Multiple pyarthrosis in human immunodeficiency virus-infected hemophiliacs

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A INGRAM, MJ INWOOD, D GREGSON, M COPPOLINO. Multiple pyarthrosis in human immunodeficiency virus-infected hemophiliacs. Can J Infect Dis 1994;5(1):33-36. Classically, a swollen, painful joint in a patient with hemophilia has been considered to be due to a hemarthrosis until otherwise proven, and treated immediately with appropriate coagulation factor replacement. Two cases of human immunodeficiency virus (HIV)-infected hemophiliacs presenting with an initial apparent hemarthrosis, complicated subsequently by numerous pyarthroses and sepsis are described. In light of the prevalence of HIV infection in the adult hemophiliac population with arthropathy, a reappraisal of the clinical caveat of immediate infusion without joint aspiration is required.

Key Words: Hemophilia, HIV infection, Pyarthrosis

Pyarthrose multiple chez des hémophiles infectés par le virus de l'immunodéficience humaine

RÉSUMÉ : Ordinairement, une articulation enflée et douloureuse chez un patient atteint d'hémophilie est, jusqu'à preuve du contraire, considérée attribuable à l'hémarthrose et elle est traitée sur-le-champ avec un facteur de coagulation substitutif. Nous décrivons ici le cas de deux hémophiles infectés par le virus de l'immunodéficience humaine (VIH) s'étant présentés initialement avec des signes d'hémarthrose, et ayant évolué vers de nombreuses pyarthroses et une septicémie. Compte tenu de la prévalence de l'infection au VIH dans la population hémophile adulte atteinte d'arthropathie, il convient de se pencher sur le risque que comporte l'administration hâtive de facteur de remplacement sans aspiration préalable de l'articulation.

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UP TO 60% OF MULTI-TRANSFUSED ADULT FACTOR VIII-deficient hemophiliacs in the Canadian population were infected with the human immunodeficiency virus (HIV) starting in the early part of the past decade as a consequence of infected pooled factor concentrates (1,2). The majority of these individuals has now had concomitant HIV infection and hemophilia for at least 10 years and can be expected to exhibit many manifestations of their progressively impaired immunity. Septic arthritis has been considered to be a rare event in hemophilia, with an estimated incidence of 0.15% per year (3-5,10). This is only three to 12 times the incidence of septic arthritis in the general population (8). The first reported case of septic arthritis in an HIV-infected hemophiliac was in 1989 (6).

We report two cases of multiple pyarthroses in HIV-infected hemophiliacs presenting with what appeared to be single joint hemorrhages. These cases are presented to illustrate the serious consequences of altered immunity and HIV-associated neutropenia in hemophiliacs with concomitant hemarthropathy and the need to question the traditional therapeutic principle of 'if in doubt, infuse' in the HIV-infected hemophiliac.

CASE ONE

A 34-year-old male with severe hemophilia A (factor VIII activity less than 0.01 U/mL) and multiple chronic hemarthropathies presented with 48 h of intermittent spiking fever and pain and swelling in both knees. The patient had been self-infusing 2500 U of factor VIII concentrate every 12 h over the previous two days on the assumption that the symptoms represented hemorrhages.

This patient had advanced immune disease with a CD4 count before admission of less than $100 \times 10^9/L$. He had no acquired immunodeficiency syndrome (AIDS)-defining illnesses, except recent wasting.

At admission, the patient's temperature was $38.8^\circ C$, heart rate was 108 beats/min, and blood pressure was 160/80 mmHg. He had severe hemophiliac arthropathy in both elbows, ankles, and knees. Swelling, erythema, warmth and exquisite pain were present in both knees and in the right elbow. Initial white blood cell count was $1.8 \times 10^9/L$ with an absolute neutrophil count of $1.134 \times 10^9/L$.

Blood cultures were done at admission and the patient was placed on intravenous piperacillin and gentamicin, and appropriate factor VIII replacement was infused. He continued to be febrile with unremitting joint pain and, at 48 h post admission, the left knee was aspirated, yielding 20 mL of frank pus. A heavy growth of *Staphylococcus aureus* was present from knee and blood samples. Cloxacillin was substituted for piperacillin. As the patient continued to be febrile with a low neutrophil count, on the fifth day, granulocyte colony-stimulating factor (G-CSF) (Neupogen Filgrastin, Amgen Inc) therapy was instituted using 300 µg/day, with a

Figure 1 Right elbow of case 2 at initial presentation showing erythema, swelling and tenderness clinically compatible with either bleeding (hemarthrosis) and/or infection

prompt rise in the absolute neutrophil count to $11.0 \times 10^9/L$. The patient defervesced within 48 h and was discharged on the 16th hospital day on cloxacillin and rifampin by mouth. He had a lengthy convalescence, and after three months still had decreased range of motion in the affected joints.

CASE TWO

A 27-year-old male with severe hemophilia A (factor VIII activity less than 0.01 U/mL) presented with three days of fever, shaking chills and right elbow and bilateral knee swelling. He had been seen as an outpatient 72 h before admission with a painful, swollen right elbow (Figure 1). A clinical diagnosis of hemarthrosis had been made and he was instructed to infuse factor VIII 2500 U every 12 h for the next 72 h, and to return if resolution did not occur.

The patient had advanced immune disease with a CD4 count of less than $100 \times 10^9/L$ before admission. He had no AIDS-defining illnesses except for recent wasting. The patient had total arthroplasty of the right knee one year before admission. The patient also had chronic elevation of liver enzymes, hepatomegaly, positive hepatitis C virus (HCV) antibody, clinically consistent with HCV-induced chronic active hepatitis.

On admission, temperature was $38.3^\circ C$, heart rate was 160 beats/min, and blood pressure 110/40 mmHg. The patient was drowsy. Both elbows (Figure 1), knees, and ankles were erythematous, swollen, warm and exquisitely painful. Prompt aspiration of the right knee yielded 100 mL of sanguineous fluid, which revealed Gram-positive cocci on Gram's staining. Subsequent cultures from the aspirate and from blood grew *S. aureus*. Admission white blood cell count was $3.6 \times 10^9/L$ with an absolute neutrophil count of $2.18 \times 10^9/L$.

The patient was placed on cloxacillin and gentamicin intravenously, but continued to be febrile and variably

Figure 2) Palpable purpura on lower extremity of case 2 secondary to systemic infection

encephalopathic. He developed palpable purpura on both legs, which was considered to be secondary to systemic infection (Figure 2). On the sixth hospital day, the absolute neutrophil count was $1.8 \times 10^9/\text{L}$. The patient was started on G-CSF therapy at $300 \mu\text{g}/\text{day}$, with a prompt rise in the absolute neutrophil count to $9.0 \times 10^9/\text{L}$.

The patient's fever resolved but the right elbow showed continuing evidence of pyarthrosis (Figure 3). He became increasingly jaundiced over the next seven days, with a rise in serum bilirubin to $450 \text{ mmol}/\text{L}$. On the 18th hospital day, renal failure developed and the patient died on the 22nd hospital day as a consequence of his hepatorenal syndrome. An autopsy was not obtained.

DISCUSSION

A hemophiliac with intra-articular bleeding displays a warm, swollen, painful joint similar to the clinical findings in septic arthritis. To date, there has been reluctance to aspirate these joints because of the frequency of their occurrence, and in the severely affected hemophiliac, the possibility of inducing further bleeding (7). Generally, conservative management with rest, ice and immediate appropriate factor infusion sufficed, although severe hemarthropathy was the all too common result of the numerous bleeding episodes in these patients. Prompt factor replacement was also necessary, as the hemophiliac often experienced the 'aura' of a hemorrhage before clinical signs become evident.

The actual rate of *S aureus* infections in HIV-infected hemophiliacs is not well studied, despite reports describing septic arthritis in hemophiliac patients since 1983 (3-5,12,13). However, it has recently been observed that joint infections are more prevalent in hemophiliacs than has been previously described (8,9,12).

Several authors have suggested that these infections result from a preceding bacteremia in an immunocompromised individual (10,11).

Figure 3) Right elbow of case 2 on 10th day of hospital admission showing obvious clinical signs of pyarthrosis with cutaneous abscess formation

S aureus bacteremia occurs at an estimated rate of 0.16% per annum in nonintravenous drug abusing HIV-infected patients with AIDS or AIDS-related complex (14). Late metastatic complications occur in approximately one-third of cases. Increased colonization rate, cutaneous abnormalities and granulocyte dysfunction all likely play a role in the increased incidence of *S aureus* bacteremia (13,14). Joint pathology in hemophiliacs likely provides a site for seeding during bacteremia, as was demonstrated in the patients described.

Based upon the experience with these two cases, one of which proved fatal, and the other requiring prolonged hospitalization and rehabilitation, the following are recommended considerations for the treatment of joint hemorrhage in HIV-infected hemophiliacs.

Diagnosis: First, if a single joint hemorrhage does not respond to appropriate factor replacement in 24 h, joint aspiration should be performed in association with blood culture and empirical antimicrobial therapy, including staphylococcal coverage initiated pending culture results.

Second, any joint hemorrhage associated with a patient's temperature of greater than 38.5°C should be aspirated and examined in association with blood cultures. One series revealed a temperature greater than 38.5°C in nine of 11 patients with pyogenic arthritis, and in only one of 67 with a hemarthrosis (13).

Third, if more than one joint has apparent simultaneous hemorrhage, then aspirations and blood cultures should be performed (6). While the frequency of multiple joint involvement in hemophiliacs with septic joints has not been reported, it appears to be more common than the multiple simultaneous hemarthrosis rate of 3.7% quoted in one large series (15).

Treatment: If Gram's stain is positive, immediate appropriate intravenous antibiotic therapy must be initiated. This should be continued for a six-week period.

If the individual has an absolute neutrophil count of

less than $1.0 \times 10^9/L$, empirical intravenous antibiotic therapy is indicated until pyarthrosis has been excluded.

In the event of proven bacterial pyarthrosis and absolute or relative neutropenia, G-CSF therapy must be a consideration, particularly if clinical response to ap-

propriate antibiotic therapy is not obtained (16). G-CSF may be preferred over GM-CSF, since it has not been shown to increase P24 antigen levels (17).

Multiple aspiration and/or surgical drainage may be necessary to prevent further joint damage, particularly in joints with previous surgical arthroplasty.

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