Osteonecrosis of the Hip in Patients with Aplastic Anemia

The incidence and clinical and magnetic resonance imaging features of osteonecrosis of the hip were evaluated in patients with aplastic anemia. Two hundred and forty-one patients with aplastic anemia were examined using MR imaging of bone marrow during the five years from 1994 to 1998. Osteonecrosis of the hip was observed on MR imaging in nineteen (15 males and 4 females, mean age 35 yr) of the 241 patients. It was present in both hips in 14 patients, and there were five cases with unilateral occurrence, with a total of 33 involved hips. All except for five hips with associated bone marrow edema revealed increased fatty marrow conversion in the proximal femoral metaphysis. In nine patients, osteonecrosis was detected without any pain. Five patients already had osteonecrosis before any medication was administered. Twelve patients received antilymphocyte globulin, and seven patients received a low dose of steroids before the MR diagnosis of osteonecrosis. Osteonecrosis of the hip frequently develops in patients with aplastic anemia (7.9%), associated with fatty marrow conversion of the proximal femoral metaphysis.

Key Words: Anemia, Aplastic; Osteonecrosis; Hip; Bone Marrow; Magnetic Resonance Imaging

INTRODUCTION

Osteonecrosis (ON) can accompany a wide variety of disease processes, such as trauma, hemoglobinopathy, exogeneous and endogeneous hypercortisolism, alcoholism, pancreatitis, dysbaric conditions, and Gaucher's disease (1-4). Following steroid therapy the increase in pressure and fat cell volume in the marrow cavity leads to a collapse of the sinusoids in the femoral head. This phenomenon may be a contributing factor to some forms of ON (5-8).

Aplastic anemia is a rare hematologic disorder characterized by hypocellular fatty marrow (9). The high fat content of the marrow in aplastic anemia results in high signal intensity (SI) on magnetic resonance (MR) images, reflecting the preponderance of fatty marrow and the relative lack of hematopoietic marrow (10-15). Using MR imaging, fat conversion has been observed to occur in the proximal femoral metaphysis of steroid-treated patients and is increased in osteonecrotic hips (8, 16-19). Treatment-related ON in patients with aplastic anemia has been reported in several cases (20-23), but a causal relationship between aplastic anemia and ON has not yet been determined.

The purpose of this study was to evaluate the incidence and clinical and MR imaging features of ON in the hips of patients with aplastic anemia whose bone marrow had been replaced by extensive fat.

MATERIALS AND METHODS

From January 1994 to May 1998, we performed MR imaging in 241 patients with aplastic anemia to assess bone marrow cellularity at the time of initial diagnosis. They were 125 male and 116 female patients with a mean age of 31 yr (range, 16-60 yr). MR imaging of bone marrow was performed with a 0.5 T (Gyroscan T5, Philips, Eindhoven, The Netherlands) superconductive MR scanner. The imaging protocol for evaluating the cellularity of bone marrow was as follows: sagittal T1-weighted image (T1W1) (TR/TE=560/30 msec) and short tau inversion recovery (STIR), (TR/TE/TI=1,400/30/120 msec) images of the lumbar spine with a 5-mm thickness, a 0.5-mm intersection gap, a 205x256 matrix, four-signal acquisition, and a 350-mm field of view and coronal T1WI of the pelvis (TR/TE=560/30 msec) with a 6-mm slice thickness and a 0.6-mm intersection gap. In a limited number of cases we used a 1.5 T (Magnetom Vision Plus, Siemens, Erlangen, Germany) superconductive MR scanner and added fat-saturated, enhanced, T1-weighted sequences.

On the coronal T1WI of the pelvis obtained during MR imaging of the bone marrow, we diagnosed ON and assessed bilaterality, as well as the extent of ON, and the marrow status of proximal femoral metaphysis, such as fatty or red, by visual inspection with the agreement of two radiologists. ON was diagnosed when the normal intense signal of the marrow fat was noticeably decreased in the subchondral region of the

Jeongmi Park, Jeongsu Jun, Yongsik Kim*, Jongwook Lee, Chunchu Kim*, Seongtae Hahn
Department of Radiology, Department of Orthopedic Surgery*, Department of Internal Medicine, The Catholic University of Korea, Seoul, Korea

Received: 10 May 2002
Accepted: 21 August 2002

Address for correspondence
Jeongmi Park, M.D.
Department of Radiology, St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 62 Youido-dong, Yongdungpo-gu, Seoul 150-713, Korea
Tel: +82-2-3779-2037, Fax: +82-2-783-5288
E-mail: jmpark@catholic.ac.kr
femoral head, as well as then the border of the necrosis was
demarcated by a rim of low signal (24, 25). The clinical pres-
ence or absence of hip pain and history of medication before
the development of ON were also evaluated.

RESULTS

Among the 241 aplastic anemia patients whose bone mar-
row was examined using MR imaging, we found ON of the
hip in 19 patients. The cumulative incidence of ON of the
hip in patients with aplastic anemia was 7.9%. There were
15 men and 4 women, who ranged in age from 19 to 46 yr
(mean 35 yr).

In 14 of these patients, both hips were affected while five
patients had unilateral ON. Therefore, a total of 33 hips were
involved. In 26 of these hips, the extent of necrosis exceeded
50% of the femoral heads but the remaining seven hips exhib-
ited only small crescentic subchondral defects. Necrotic areas
revealed early change of high SI isointense to adjacent fat mar-
row or only slightly decreased SI. All hips exhibited marked
fatty marrow conversion with the exception of the five hips
associated with marrow edema in the proximal femoral meta-
physis.

Five patients (No. 6, 10, 12, 14, 18) already had ON at the
time of MR imaging despite having no history of previous
medication (Fig. 1). Hip pain was reported in ten of the nine-
teen patients. Twelve patients received antilymphocyte globulin
six months to four years before MR imaging (Fig. 2). In seven
patients, corticosteroid (prednisolone, 4 mg/kg daily initially,
then tailing off to zero over 3 weeks) was also administered
for prevention of serum sickness and androgen was adminis-

Fig. 1. A 42-yr-old woman (patient No.18) with moderate aplastic
anemia shows unilateral osteonecrosis on the left femoral head on a
coronal T1-weighted MR image (560/30) of the pelvis. Although
there was no evidence of osteonecrosis on the right side, the
proximal femoral metaphysis showed high signal intensity, indicat-
ing that the marrow was predominantly fatty. At the time of this
initial MR imaging, this patient already had an osteonecrosis of the
hip but had no pain; the patient had no history of prior medication.

Fig. 2. A 33-yr-old woman (patient No.15) with severe aplastic anemia. (A) Coronal T1-weighted MR image (560/30) of the pelvis shows
diffuse heterogeneous high-signal intensity of the pelvic marrow, indicating fatty replacement. Proximal femoral metaphysis also shows
marked fatty conversion. (B) Coronal T1-weighted MR image (560/30) of the pelvis 15 months after immunotherapy shows a large area of
osteonecrosis in both femoral heads.
tered to seven of the patients before MR imaging. The MR imaging and clinical findings are summarized in Table 1.

**DISCUSSION**

Aplastic anemia is a potentially severe marrow disorder characterized by peripheral pancytopenia and marrow that is largely devoid of hematopoietic cells; while retaining the basic marrow architecture or stroma, hematopoietic cells are replaced by large amounts of fat (9). MR imaging has been proposed as a non-invasive and relatively rapid method for evaluation of the bone marrow composition. An aplastic marrow demonstrates focal or diffuse bright SI according to the amount of replaced fatty marrow on T1WI and fatty infiltration in bone marrow can be confirmed by fat suppression images (10-14). Meanwhile, as we evaluated the cellularity of bone marrow using MR imaging for initial assessment of severity in patients with aplastic anemia, we found ON of the hip in 19 of the 241 patients with aplastic anemia during the 4 yr and 5 months. There were few data on the incidence or prevalence of ON among corticosteroid-treated patients and other groups at risk (1). A systemic review of the published literature estimated the incidence of ON of the hip in long-term steroid treatment to be approximately 5 to 10% (26, 27). ON, especially of the femoral head, in association with chronic alcoholism is fairly common. The incidence rate among alcoholics may not be as high as expected with the incidence of 5.3% in medically treated alcoholics (28, 29). Radiographic and pathologic characteristics of ON in patients with aplastic anemia are not unique, being evident in cases of bony necrosis due to other causes.

In hematopoietic marrow, the vascular structure is characterized by a rich and arborized sinusoidal system. As fatty marrow cell masses increase, the sinusoidal system is replaced by capillaries which are sparse. In the fatty marrow, perfusion of the marrow decreases gradually, and consequent vascularization of this marrow is ineffective due to venous stasis. As a result of this characteristic vascular structure, fatty marrow is more vulnerable to ischemia than hematopoietic marrow (12). Alternatively, since ischemia or poor perfusion is known to be a factor that induces fatty marrow conversion, such conversion is more accelerated in the marrow cavity where fatty marrow cells begin to be distributed. MR imaging was used to assess marrow composition because it provides information on the amount of fat in bones (8, 10-12, 17, 30-32). In fact patients with ON have an increased incidence of predominantly fatty marrow in the intertrochanteric portion of the femur depicted by MR image (17) and the ratio of fatty marrow conversion of the proximal femoral metaphysis to that of the greater trochanter measured on T1WI is increased (16). Therefore MR imaging has enabled researchers to assess the significant increase in the conversions of fatty marrow in the proximal femoral metaphysis and the osteonecrotic hips of patients treated with steroids (8, 16, 17). In our 28 hips, proximal femoral metaphysis revealed marked fatty marrow conversion irrespective of the age of the patient.

ON has been reported in patients with aplastic anemia

| Patient No. | Age (yr) | Sex | Diagnosis | Bilaterality of ON | Defect size | PFM | Interval (yr) | Hip pain | Treatment |
|-------------|---------|-----|-----------|-------------------|------------|-----|--------------|----------|-----------|
| 1           | 19      | M   | SAA       | Both              | Small      | Fatty | 1.5          | -        | +         |
| 2           | 19      | M   | SAA       | Both              | Large      | Fatty | 1            | -        | +         |
| 3           | 21      | M   | MAA       | Both              | Large      | Fatty | 1            | -        | +         |
| 4           | 24      | F   | SAA       | Both              | Large      | Fatty | 2            | +        | -         |
| 5           | 25      | M   | MAA       | Both              | Large      | Fatty | 8            | +        | -         |
| 6           | 26      | M   | MAA       | Left              | Small      | Fatty | 1            | -        | -         |
| 7           | 26      | M   | SAA       | Both              | Small      | Fatty | 4            | -        | +         |
| 8           | 28      | M   | SAA       | Both              | Large      | Fatty | 1            | +        | +         |
| 9           | 29      | M   | MAA       | Both              | Large      | Fatty | 1            | +        | +         |
| 10          | 29      | M   | SAA       | Right             | Small      | Fatty | 0.5          | -        | -         |
| 11          | 31      | F   | MAA       | Both              | Large      | BME   | 0.5          | +        | -         |
| 12          | 31      | M   | MAA       | Right             | Large      | BME   | 2            | +        | -         |
| 13          | 32      | M   | SAA       | Both              | Large      | Fatty | 3            | +        | -         |
| 14          | 33      | M   | MAA       | Both              | Large      | Fatty | 3            | +        | -         |
| 15          | 33      | F   | SAA       | Both              | Large      | Fatty | 1.3          | -        | +         |
| 16          | 35      | M   | SAA       | Both              | Large      | BME   | 9            | +        | +         |
| 17          | 36      | M   | SAA       | Both              | Large      | Fatty | 0.6          | +        | +         |
| 18          | 42      | F   | MAA       | Left              | Small      | Fatty | 2            | -        | -         |
| 19          | 46      | M   | MAA       | Left              | Large      | Fatty | 2.5          | +        | -         |

ON: Osteonecrosis, PFM: proximal femoral metaphysis, BME: bone marrow edema, Interval (years): Interval from diagnosis of aplastic anemia to development of osteonecrosis, MAA: moderate aplastic anemia, SAA: severe aplastic anemia, Small: osteonecrosis less than 50% involvement of femoral head, Large: osteonecrosis over 50% involvement of femoral head, -: absence, +: presence.

Table 1. Summary of MR imaging and clinical findings in osteonecrosis of the hip in patients with aplastic anemia
treated with antilymphocyte globulin followed by high doses of corticosteroids. In contrast there were no cases of ON with aplastic anemia treated with an antilymphocyte globulin but using a short course of low-dose steroid (20-23). In the present study, ON was diagnosed in five patients with aplastic anemia before any medication was administered. Reviewing patients’ medical histories, prior to immunotherapy with antilymphocyte globulin had been done six months to four years previously and during that time corticosteroids were only administered in small doses for short periods of time (prednisolone, 4 mg/kg daily, tailing off to zero over three weeks) in order to prevent serum sickness caused by antilymphocyte globulin therapy. We therefore speculate that increased fatty infiltration in the bone marrow of patients with aplastic anemia may be a key factor in the development of ON of the hip.

Our study has several limitations. First, we assessed fatty marrow conversion of proximal femoral metaphysis visually and not quantitatively. Secondly, we could not explain why only a unilateral hip was involved with ON in five patients despite the occurrence of bilateral extensive fatty conversion in the proximal femoral metaphysis. Thirdly, longitudinal MR imaging was not undertaken, and only five patients (No. 1, 2, 11, 12, 15) had MR imaging before and after development of ON. Therefore, we must undertake further longitudinal studies to assess the possible roles of antilymphocyte globulin, corticosteroid, or combination therapy in the development of ON in patients with aplastic anemia.

In conclusion, we demonstrated ON of the hip developed frequently in patients with aplastic anemia, its cumulative incidence for 4 yr and 5 months being about 7.4%. Increased fatty marrow conversion of proximal femoral metaphysis may be associated with ON of the hip in patients with aplastic anemia.

ACKNOWLEDGMENT

We thank Bonnie Hammi at Department of Radiology in University Hospitals of Cleveland, Cleveland, OH, U.S.A., for her editorial assistance in the preparation of the manuscript.

REFERENCES

1. Sweet DE, Madewell JE. Pathogenesis of Osteonecrosis. In: Resnick D, Niwayama G, eds. Diagnosis of Bone and Joint Disorders. Ed 3. Philadelphia: WB Saunders, 1995: 3445-94.
2. Ficat RP. Idiopathic bone necrosis of the femoral head: Early diagnosis and treatment. J Bone Joint Surg 1985; 67B: 3-9.
3. Arlet J. Nontraumatic avascular necrosis of the femoral head. Past, present, and future. Clin Orthop 1992; 277: 12-21.
4. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992; 326: 1473-9.
5. Yamamoto T, Irisa T, Sugioka Y, Sucishi K. Effects of pulse methylprednisolone on bone and marrow tissues. Arthritis Rheum 1997; 40: 2055-64.
6. Wang GJ, Sweet DE, Reger SI, Thompson RC. Fat-cell changes as a mechanism of avascular necrosis of the femoral head in cortisone-treated rabbits. J Bone Joint Surg 1977; 59A: 729-35.
7. Cui Q, Wang GJ, Balian G. Steroid-induced adipogenesis in a pluripotential cell line from bone marrow. J Bone Joint Surg 1979; 1054-63.
8. Vande Berg BC, Malghem J, Lecouvet FE, Devogelaer JP, Maldaague B, Houssiau FA. Fat conversion of femoral marrow in glucocorticoid-treated patients: a cross-sectional and longitudinal study with magnetic resonance imaging. Arthritis Rheum 1999; 42: 1405-11.
9. Young NS. Aplastic anaemia and related bone marrow failure syndrome. In: Bennet and Plum, ed. Cecil Textbook of Medicine 20th ed. Vol 1 Philadelphia: WB Saunders, 1996: 831-6.
10. Mouloupoulos LA, Dimopoulos MA. Magnetic resonance imaging of the bone marrow in hematologic malignancies. Blood 1997; 90: 2127-47.
11. Steiner RM, Mitchell DG, Rao VM, Schweitzer ME. Magnetic resonance imaging of diffuse bone marrow disease. Radiol Clin North Am 1993; 31: 383-409.
12. Vogler JB III, Murphy WA. Bone marrow imaging. Radiology 1988; 168: 679-93.
13. Kusumoto S, Jinmai I, Matsuda A, Murohashi I, Bessho M, Saito M, Hisashima K, Heshiki A, Minamihisamatsu M. Bone marrow patterns in patients with aplastic anaemia and myelodysplastic syndrome: observations with magnetic resonance imaging. Eur J Haematol 1997; 59: 155-61.
14. Amano Y, Kumazaki T. Proton MR imaging and spectroscopy evaluation of aplastic anaemia: three bone marrow patterns. J Comput Assist Tomogr 1997; 21: 286-92.
15. Park JM, Lim GY, Kim EN, Lee JM, Kim DW, Han CW, Kim CC. Evaluation of severity in aplastic anaemia by MR imaging. J Korean Radiol Soc 1999; 40: 347-54.
16. Koo KH, Dussault RG, Kaplan PA, Ahn IO, Kim R, Devine MI, Cui Q, Cho SH, Wang GJ. Fatty marrow conversion of the proximal femoral metaphysis in osteonecrotic hips. Clin Orthop 1999; 361: 159-67.
17. Mitchell DG, Rao VM, Dalinka M, Spritzer CE, Axel L, Gefter W, Kricun M, Steinberg ME, Kressel HY. Hematopoietic and fatty bone marrow distribution in the normal and ischemic hip: new observations with 1.5-T MR imaging. Radiology 1986; 161: 199-202.
18. Coleman BG, Kressel HY, Dalinka MK, Scheiber ML, Burk DL, Cohen EK. Radiographically negative avascular necrosis: Detection with MR imaging. Radiology 1988; 168: 525-8.
19. Chun HJ, Park JM, Kim JY, Lim GY, Yang PS, Kim EN, Kim CY, Shinn KS. Marrow pattern in the proximal femoral metaphysis of patients with osteonecrosis of the femoral head and normal subjects: comparison on MR images. J Korean Radiol Soc 1996; 35: 117-22.
20. Prindull G, Weigel W, Jentsch E, Enderle A, Willert HG. Aseptic osteonecrosis in children treated for acute lymphoblastic leukemia and aplastic anemia. Eur J Pediatr 1982; 139: 48-51.
21. Dyreborg E, Pilgaard S. Osteonecrosis in three young men previously treated with steroid for aplastic anaemia. Acta Orthop Scand 1974;
22. Facon T, Walter MP, Fenaux P, Morel P, Dupriez B, Gardin C, Jouet JP, Bauters F. Treatment of severe aplastic anemia with antilymphocyte globulin and androgens: a report on 33 patients. Ann Hematol 1991; 63: 89-93.

23. Marsh JC, Zorbas A, Hows JM, Chapple M, Gordon-Smith EC. Avascular necrosis after treatment of aplastic anemia with antilymphocyte globulin and high-dose methylprednisolone. Br J Haematol 1993; 84: 731-5.

24. Mitchell DG, Kressel HY, Arger PH, Dalinka M, Spritzer CE, Steinberg ME. Avascular necrosis of the femoral head: morphologic assessment by MR imaging, with CT correlation. Radiology 1986; 161: 739-42.

25. Mitchell DG, Rao VM, Dalinka MK, Spritzer CE, Alavi A, Steinberg ME, Fallon M, Kressel HY. Femoral head avascular necrosis: correlation of MR imaging, radiographic staging, radionuclide imaging, and clinical findings. Radiology 1987; 162: 709-15.

26. Harrington KD, Murray WR, Kountz SL, Belzer FO. Avascular necrosis of bone after renal transplantation. J Bone Joint Surg 1971; 53A: 203-15.

27. Tervonen O, Mueller DM, Matteson EL, Velosa JA, Ginsburg WW, Ehman RL. Clinically occult avascular necrosis of the hip: prevalence in an asymptomatic population at risk. Radiology 1992; 182: 845-7.

28. Jacobs B. Epidemiology of traumatic and nontraumatic osteonecrosis. Clin Orthop 1978; 130: 51-67.

29. Orlic D, Jovanovic S, Anticevic D, Zecevic J. Frequency of idiopathic aseptic necrosis in medically treated alcoholics. Int Orthop 1990; 14: 383-6.

30. Moore SG, Dawson KL. Red and yellow marrow in the femur: age-related changes in appearance at MR imaging. Radiology 1990; 175: 219-23.

31. Vande Berg BC, Lecouvet FE, Moysan P, Maldague B, Jamart J, Malghem J. MR assessment of red marrow distribution and composition in the proximal femur: correlation with clinical and laboratory parameters. Skeletal Radiol 1997; 26: 589-96.

32. Koo KH, Dussault R, Kaplan P, Kim R, Ahn IO, Christopher J, Song HR, Wang GJ. Age-related marrow conversion in the proximal metaphysis of the femur: Evaluation with T1-weighted MR imaging. Radiology 1998; 206: 745-8.