Inhibitor와 중심정맥 접근장치를 갖고 있는 혈우병 B 청소년 환자에서 발생한 패혈관절염과 감염심내막염

김지수・박영실
강동경희대학교병원 소아청소년과

Septic Arthritis and Infective Endocarditis in an Adolescent Hemophilia B Patient with an Inhibitor and a Central Venous Access Device

Jisu Kim, M.D. and Young Shil Park, M.D., Ph.D.
Department of Pediatrics, Kyung Hee University Hospital at Gangdong, Seoul, Korea

Central venous access devices (CVAD) provide hemophilic patients, particularly children, with prolonged reliable venous access to promote routine factor replacement therapy. However, one of the significant complications of CVAD use is infection. We report the case of a severe hemophilia B patient with an inhibitor who developed septic arthritis and infective endocarditis associated with methicillin-resistant *Staphylococcus aureus* infection originating from a CVAD. Our patient had an underlying condition of congenital heart disease, one of the risk factors for infective endocarditis. Unfortunately, the antibiotic therapy did not have a significant effect. An echocardiogram revealed vegetation on the right ventricular moderate band and surgery was determined to be the best course of action. Septic arthritis and endocarditis rarely occur in hemophilia patients, however, they must be taken into account in hemophiliacs with continuing bacteremia.

Key Words: Central venous access devices, Hemophilia B, Ventricular septal defect, Infective endocarditis, Septic arthritis

Introduction

Hemophiliacs should receive several factor replacement administrations per week as part of their prophylactic therapy schedule. The use of CVAD in these patients allows repeated factor replacement infusions to be administered more easily [1].

The insertion and successive use of a CVAD may be complicated by infections [1]. Among human immunodeficiency virus (HIV) non-infected hemophiliacs, catheter-related infections occur in about one-half of the cases [2]. *Staphylococcal* species are the most common causative organisms, and Gram-negative bacilli are followed (*Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.) [3]. Bacterial endocarditis is tremendously scarce in immune-competent patients who are taking a CVAD but it should be taken into consideration in cases where continuing bacteremia is detected [1].

Septic arthritis and infective endocarditis are scarce com-
Complications of CVAD use in hemophiliacs [2,4]. Here we report a case of septic arthritis and infective endocarditis secondary to the use of a CVAD.

**Case Report**

An 18-year-old severe hemophilia B patient with an inhibitor was admitted to our facility due to a 10-day fever and painful swelling of the left elbow for about 2 days. The patient had been treated with recombinant activated factor VII concentrate (rFVIIa) on demand at an outpatient clinic.

The diagnosis of hemophilia B was made at another hospital when this patient was about 8 months old. He had a history of anaphylaxis to coagulation factor IX (FIX) when he was 22 months old, and he was transferred to our hospital at the age of 8 years. His historical peak inhibitor titer was 155 Bethesda units when he was 9 years old, but it was borderline when he was 13 years old, and it has been negative since he was 14 years old. He underwent regular follow-ups for a perimembranous ventricular septal defect (VSD) that was diagnosed at birth. This patient began taking oral oxcarbazepine at 14 years old due to epilepsy, and he wore orthoses after being diagnosed with kyphosis and scoliosis by physicians at the Department of Rehabilitation Medicine. In the same year, this patient was diagnosed with hypopituitarism and he began growth hormone therapy. His bleeding episodes, such as hemarthrosis and soft tissue hematomas, were frequent, and many rFVIIa injections were needed. A CVAD was inserted on the right internal jugular vein when the patient was 14 years old because his peripheral venous access was poor due to a contracture that occurred following a previous hematoma in his left arm. The CVAD function was poor when he was 17 years old, so it was removed and reinserted on the same side. There have been no problems with its functioning since then.

This patient visited the outpatient clinic 9 months after the CVAD reinsertion due to a high-grade fever, watery diarrhea, and abdominal pain for 10 days. He had also developed left elbow pain for 2 days and right elbow pain for 1 day. At the time of his visit, his heart rate was regular with a grade 3/6 pansystolic murmur, as usual, at the left lower sternal border due to the VSD. The abdominal physical examination findings revealed slightly hyperactive bowel sounds and periumbilical tenderness. The patient’s left elbow showed no redness, but swelling, heating sensation, tenderness and limited range of motion were detected. The right elbow was not red, but there was swelling, tenderness, and limited range of motion. His initial vital signs were as follows: blood pressure, 91/70 mmHg; heart rate, 80/min; respiratory rate, 20/min; and body temperature, 39.4°C. The initial blood test results were as follows: white blood cell count, 18.39×10^3/µL (reference value: 4.0-10.0×10^3/µL) with 90.0% neutrophils (reference value: 40.0-60.0%); hemoglobin, 11.6 g/dL (reference value: 13.0-17.0 g/dL); hematocrit, 36.4% (reference value: 39.0-52.0%); platelets, 148×10^3/µL (reference value: 130-350×10^3/µL); and C-reactive protein (CRP), 32.5 mg/dL (reference value: 0.0-0.5 mg/dL); coagulation factor IX level, <1%; inhibitor titer, negative. A urinalysis showed pyuria. His chest X-ray showed that the CVAD was in the right chest (Fig. 1). Ultrasonography of the left elbow showed a hematoma in the left extensor carpi radialis longus muscle and hemarthrosis of both elbow joints (Fig. 2). Moreover, a magnetic resonance imaging scan of the left elbow revealed hemarthrosis and a hematoma (Fig. 3), and the abdominal computed tomography scan suggested acute pyelonephritis.

**Fig. 1.** Chest X-ray of the patient showing pulmonary edema in both lungs, the central venous access device, and scoliosis.
This patient was treated with rFVIIa at a dose of 340 IU every 6 hours (4.5 IU/kg/dose) and intravenous cefotaxime at a dose of 2 g every 6 hours. Nevertheless, his fever persisted. On day 3 of hospitalization, we confirmed that the interim results of the central and peripheral blood culture and the urine culture were positive for methicillin-resistant *Staphylococcus aureus* (MRSA), so intravenous vancomycin was started at a dose of 1 g every 12 hours.

On day 6 of hospitalization, CRP decreased to 16.2 mg/dL, but the fever persisted and the CVAD was removed. Ultrasound-guided aspiration of the left elbow was performed on the following day. Approximately 125 mL of bloody pus was aspirated, the culture of which was positive for MRSA, and a cytological examination showed a red blood cell count of $410 \times 10^3/\mu L$ and a white blood cell count of $180 \times 10^3/\mu L$. Septic arthritis was suspected based on these findings and the patient underwent open synovectomy and debridement of the left elbow. When the joint was opened, the pus had spread from the left elbow joint to the distal muscle portion between the biceps and brachialis of the upper arm. Moreover, the left elbow joint was filled with infected granulation tissue, which was associated

**Fig. 2.** Ultrasonography of the elbows. (A) Left: A hematoma [5.5 (length) \times 1.4 (transverse) \times 1.1 (thickness) cm in size] suggestive of synovitis and hemarthrosis of the elbow joint. (B) Right: Hemarthrosis of the elbow joint.

**Fig. 3.** Magnetic resonance image of the left elbow reveals hemarthrosis and a hematoma [about 8.6 (length) \times 1.6 (transverse) \times 1 (thickness) cm in size].
with severe cartilage and bone destruction.

On day 8 of hospitalization, an echocardiogram showed vegetation on the right ventricular (RV) moderate band, which suggested infective endocarditis, and surgery was determined to be the best course of action (Fig. 4). This patient was transferred to another hospital for the operation.

Discussion

The most effective treatment strategy for patients with severe hemophilia is replacement therapy with coagulation factor concentrates [5]. Treating hemophilia requires appropriate venous access over a prolonged period of time to administer the clotting factors. To ensure such access, CVAD have been applied since the 1980s to promote opportune and prophylactic treatments [6].

The most common indication for removing a CVAD is infection [6,7]. One large countrywide study of 106 CVAD in 58 pediatric patients with 137,971 CVAD follow-up days reported very low CVAD-related bloodstream infection rates of 0.12/1,000 CVAD days for all patients and 0.10/1,000 for the patients without an inhibitor [8].

Infective endocarditis is a severe but rare complication in immune-competent patients carrying a CVAD [2,9]. *S. aureus* and Streptococcus of the viridans group are the bacteria most commonly implicated in the cause of infective endocarditis [10]. However, congenital heart disease (CHD) is the major risk factor for infective endocarditis. VSD is the most common CHD. If not surgically corrected, it is the CHD most commonly involved in infective endocarditis. Our patient exhibited an unrepaired VSD, and the incidence of infective endocarditis in patients with unrepaired VSDs is 1.5-2.4/1,000 general population-years [11].

The first step in the treatment of bacterial endocarditis is a long-term intravenous antibiotic administration for approximately one month depending on the sensitivity of the culture. However, surgery is used in about 50% of all patients with infective endocarditis due to serious complications [12]. Our patient’s echocardiogram showed >3 cm vegetation on the RV moderate band. This finding indicated the need to consider surgery, and our patient was transferred to another hospital for treatment after consulting with a heart surgeon.

The incidence of septic arthritis in hemophilia patients is 15-40 times higher than that in the general population [13-15]. An age of over 30 years, the existence of an inhibitor, an invasive intervention within the last year, the existence of more than one affected joint, and an ethnicity other than Caucasian are important risk factors for the evolution of a septic joint. However, the use of a CVAD and an HIV infection have not been related to septic arthritis [15]. Our patient was HIV-negative but he had an inhibitor, two affected joints, and an ethnicity other than Caucasian as risk factors for septic arthritis. Joint infections are generally hematogenous, and the most common contributory germs are staphylococcal and streptococcal species. The culture of the aspirated joint pus from the patient’s left elbow was positive for *S. aureus* which was confirmed by his blood culture.

Our patient was a hemophilia B patient with an inhibitor and he also had VSD and hypopituitarism. It is very rare that all three of these comorbidities appear together in one person at the same time. In this case, a suspected syndrome was not yet known.

Infective endocarditis and septic arthritis are infrequently occurring infectious complications in hemophilia patients. However, our hemophilic patient had an unrepaired VSD, the most common CHD related to infective endocarditis. The use of a CVAD has altered the management approach to these patients. However, septic arthritis and infective en-
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docarditis can arise in hemophiliacs with specific risk factors [9].

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