as asymmetric renal excretion. Repeat intravenous pyelogram revealed an abscess adjacent to the right pubic symphysis, with extrinsic compression of the bladder.

Immediately following transfusion of HL-A compatible, single donor, fresh, irradiated platelets, the left humerus, right distal tibia and fibula and left femur were selectively drained. The tibial lesion communicated with the ankle joint through the syndesmosis. A large pelvic abscess was also drained. No abnormal hemorrhagic difficulties were encountered during these procedures. All wounds were left open, with drains in place.

Postoperatively, the patient remained febrile for three days, until gentamycin was added to his antibiotic regimen. The remainder of the patient's hospital course was benign, the drains were progressively advanced and removed, and all the wounds closed spontaneously without any unexpected bleeding.

Case 2: This fifteen-year-nine-month-old male with Gaucher's disease (diagnosed at age six years) was admitted for evaluation of a painful, swollen left knee. He had been in good health except for chronic splenomegaly, anemia, neutropenia, and thrombocytopenia. Eight weeks prior to admission the patient developed a painful swelling of his left knee. He was self-treated with local heat and bed rest, and his symptoms resolved within one week. Six weeks prior to admission his symptoms recurred, and he was seen by an orthopaedist who recommended continued bed rest. He developed daily fevers to 39°–40° C and was seen three weeks prior to admission at another hospital. Blood cultures and radiographs were negative. Clinical impression was osteomyelitis, but despite a five-week history of symptoms and a fluctuant mass behind the knee, conservative therapy was chosen because of the patient's underlying coagulopathy. He was given oral penicillin for three weeks, but fever persisted and he had increasing swelling and discomfort. He also experienced a fifteen-pound loss during these eight weeks.

On admission to Yale-New Haven Hospital, he was a pale, thin male with a temperature of 39° C. His left distal thigh and knee were swollen, tender, warm, indurated and fluctuant. The knee joint had no palpable effusion and had approxi-

mately thirty degrees of painful motion (from 30° to 60° flexion). Except for a soft systolic murmur and organ megaly consistent with his Gaucher's disease, the remainder of the physical examination was normal. Initial laboratory data included a hemoglobin of 6.8 grams percent, platelet count of 110,000/mm^3, and erythrocyte sedimentation rate of 51 mm/hr. The acid phosphatase was elevated to 21.2 IU/liter (normal 0–8). Radiographs of the distal femur showed soft tissue swelling and periosteal new bone formation consistent with osteomyelitis of the distal femur.

On the day of admission, following transfusion with fresh blood and fresh frozen plasma, he was taken to the operating room, where approximately 400 ml of purulent material were drained from an abscess cavity occupying the popliteal and retrofemoral spaces, encasing a portion of the sciatic nerve and the popliteal vessels, and communicating with multiple cortical defects in the posterior, distal femur. The findings were compatible with osteomyelitis with spontaneous posterior decompression. Gram stain and culture of this purulent material were negative. Active, generalized bleeding was controlled with thrombin and gelfoam. However, on the fifth post-operative day, he began to have active bleeding from the wound, despite normal coagulation status (prothrombin time, 15.5 seconds/control, 11.3 seconds; partial thromboplasin time, 39.2 seconds/control, 32.0 seconds; fibrinogen, 190 mg%; thrombin time, 25.5 seconds/control, 21.8 seconds; platelet count, 230,000/mm^3). He was taken to the operating room, the wound explored, and two small arterial bleeders were ligated. Again, generalized small vessel bleeding was controlled with thrombin/gelfoam. He had received five doses of percodan, which contains aspirin, during the preceding two days. Since this may have contributed to the increased bleeding, this was discontinued. Despite this, several subsequent dressing changes in the operating room were associated with excessive small vessel bleeding from the granulation tissue. Pressure dressings were necessary to control bleeding. He was treated with intravenous antibiotics for six weeks and continued oral medication for another six weeks. Two years later he has no evidence of recurrent disease, and has full function of the knee and leg.

DISCUSSION

Hemorrhagic disorders pose a special problem in the management of pediatric patients with acute osteomyelitis. Undue concern for the clotting abnormalities may introduce hesitancy in proceeding with necessary surgical decompression. Many authors have stressed that osseous destruction is excessive and permanent disability may follow when there is a delay either in diagnosis or initiation of appropriate surgical drainage [1–4]. The same principles of management should be applied, as much as possible, to patients with underlying acute or chronic bleeding disorders. Further, the hyperemic response to the infection increases with time, and thereby enhances the potential for increased bleeding from granulation tissue. Many of these hemorrhagic disorders of childhood are accompanied by immune-deficiency states in which a subnormal or abnormal clinical response to infection may be common [2]. The dissemination of infection may be quite rapid in patients with deficient immune systems as in the first patient. This concomitance further underscores the need for prompt and effective management, with early surgical drainage being preferable.

Wiskott-Aldrich syndrome is an X-linked recessive disorder with thrombocytopenia, eczema, and increased susceptibility to infection [5,6]. It is a highly fatal condition. Severe infection, bleeding, or malignant lymphoma often cause death in infancy or childhood, with survival to puberty rare [7]. The underlying defect appears to be in the afferent limb of the immune system, where there is defective recognition

of the antigen [7-10]. Survival may be improved by treating the thrombocytopenia, with platelet transfusions being the mainstay of therapy in mild cases [10]. Transfer factor, which transfers specific, cell-mediated immunity from skin-test positive donors to skin-test negative recipients, is capable of inducing a chronically acceptable level of cell-mediated immunity in approximately half the patients with various immunodeficiency states, including Wiskott-Aldrich syndrome. Some patients with Wiskott-Aldrich syndrome also demonstrate improvement in bleeding tendencies with transfer factor infusion [11]. Faraci et al. demonstrated that major abdominal surgery was possible in these thrombocytopenic patients with appropriate management [12]. However, the patient more rapidly destroys donated platelets with each successive transfusion, such that pure platelet infusions should be reserved, as much as possible, for potentially life-threatening situations. Case 1 had developed an extreme sensitivity to platelet transfusions.

The first case demonstrated many of these aforementioned points. The osteomyelitis initially appeared to be localized to the distal tibia, fibula and ankle joint, with all three regions in communication through the synovial recess extending toward the syndesmosis. It seems likely that the hematogenous source was the pustule on the finger, present approximately a week prior to symptom onset. Because of the presence of purulent material, surgical decompression was recommended, but due to his low platelet count, deferred, and chemotherapeutic management alone was instituted. Despite adequate blood levels of antibiotic, the infection still became widespread. Subsequent surgical decompression after platelet transfusion resulted in rapid improvement. Probably earlier drainage would have prevented widespread dissemination of the relatively localized foci of osteomyelitis and septic joint. The multiple open wounds, even with surgically fenestrated metaphyses, did not bleed excessively during or after surgery.

Gaucher's disease is an uncommon metabolic disorder which has been described in approximately one thousand patients [13,14]. The underlying defect appears to be deficient activity of a beta-glucosidase which catalyzes the cleavage of glucose from glucosyl ceramide, resulting in the accumulation of excessive glucosyl ceramide within distinctive Gaucher's cells in the spleen, liver and bone marrow. Increasing masses of such cells cause organs such as the spleen, liver and lymph nodes to enlarge. Intraosseous cellular proliferation replaces normal marrow components and may cause avascular necrosis, bone pain and pathologic fractures [13,14]. Pratt et al. demonstrated immunoglogulin abnormalities in patients with Gaucher's disease and hepatosplenomegaly; such patients had aseptic necrosis of bone, chronic infection, or both [15]. Younger patients may exhibit several species of gamma-globulin, while older patients, in contrast, show monoclonal increases. The frequent association of Gaucher cells and plasma cells [15,16] has led to the suggestion that this may stimulate abnormal antibody formation eventuating in dysglobulinemia [16]. Gaucher cells have been specifically examined for the presence of antigen-antibody reactions, but the results have been equivocal [17,18]. Like many other lipids, glycosyl ceramide is a potent haptene [19]. However, circulating antibodies to this and other glycolipids have not yet been conclusively demonstrated in Gaucher's disease.

In the second case undue concern for the patient's coagulopathy significantly delayed appropriate surgical decompression. As a result, there was progressive bone destruction, functional loss and inanition. With appropriate platelet and blood transfusions and surgical drainage the patient's course was rapidly reversed. However, the excessive amount of inflammatory tissue surrounding the large retrofemoral and popliteal abscess cavity bled frequently and was quite difficult to control as

effectively as desired. Certainly, early drainage prior to formation of such a large cavity would have lessened this particular hemorrhagic complication from the reparative granulation tissue.

The common factors in these two patients were thrombocytopenia and immunodeficiency. The immunodeficient state affects the usual course of the disease by altering the host response. Even the presence of seemingly appropriate levels of antibiotics may not be sufficient to treat osteomyelitis when the patient is incapable of a concomitant cellular response. Surgical drainage accomplishes two important factors: first, the infection is decompressed externally, minimizing the tendency to local chondrosseous destruction and hematologic spread, and second, vascular granulation tissue can replace the evacuated cavity, bringing both antibiotics and cells. This is particularly effective in the metaphysis, where the reticuloendothelial cells are normally minimal [12,20,21].

. Antibiotic therapy is only one important measure in the treatment of acute osteomyelitis [22]. So promising were these drugs when first introduced that surgery was prematurely de-emphasized [20]. Recently Rhodes suggested that acute osteomyelitis could be cured by antibiotic therapy alone, if treated within the first four days of disease onset [23]. Likewise, Blockey and Watson advocated the use of antibiotics alone if treatment was instituted within seventy-two hours [24]. A major problem is "onset of disease." The patient may not become symptomatic until the infectious process penetrates the metaphyseal fenestra [25,26], and elevates the pain-responsive periosteum. Realistically, this process probably takes three to four days. Thus the patient with symptoms for only two or three days may, in fact, have had the disease several days longer. Further, Blockey and Watson may be criticized because of lack of long-term follow-up [24]. Morrey and Peterson found a significant number of recurrences a year or more following initial treatment with antibiotics alone [27]. As Ferguson has emphasized, there is a great temptation to treat this disease "conservatively" with antibiotics, but whenever this has been done, the experience in the literature indicates that the incidence of complications rises [28].

Some indications for surgery are obvious. When purulent material is present (usually under pressure), early decompression is essential [25,28]. If there is radiographic evidence of an osteolytic lesion in the metaphysis, drainage is also indicated. In Case 1, the lytic lesions were probably delayed by the patient's cellular deficiency; in Case 2, radiographic changes were somewhat masked by the osseous changes caused by the Gaucher's disease. Further, considerable amounts of bone must be destroyed before an intraosseous lesion is radiographically evident. The involved bone may be rendered ischemic during early stages of the infectious process, limiting penetrability of antibiotics.

Early diagnosis and early administration of adequate chemotherapy, in conjunction with judicious surgical decompression, afford the best chances for complete cure. Surgical drainage is an adjuvant to normal host defenses. The presence of underlying immunodeficiencies renders normal host defense mechanisms inadequate and reinforces the need for an aggressive approach that includes surgery early in the disease course to prevent local and distant dissemination. Hemorrhagic deficiencies usually can be effectively handled prior to and during surgery, and should not be a contraindication, per se, to the use of open drainage.

REFERENCES

1. Eyre-Brooke AL: Septic arthritis of the hip and osteomyelitis of the upper end of the femur in infants. J Bone and Joint Surg 42-B:11, 1960
2. Kuo KN, Lloyd-Roberts GC, Orme IM, et al: Immunodeficiency and infantile bone and joint infection. Arch Dis Child 50:51, 1975

3. Lloyd-Roberts GC: Suppurative arthritis of infancy; some observations upon prognosis and management. J Bone and Joint Surg 42-B:706, 1960

4. Roberts PH: Disturbed epiphyseal growth at the hip after osteomyelitis in infancy. J Bone and Joint Surg 52-B:692, 1970

5. Wiskott A: Familiarer, angeborener Morbus Werlhofli? Monatsschr Kinderheilkd 68:212, 1937

6. Aldrich RA, Steinberg AG, Campbell DC: Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics 13:133, 1954

7. Sellars WA, South MA: Wiskott-Aldrich syndrome with 18-year survival. Am J Dis Child 129:622, 1975

8. Blaese RM, Strober W, Waldman TA: Immunodeficiency in Wiskott-Aldrich Syndrome. Birth Defects 11:250, 1975

9. Cooper MD, Chase HP, Lowman JT, et al: Wiskott-Aldrich Syndrome. An immunologic deficiency disease involving the afferent limb of immunity. Am J Med 44:499, 1968

10. Millekin LE: Wiskott-Aldrich Syndrome. A treatable immune disorder. Missouri Med 70:764, 1973

11. Levin AS, Spitler LE, Fudenberg HH: Transfer factor I: methods of therapy. Birth Defects 11:445, 1975

12. Faraci RP, Hoffstrand HJ, Witebsky FG, et al: Malignant lymphoma of the jejunum in a patient with Wiskott-Aldrich Syndrome. Arch Surg 110:218, 1975

13. Amstutz HC, Carey EJ: Skeletal manifestations and treatment of Gaucher's disease. J Bone and Joint Surg 48-A:670, 1966

14. Fredrickson DS, Sloan HR: Glucosyl ceramide lysidase. In The Metabolic Basis of Inherited Disease. Ed. 3. New York: McGraw-Hill, 1972

15. Pratt PW: Immunoglobulin abnormality in Gaucher's disease. Blood 31:633, 1968

16. Pennelli N, Scaravilli F, Zacchello F: The morphogenesis of Gaucher cells investigated by electron microscopy. Blood 34:331, 1969

17. Fisher ER, Reidbord H: Gaucher's disease: pathogenetic considerations based on electron microscopic and histochemical observations. Am J Path 41:679, 1962

18. Lake BD: A histochemical study of Gaucher's disease and Niemann-Pick's disease. J Roy Micro Soc 86:417, 1966

19. Rapport MM, Graf L: Immunochemical reactions of lipids. Prog Allerg 13:274, 1969

20. Boland AL: Acute hematogenous osteomyelitis. Orthop Clin N Amer 3:225, 1972

21. Clawson DK, Dunn AW: Management of common bacterial infections of bones and joints. J Bone and Joint Surg 49-A:164, 1967

22. Winters JL, Cahen I: Acute hematogenous osteomyelitis, J Bone and Joint Surg 42-A:691, 1960

23. Rhodes KH: Antibiotic management of acute osteomyelitis and septic arthritis in children. Orthop Clin N Amer 6:915, 1975

24. Blockey NJ, Watson JT: Acute osteomyelitis in children. J Bone and Joint Surg 44-B:841, 1962

25. Ogden JA, Lister G: The pathology of neonatal osteomyelitis. Pediatrics 55:474, 1975

26. Ogden JA: The development and growth of the musculoskeletal system. In Albright JA, Brand R: The Basic Science of Orthopaedics. New York: Appleton-Century-Crofts, in press

27. Morrey BF, Peterson HA: Hematogenous pyogenic osteomyelitis in children. Orthop Clin N Amer 6:935, 1975

28. Ferguson AB: Osteomyelitis in children. Clin Orthop 96:51, 1973