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SPECIAL REPORT

Accumulation of microdamage and low bone mass in the femoral head as a cause of subchondral insufficiency fracture in a patient with osteogenesis imperfecta

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Abstract
Subchondral insufficiency fractures of the femoral head are generally considered to be osteoporosis-related fragility fractures. There have been reports of microfractures being found in subchondral bone on pathological examination. However, the mechanism of these microfractures is not known. In this report, we describe a patient with osteogenesis imperfecta who developed a subchondral insufficiency fracture of the femoral head after a fall that had resulted in a subcapital femoral neck fracture. Bipolar hemiarthroplasty was performed, and bone at the femoral head and neck was sampled for pathophysiological examination. Hematoxylin and eosin staining revealed microfractures and microcallus in the subchondral bone in the femoral head, indicating healing of a subchondral insufficiency fracture before the subcapital femoral neck fracture. Moreover, decreased bone volume and accumulated microdamage were observed in the subchondral bone but not in the cancellous bone in the femoral neck. These findings suggest that subchondral insufficiency fracture of the femoral head is a stress fracture caused by accumulation of microdamage in fragile subchondral bone.

Keywords Microdamage · Subchondral insufficiency fracture · Osteogenesis imperfecta · Osteoporosis · Femoral head

Introduction

Osteogenesis imperfecta (OI) is an inherited disease that is characterized by osteopenia and bone fragility and has been classified into four types by Sillence [1] as follows: type 1, characterized by osseous fragility, distinctly blue sclerae, and hearing impairment; type 2, characterized by extremely severe osseous fragility, stillbirth, or neonatal death; type 3, characterized by moderately severe to severe osseous fragility, normal sclerae (blue in infancy), and severe deformity of the long bones and spine; and type 4, an intermediate type between types 1 and 3. OI is usually caused by mutation in the type 1 collagen gene, which is the main substrate protein in bone. Extraosseous symptoms include joint laxity, blue sclerae, dental dysplasia, and hearing impairment [2]. OI is reported to be associated with transient osteoporosis of the hip (TOH) [3–5], but not with subchondral insufficiency fracture (SIF) of the femoral head. SIF of the femoral head was initially reported as an osteoporosis-related fragility fracture by Bangil et al. [6]; subsequent pathologic studies by Yamamoto et al. [7] and Hagino et al. [8] found microfractures in the subchondral bone, but the mechanism of these microfractures remains unknown. Here, we report our pathologic and histomorphometric assessment of SIF of the femoral head in a patient with OI who underwent hemiarthroplasty to treat a subcapital femoral neck fracture after a fall. The patient and his family provided written informed consent for the data from his case to be submitted for publication.

Case report

A 42-year-old man was referred to us by another hospital with a 1-month history of hip pain without trauma and abnormal findings on magnetic resonance imaging (MRI). He was 143 cm tall (height less than − 2 SD below the

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mean), his weight was 56 kg, and he had blue sclerae. He had sustained a left femoral diaphyseal fracture in childhood that was treated at the children's hospital, at which time OI was diagnosed. He had undergone surgery for dislocation of a shoulder joint and a knee avulsion fracture in adulthood. His father also had a diagnosis of OI. The patient's past medical history included alcoholic hepatitis and hypertension. Plain radiographs at the time of the first medical examination did not reveal any abnormality in the hip joint (Fig. 1a). However, T1-weighted MRI showed a low-signal line under the joint surface in a low-intensity area extending from the subchondral bone to the femoral neck (Fig. 1b, white arrow). T2-weighted images showed a low-signal line under the joint surface in a high-intensity area with a bone marrow edema pattern (Fig. 1c, black arrow). Past reports [9, 10] suggest that these findings were SIF. Bone mineral density (BMD) was evaluated by dual-X-ray absorptiometry using a Lunar iDEXA (GE Medical Systems, Milwaukee, WI, USA). BMD was 0.872 g/cm^2 (T score, − 2.7) at the lumbar spine, 0.664 g/cm^2 (T score, − 2.2) at the right femoral neck, and 0.528 g/cm^2 (T score, − 3.2) at the left femoral neck. Levels of the bone metabolism markers tartrate-resistant acid phosphatase 5b and osteocalcin were 204 mU/dL (normal range 170–590 mU/dL) and 4.8 ng/mL (2.5–13 ng/mL), respectively. Based on these findings and past reports [6–10], the diagnosis was osteoporosis-related SIF caused by OI. We suggested that he start treatment for the osteoporosis and scheduled an appointment to do so 2 weeks later. The patient was treated conservatively and instructed to avoid weight bearing using a pair of crutches. However, 6 days later, he was transported to our hospital with severe hip pain after a fall. Plain radiographs and computed tomography images showed a large displaced left subcapital femoral neck fracture (Fig. 1d, e). Severe osteoporosis and the large displaced fracture raised concern for late segmental collapse of the femoral head, so hemiarthroplasty was performed despite the patient being middle aged (Fig. 1f). Findings on examination of the sectioned surface of the cartilage and subchondral bone of the femoral head were normal, but the subcapital cancellous bone of the femoral neck was crushed and impacted (Fig. 2a). It was predicted that osteosynthesis would not have a good outcome because one-third of the femoral head above the femoral neck had collapsed. The central 1-cm-wide segment of the femoral head and impacted neck in the sagittal plane was cut in the coronal plane. Specimens were then stained with hematoxylin and eosin for pathologic diagnosis and with Villanueva bone stain [11] for bone histomorphometry. Additional specimens were stained en bloc with 1% basic fuchsin and embedded in methyl methacrylate for assessment of microdamage [12]. Ground sections measuring 30 µm and 100 µm thick were obtained for analysis of histomorphometry and microdamage, respectively. Histomorphometry and microdamage were assessed in 5 × 5 mm areas of cancellous bone (Fig. 1a, the

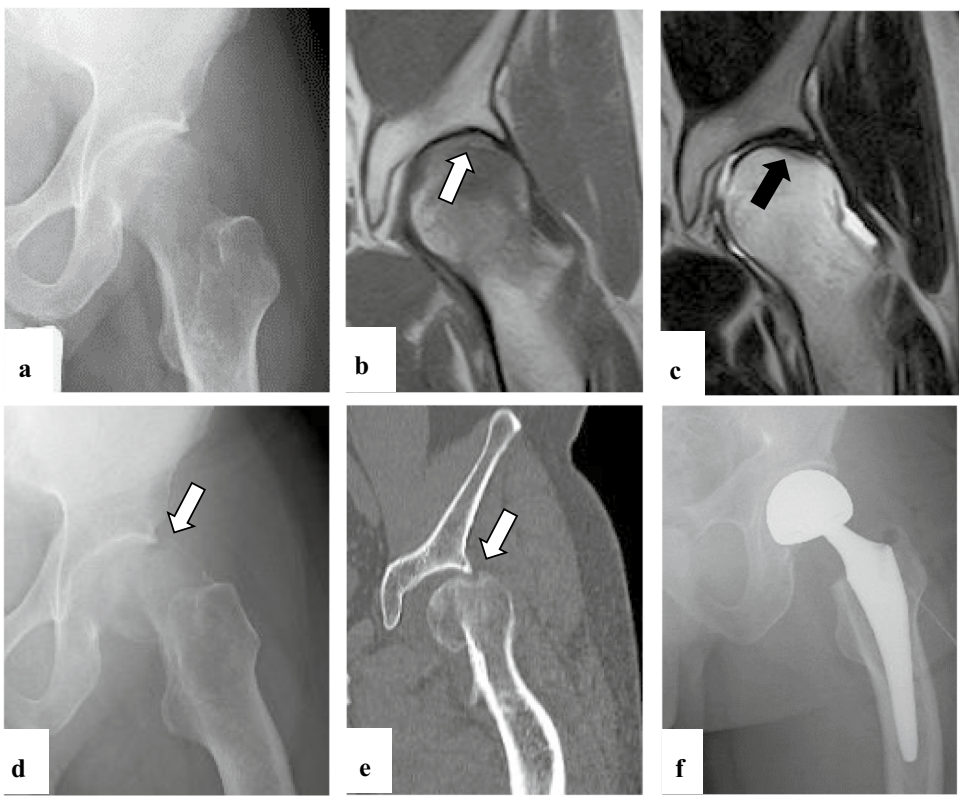

Fig. 1 Progression of findings on imaging. **a** Plain radiograph of the left hip at the time of our first clinical examination did not reveal any abnormalities. **b** A T1-weighted magnetic resonance image shows a low-signal line under the joint surface in a low-intensity area from the subchondral bone to the femoral neck (white arrow). **c** A T2-weighted magnetic resonance image shows a low-signal line under the joint surface in a high-intensity area with a bone marrow edema-like pattern (black arrow). **d** A plain radiograph obtained immediately after the patient sustained a fall shows a subcapital femoral neck fracture (white arrow). **e** A computed tomography image shows a large displaced subcapital femoral neck fracture (white arrow). **f** A plain radiograph obtained after bipolar hemiarthroplasty was performed

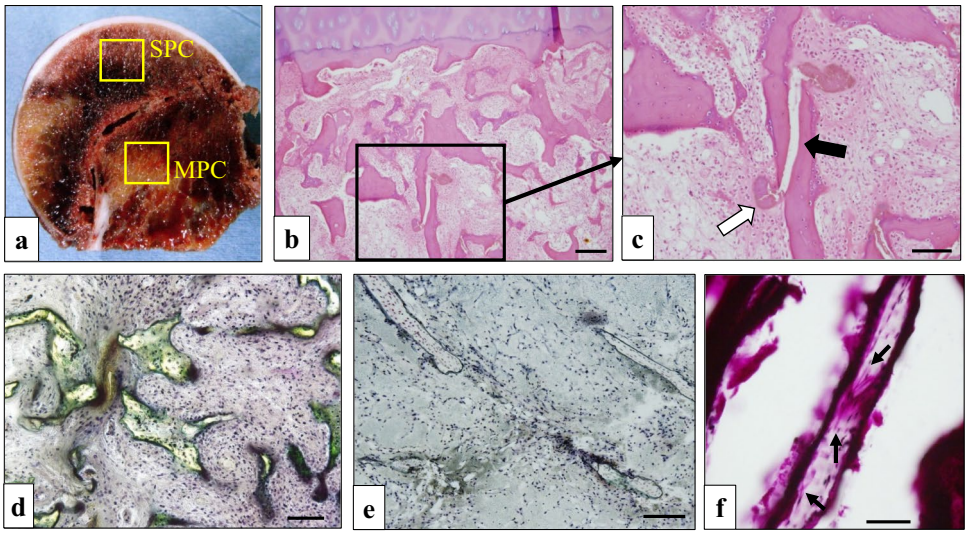

Fig. 2 Images of bone samples, **a** cut surface of the femoral head and impacted neck. Histomorphometry and microdamage were assessed in 5×5 mm areas of cancellous bone (the upper yellow square indicates the subchondral principal compressive region [SPC]; the lower yellow square indicates the zone near the medial cortex in the principal compressive region [MPC], as defined by Fazzalari et al. [13]), **b** a section of the SPC stained with hematoxylin and eosin shows a fractured trabecular bone. Scale bar 200 µm. **c** Enlarged fractured trabecular bone (black arrow) showed microfractures with microcallus formation (white arrow). Scale bar 100 µm. **d** A section of the SPC with Villanueva bone stain shows fewer and thinner trabeculae. Scale bar 100 µm. **e** A section of the MPC with Villanueva bone stain shows fewer connections and thinner trabeculae than the section of the SPC. Scale bar 100 µm. **f** En bloc bone stain with 1% basic fuchsin for assessment of microdamage shows a large amount of microcracks (black arrow). Scale bar 100 µm

upper yellow square indicates the subchondral principal compressive region [SPC], as defined by Fazzalari et al.) [13]. We also performed histomorphometry and evaluated microdamage in 5×5 mm areas of cancellous bone in the femoral neck (Fig. 1a, the lower yellow square indicates the zone near the medial cortex in the principal compressive region [MPC], as defined by Fazzalari et al. [13]) using a similar method. Femoral head specimens were collected from 5 male cadaveric controls without bone disease (mean age 85.2 years) to compare the subchondral cancellous bone under the weight-bearing surface (SPC). Histomorphometric measurements were performed using a semi-automated digitizing image analyzer that consisted of a light or epifluorescent microscope and a digitizing pad connected to a computer with histomorphometric software (System Supply Co. Ltd., Nagano, Japan). All measurements were performed in a blinded manner by one histomorphometrist. All parameters were measured and identified in accordance with the terminology devised by the American Society for Bone and Mineral Research nomenclature committee [14]. Microdamage in bone was defined as a typical crack shape with a certain depth of field and a surrounding halo of increased basic fuchsin staining. Crack density, mean crack length, and crack surface density were measured using the method reported by Burr et al. [12].

Hematoxylin and eosin staining of the subchondral bone of the femoral head revealed fractured trabecular bone (Fig. 2b, square area; 2c, black arrow) with associated microfractures and microcallus formation (Fig. 2c, white arrow). Villanueva staining of sections of subchondral bone in the femoral head and cancellous bone of the femoral neck revealed a poor trabecular bone structure and osteopenia, respectively (Fig. 2d, e). Histomorphometry of these sections showed a marked decrease in bone volume and trabecular thickness when compared with the cadaveric controls (Table 1). Fazzalari et al. reported on the histomorphometry and microdamage occurring in the normal femoral head [13, 15], and the SPC and MPC mentioned in their study corresponded to our measured areas of subchondral cancellous bone and cancellous bone in the femoral neck, respectively. However, the decreases in bone volume and trabecular thickness in our patient were greater than those reported by Fazzalari et al. [13]. Assessment of microdamage showed that the mean microcrack length was comparable and that the microcrack density in the SPC of the femoral head was larger than at the site of the MPC of the femoral neck and the SPC of the femoral head in the cadaveric controls (Table 2). A subsequent study by Fazzalari et al. [15] found less microdamage in the SPC and MPC than in our case. One month postoperatively, our patient had a stable T-cane gait and was discharged from hospital to home taking alendronate 35 mg/week for osteoporosis. At his last follow-up visit, 3 years after surgery, the patient's BMD at the lumbar spine had improved to 0.903 g/cm^2 (T score, − 1.4). He was able to walk without a cane and return to work. His Harris hip score was 92 points [16].

Table 1 Histomorphometric analysis of cancellous bone of femoral head (SPC) and neck (MPC)

Histomorphometric parameter	Present case		CNT SPC	Fazzalari [13]	
	SPC	MPC		SPC	MPC
Bone volume (%)	13.1	5.7	19.2	26.9	32.9
Tb.Th (μm)	25.6	49	196.9	423.0	656.0
Tb.Sp	169.6	814.6	1225.8	1185.0	1337.0
Tb.N	5.1	1.16	1.0		
OS/BS (%)	0.54	5.2	17.8	8.4	5.7
O.Th (μm)	6.5	9.4	25.5		
ES/BS (%)	4.8	4.4	3.6	1.7	2.4

Bone volume and trabecular thickness of SPC and MPC in the present case were extremely smaller than CNT and 14 men cadavers from Fazzalari [13]. It is suggested that severe osteoporosis existed in the present case

SPC subchondral principal compressive region, *MPC* medial cortex in the principal compressive region, *CNT* cadaveric controls, *Tb.Th* trabecular thickness, *Tb.Sp* trabecular separation, *Tb.N* trabecular number, *OS* osteoid surface, *BS* bone surface, *O.Th* osteoid thickness, *ES* eroded surface

Discussion

OI is a hereditary disease caused by abnormality of type 1 collagen, is characterized by bone fragility and frequent fractures, and sometimes causes TOH [3–5]. Noorda et al. [3] reported a decrease in the number of very slender bony trabeculae and the presence of microfractures in trabecular bone in a core biopsy taken from the femoral head in a patient with OI and TOH. In our case, decreased thickness of trabeculae was observed in the cancellous bone of the femoral head and neck, along with many microfractures and microcallus formation in the trabeculae of the subchondral bone at the femoral head. Considering the similarity of these findings to SIF [7, 8], TOH and SIF of the femoral head are possibly the same entity. There is no literature on histomorphometry of the femoral head in OI, so we were unable to compare our histomorphometry findings with those in other reports. Our cadaveric controls were more osteoporotic than the controls in the study by Fazzalari et al. (14 men of mean age 44.1 years) [13]; however, mean age appears to explain the differences in the data between the studies. The bone volume in our patient with OI was markedly smaller than that in the study reported by Fazzalari et al. [13]. When compared to the reports by Shapiro et al. [17] and Iwamoto et al. [18], who measured bone volume in a biopsy from the iliac crest in patients with OI, the findings in our case suggest severe osteoporosis. We were unable to find any studies assessing microdamage in the femoral head in patients with SIF. Comparison of the SPC in our patient with that in our five cadaveric controls and those of Fazzalari et al. [15] and Mori et al. [19] showed that crack length was similar but crack density was larger in our case (Table 2). Mori et al. assessed microdamage in the SPC with and without femoral neck fracture, and found that crack density did not differ significantly between them [19]; femoral neck fracture probably did not add microdamage in the femoral head. We suggest that microdamage had already accumulated in our patient before the subcapital femoral neck fracture. SIF of the femoral head is often seen in elderly patients with osteoporosis [6–10]. However, younger patients with OI can also develop SIF of femoral head as a result of accumulation of microdamage. Mori et al. reported that accumulation of microdamage is a cause of stress fractures [20], and SIF of the femoral head may have a similar pathophysiology.

This is the first report on histomorphometric and microdamage assessment at the femoral head in a patient with OI and SIF. There have been reports of the histology of TOH with OI, but there have not been any reports of SIF of the femoral head in these patients. The findings of this report will help to elucidate the pathophysiology of SIF of the femoral head in OI.

This study had some limitations. Our controls were normal cadaveric samples and did not have OI; therefore, they did not provide true control data for the present case. We did not perform iliac bone biopsy and investigated only tartrate-resistant acid phosphatase 5b and osteocalcin as bone turnover markers; their values were normal, but we cannot state

Table 2 Assessment of microdamage in cancellous bone of femoral head and neck

Microdamage parameter	Present case		CNT	Fazzalari [15]		Mori [19]
	SPC	MPC	SPC	SPC	MPC	SPC
Crack density (mm^2)	6.1	0.3	0.6	0.51	0.38	0.35
Crack length (μm)	40.5	51.5	50.4	59	79	74.6
Crack surface density (μm/mm^2)	254.4	15.4	35.6	25.0	29.7	26.1

Crack length of SPC and MPC in the present case was comparable for CNT and not so different from normal 12 cadavers by Fazzalari [15] and with femoral neck fractured by Mori [19]. However, crack density of SPC in the present case was extremely larger than others. It is suggested that many microcrack of SPC in the present case had already existed before subcapital femoral neck fracture

whether bone turnover increased or decreased in general by bone biopsy.

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Compliance with ethical standards

Ethical approval The study was approved by the ethics commission of our institution.

Informed consent Written informed consent was obtained from the patient and his family.

Conflict of interest None of the authors has any conflict of interest associated with this study.

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