□ Case Report □

Long-term recombinant interferon-γ treatment in 2 cases of osteopetrosis

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Osteopetrosis, a rare osteosclerotic bone disease characterized by a defect in osteoclast function and the reduced generation of superoxide by leukocytes, can be classified into several types based on their mode of inheritance, age of onset, severity, and associated clinical symptoms. Stem cell transplantation is the only curative therapy for the infantile malignant type, although alternative treatments, such as corticosteroids, calcitriol, and interferon (IFN)-γ have been attempted in patients with milder clinical types. In addition, IFN-γ therapy has been reported to increase bone resorption and hematopoiesis and to improve leukocyte function. Here, we present the cases of two patients with osteopetrosis who benefited from either 3 or 6 years of INF-γ therapy that resulted in improved blood counts and no further pathological fractures. **(Korean J Pediatr 2007;50:1129-1133)**

Key Words : Osteopetrosis, Osteoclast, Interferon-γ

Introduction

Several names have been used to describe the rare hereditary bone disorder with a rocklike appearance: Albers-Schönberg disease, marble bone disease, and osteopetrosis[1]. Osteopetrosis comprises a group of disorders resulting from decreased osteoclast function and hence decreased bone resorption. The accumulation of sclerotic bone compromises the marrow space and cranial-nerve foramina, predisposing patients to blindness, hearing impairment, cytopenia, hepatosplenomegaly, and pathologic fractures.

The true incidence of osteopetrosis is unknown because many patients with mild disease may be underdiagnosed. Only a few cases have been reported in Korea, with two patients showing hematologic improvement with prednisolone therapy[2, 3].

In cases of infantile malignant osteopetrosis, the most severe form with a rapidly deteriorating course early in life, stem cell transplantation (SCT) is curative[4, 5]. However, for patients who lack a matched donor or patients with milder disease, various medical interventions have been attempted, including corticosteroids, high-dose calcitriol, and IFN-γ[6-8].

The use of IFN-γ in osteopetrosis was inferred from its beneficial effect in chronic granulomatous disease, a rare genetic disorder of superoxide generation in which IFN-γ therapy resulted in increased superoxide generation and fewer infections[9]. The generation of superoxide by peripheral-blood leukocytes is also defective in patients with osteopetrosis[10]. Key et al. reported their long-term experience of subcutaneous injection of IFN-γ (1.5 μg/kg/dose, three times per week) in 14 patients with severe osteopetrosis[6].

Here, we present our experience of long-term IFN-γ treatment in two patients with osteopetrosis who have been followed without transfusion support or further fractures for either 3 or 6 years.

Case Report

Case 1

A 6-year-old boy was transferred to our hospital because of pallor and general weakness for 1 month. His birth was uneventful, with a birth weight of 3.7 kg. He had no history

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of major illness or hospitalization, and no related family history.

His vital signs were stable and growth profiles were normal. On physical examination, he looked pale, and huge hepatomegaly (5 cm below the costal margin) and splenomegaly (7 cm below the costal margin) were found. A grade 2/6 systolic murmur was auscultated at the left lower sternal border. No lymph nodes were palpable.

The blood counts showed pancytopenia, with a white blood count (WBC) of 3,500/μL, neutrophil of 800/μL, hemoglobin of 6.9 g/dL and platelets of 88,000/μL. Liver and renal function tests, and other biochemical profiles were all within normal limits. Arterial blood gas analysis showed no acidosis (pH 7.39, bicarbonate 27.8 mmol/L). The parathyroid hormone level was also normal. It was very difficult to get a bone marrow specimen due to repeated dry taps. Marrow smears showed no apparent abnormal cells.

The skeletal radiograph showed abnormal appearing bones characterized by an increased overall density (Fig. 1A). The dental examination indicated generalized teeth weakness. The ophthalmologic examination and brain stem auditory evoked potential were normal.

He had no HLA-matched donor. Oral prednisolone was administered at 1 mg/kg/day for 1 month, resulting in a slight improvement in the blood counts. No transfusion was needed. Then, he was placed on IFN-γ at 1.5 μg/kg/dose subcutaneously three times a week for 3 years. The organomegaly decreased gradually and radiologic improvement was observed (Fig. 1B). The IFN-γ treatment has been reduced to twice a week for 3 years. With IFN-γ therapy, his blood counts have remained in the normal range. He has been transfusion-free and no pathologic fractures have occurred. The IFN-γ therapy was not associated with any serious adverse reaction.

Case 2

A 9-year-old boy visited a dental clinic because of generalized teeth weakness, mobility, and premature loss. He was born uneventfully, with a birth weight of 3.5 kg. He had no history of illness, hospitalization, or fracture, and no family history of consanguinity was reported.

His growth profiles and developmental quotients were normal. On physical examination, he had hepatomegaly and splenomegaly (each 3 cm below the costal margin). The initial blood counts were WBC 8000/μL, hemoglobin 12.8 g/dL, and platelets 258,000/μL. Arterial blood gas analysis showed no acidosis (pH 7.56, bicarbonate 21.0 mmol/L). The peripheral blood smear was normal. Simple radiographs showed diffuse sclerotic changes of the long bones (Fig. 2A), and brain computerized tomography (CT) revealed basal skull thickening and sclerosis. The bone scan was also compatible with osteopetrosis. The ophthalmologic examination was normal. No specific treatment was initiated.

Six months later, he developed a dental abscess and was treated. Two years later, he underwent orthopedic surgery for pathological fractures of both femoral necks (Fig. 2B). His organomegaly was aggravated in the interim and his blood counts decreased. IFN-γ therapy was started, but

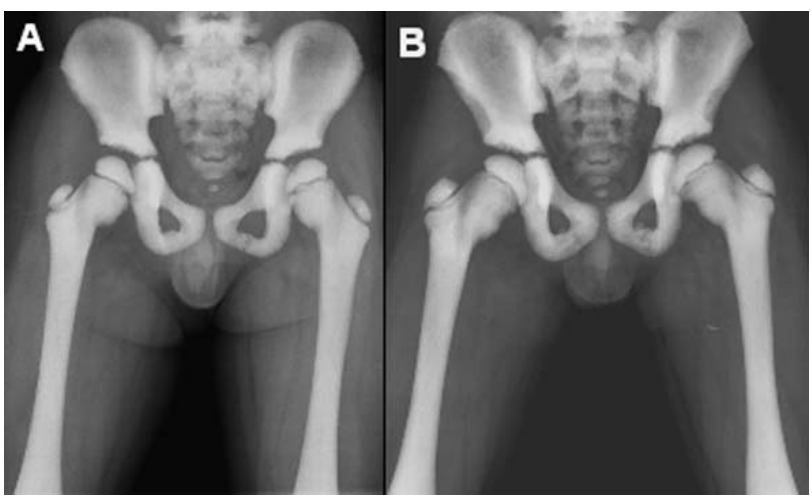

Fig. 1. Radiographs of both hips in patient 1. The characteristic increased overall bone density is shown (A). After 3 years of interferon-γ treatment, the density of the iliac bone decreased (B).

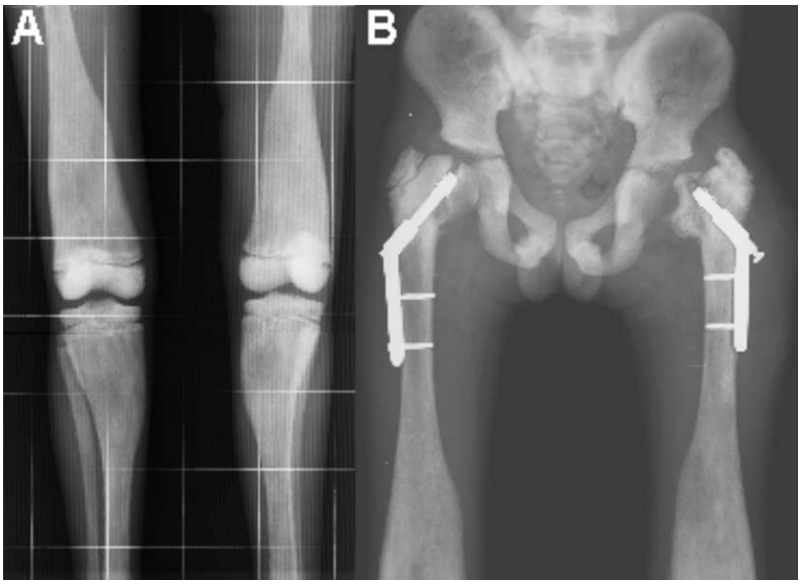

Fig. 2. Radiographs of both knees and hips of patient 2 showing diffuse sclerotic changes of the femur and tibia (A). Internal fixation was used to treat pathologic fractures of both femoral necks (B).

discontinued shortly afterward because his parents refused the treatment, which caused high fevers up to 40°C, nausea, and vomiting after injections.

When he became 13 years old, his blood counts decreased further: WBC 5,300/μL, hemoglobin 5.6 g/dL, and platelets 82,000/μL. He required regular red cell transfusions every month (a total of eight) and his spleen was enlarged to a level below the umbilicus. IFN-γ therapy (1.5 μg/kg/dose subcutaneous injection, three times a week) was resumed with heavy premedication, and the adverse reactions became more tolerable with time. After initiating IFN-γ therapy, he became less transfusion-dependent and has not needed transfusions in the last 3 years. No fracture has occurred in that period, although his spleen size remains unchanged.

Discussion

Osteopetrosis is a rare osteosclerotic bone disease characterized by a defect in osteoclast function and the reduced generation of superoxide by leukocytes[6]. Four types of osteopetrosis have been described[11-13]. The severe infantile or malignant type is apparent at birth or during the neonatal period, with clinical manifestations that include hepatomegaly, splenomegaly, lymphadenopathy, blindness, fractures, osteomyelitis, and severe anemia. These patients do not usually live beyond the age of 20 years. This type is associated with mutations in the TCIRG and CLCN7 genes[11, 12]. The second type is osteopetrosis with renal tubular acidosis and cerebral calcifications caused by a deficiency of carbonic anhydrase II (CAII) and mutations in the gene encoding the CAII protein[13]. In the third benign type, which has autosomal dominant inheritance, the patients are usually asymptomatic and are only diagnosed when radiographs are taken for some other purpose. The last type is intermediate in severity, with clinical features ranging from asymptomatic to those of the infantile malignant type, and affects both children and adults. The inheritance is autosomal recessive[14]. Both our patients likely had the last type of osteopetrosis based on the clinical findings and family history, although mutation analysis was not available.

For the infantile malignant type, SCT is the only treatment that can significantly alter the course of the disease[4]. However, SCT is associated with a high incidence of adverse outcomes, especially when alternative stem cell sources are utilized. The European Bone Marrow Transplant Group reported that the survival with osteoclast function is 73-79% following a genotypically HLA-identical transplant, and 38-43% after alternative donor transplants[15, 16]. Other less-aggressive treatment modalities have been attempted, including corticosteroids, high-dose calcitriol, and IFN-γ[6-8]. However, the usefulness of steroids or calcitriol has not been widely accepted, despite some short-term benefits in early studies[6, 18].

Based on its beneficial effect in chronic granulomatous

disease, IFN-γ was tried in patients with osteopetrosis, in whom the generation of superoxide by peripheral-blood leukocytes is defective[18]. In an animal study, IFN-γ treatment increased the marrow space in mice with osteopetrosis and microphthalmos[18]. An invitro study about IFN-γ treatment on superoxide production by osteoclasts showed that the size and number of nucleoli, and acid production by osteoclasts in osteopetrosis patients all improved after IFN-γ treatment[19].

Moreover, Key et al.[6] reported very encouraging results with recombinant human IFN-γ (1.5 μg/kg/dose, three times per week). After 6 months of therapy, all 14 patients showed decreases in trabecular bone area and increases in the bone marrow space. Both the hemoglobin levels and superoxide generation by granulocyte-macrophage colonies increased. The treatment with IFN-γ for 18 months stabilized or improved the clinical conditions in all1 1 patients who completed the full 18-month treatment, and none of the 14 patients treated for at least 6 months died[6].

In our cases, both patients exhibited a reduction in organomegaly after IFN-γ treatment; the first case showed radiologic improvement, and the second showed improved blood counts. Both patients are now free of further pathologic fractures and are transfusion-independent.

Considering the possibility of adverse effects and complications after SCT, IFN-γ treatment is a reasonable therapeutic option for patients who have a mild clinical course or are not candidates for SCT. In addition, this therapy can be used to stabilize the clinical course before transplantation.

한 글 요 약

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골화석증은 뼈파괴세포의 기능의 이상과 백혈구의 과산화물 생성 이상을 특징으로 하는 드문 골경화성 질환으로, 유전방법이나 발병나이, 증상, 증상의 정도 등에 따라 몇 가지 아형으로 분류된다. 악성형 골화석증의 궁극적 치료 방법은 조혈모세포이식이지만, 조직형 일치 공여자가 없는 경우나 비교적 양성인 만성형 골화석증에서는 스테로이드나 carcitriol, 인터페론 감마 등의 치료를 시도해 볼 수 있다. 특히 인터페론 감마 치료는 골흡수를 증가시키고, 조혈 기능과 백혈구 기능을 향상시킨다고 보고되고 있다. 본 저자들은 약 6년, 3년 동안 인터페론 감마 치료 후 각각 수혈, 골절과 같은 다른 합병증 없이 조절되고 있는 골화석증 2례에 대해 보고하는 바이다.

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