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CASE REPORT

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Heterotopic ossification in bilateral knee and hip joints after long-term sedation

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Introduction

Heterotopic ossification (HO) is one of the disorders causing ankylosis. This syndrome is most commonly seen following neurological disorders such as traumatic brain or spinal-cord injury, or following joint surgery or severe burns [1–4]. HO occurring in a heavily sedated and immobilized patient in the absence of any anatomical central nervous system lesion is unusual (although Dellestable et al. [5] reported this in five patients undergoing artificial ventilation). Pathogenic mechanisms and appropriate treatments, including surgical timing for excision, have, therefore, not been defined for this form of HO. Herein we report procedures, including monitoring of ossification markers, which resulted in good prognosis, for a patient with HO following long-term sedation with artificial ventilation.

Case report

The patient was a 42-year-old man with limited joint motion of the bilateral hips and knees. He had undergone valve-replacement surgery for aortic incompetence. He developed methicillin-resistant *Staphylococcus aureus* (MRSA) fibrous mediastinitis with swelling at the surgical site on postoperative day 14. Intermittent irrigation of the incision, under intubation anesthesia, was therefore performed, for 44 days, from postoperative days 16 to 59. After MRSA screenings yielded negative results, the patient displayed limited joint motion in the bilateral hips and knees, and was referred to our institute 3 months after the cessation of the long-term sedation.

On admission, passive and active range of motion (ROM) in the knee joints was 20°–40° flexion in the right knee and 10°–30° flexion in the left knee. The ROM for flexion/extension, adduction/abduction, and internal/external rotation in the right and left hip joints was 50°/–30°, 30°/10°, and 0°/20° in the right hip and 70°/–50°, 40°/0°, and 30°/–10° in the left hip, respectively. No pain was reported on motion in any joint, but he was unable to stand without assistance. Ambulatory ability was restricted to a slow gait over a short distance.

Radiography of the knee joints revealed HO from the medial epicondyle of the femur to the inferior facet of the patella (Fig. 1a–c). Radiography of the hip joints showed HO from the greater trochanter to the acetabular edge. Bone scintigraphy, using 99m technetium-labeled methylene diphosphonate, showed very high incorporation in the bilateral hip and knee joints, and slightly elevated incorporation in the left shoulder joint (Fig. 2).

Levels of the bone metabolic markers serum alkaline phosphatase (ALP), serum intact osteocalcin (iOC), and urinary deoxypyridinoline (DPD/creatinine [Cre]) were high, at: 488 IU/l (normal, 70–300 IU/l); 19.5 ng/ml (normal, <7 ng/ml); and 21.2 nmol/mmol Cre (normal, 2.1–5.4 nmol/mmol Cre), respectively (Fig. 3).

The patient received oral administration of disodium etidronate, 1000 mg/day, and indomethacin, 50 mg/day, until the day before surgery was performed for HO. Exercises had been performed to maintain ROM. For 7 months from the time of admission to our institute, and for 4–10 months after his emergence from long-term sedation with artificial ventilation, no new development of HO was detected on

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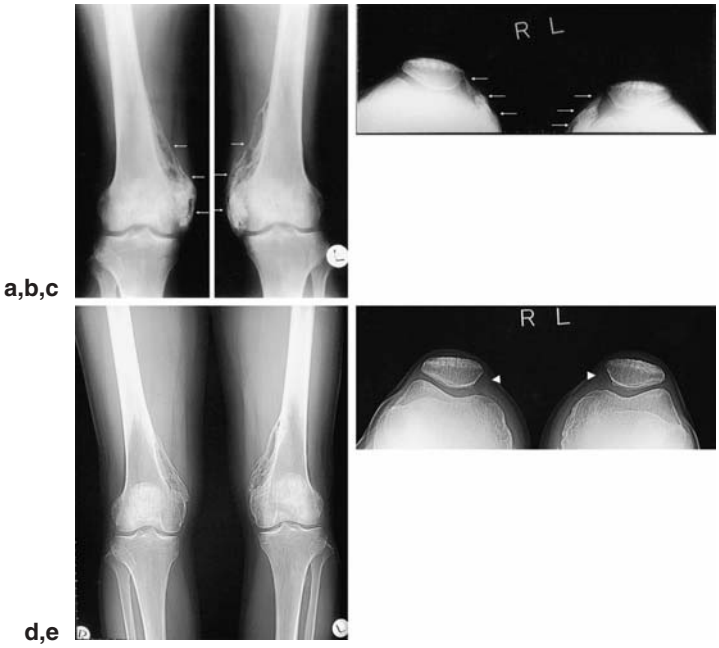

Fig. 1. Radiography of knee joints before and after resection. **a–c** Heterotopic ossification (HO; *arrows*) before resection, from the medial epicondyle of the femur to the inferior facet of the patella. **a** Anteroposterior (AP) view of right knee; **b** AP view of left knee; **c** skyline view. **d,e** No recurrence of HO (*arrowheads*) in **e** was detected in knee joints at 4.5 years postoperatively

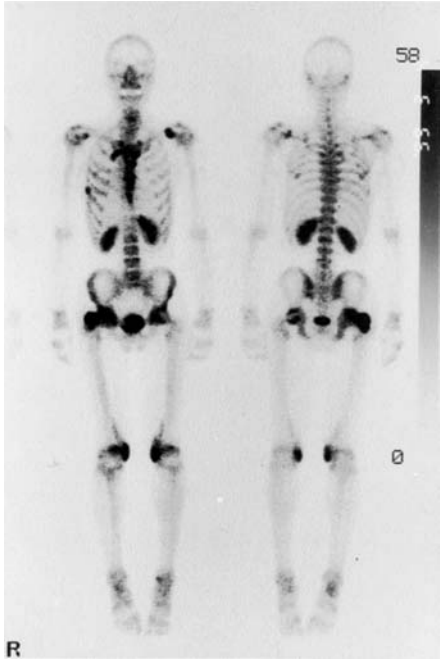

Fig. 2. Bone scintigrpahy, using 99m technetium-labeled methylene diphosphonate, before resection. high incorporation is apparent in the bilateral hip and knee joints, with slightly elevated incorporation in the left shoulder joint

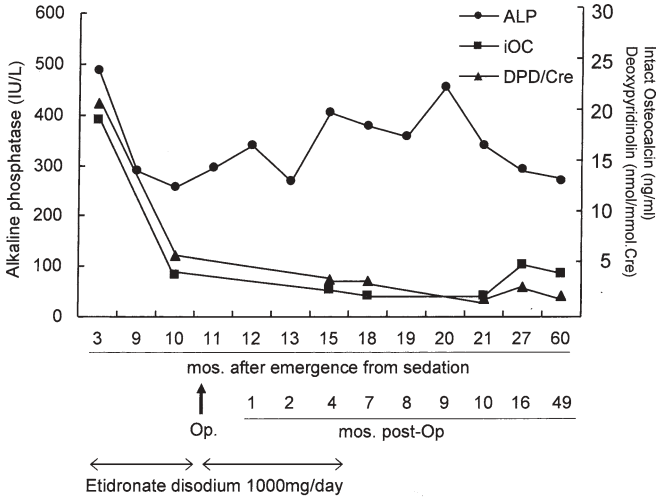

Fig. 3. Time course of biochemical markers of bone metabolism. Alkaline phosphatase (*ALP*) and serum intact osteocalcin (*iOC*) levels decreased to within normal ranges by 10 months after the cessation of long-term sedation. The urinary deoxypyridinoline/creatinine (*DPD/Cre*) level was still slightly higher than the normal range at 10 months. The ALP level increased temporarily at 4–10 months postoperatively (*post-Op*), and had normalized at 18 months postoperatively. Serum iOC and uninary DPD/Cre levels were within normal ranges throughout the follow-up period, *mos.*, months

radiography or computed tomography. Serum levels of ALP and iOC were normalized (serum ALP, 258 IU/l; serum iOC, 4.1 ng/ml) by 10 months after the cessation of long-term sedation. However, urinary DPD/Cre remained slightly above the normal range (6.1 nmol/mmol Cre) at this time. These data, showing no progression of HO and decreased levels of bone metabolic markers, implied the maturation of HO.

Areas of HO were thus resected at 11 months after the end of long-term sedation. Intraoperative macroscopic findings showed that areas of HO were located in the joint capsule and extracapsular muscle, and collateral ligaments were easily separated from the HO. Partial resection of the HO was performed until suitable ROM was achieved. This resulted in amelioration of the limited joint motion, in which ROM was changed from 115° to 0° of flexion in the left knee and from 110° to 0° of flexion in the right knee. Histological examination showed that most areas of resected HO were lamellar bone, with woven bone revealed in a few areas (Fig. 4a, b). No cartilage was present in the resected bone tissue.

Postoperative administration of disodium etidronate and indomethacin, and ROM exercises were employed from postoperative day 1 until 6 months after surgery. Postoperatively, the patient was able to stand unaided and he regained good ambulatory ability without any operative intervention at the hip joints. In view of the high risk of surgery-associated hemorrhage (due to warfarin sodium administration after the patient's aortic valve replacement) and the risk of development of thrombus if administration of warfarin sodium was suspended, resection of HO of the hip joints was not undertaken. The patient resumed office work 6 months after the knee operation. As of 4 years and

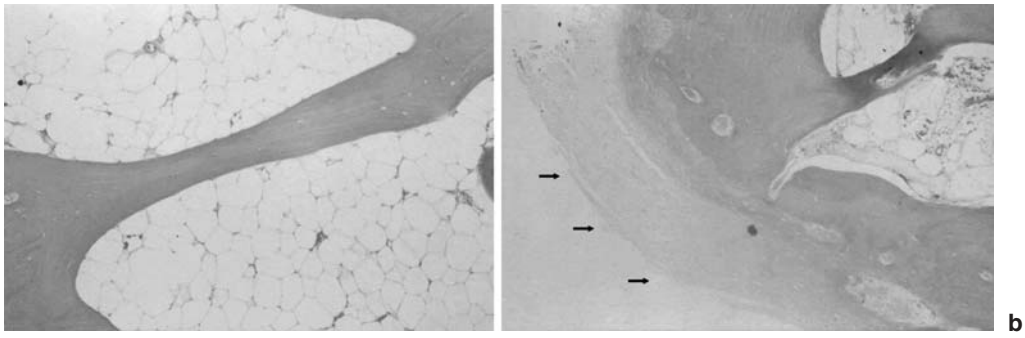

Fig. 4. Histological findings. Most areas of resected HO were lamellar bone (**a**), with woven bone in a few areas *Arrows* show woven bone area. (**b**) (hematoxylin and eosin, ×100 **a** and **b**)

6 months postoperatively, good ROM of the knee joints was maintained, with 110° to –5° of flexion in the left knee and 95° to –5° of flexion in the right knee. No recurrence of HO was detected in knee joints on radiography at 4.5 years postoperatively (Fig. 1d, e). ROM in the hip joints improved slightly without surgery, possibly due to increased daily motion of the hip joints. No progression of HO has been detected in hip joints on radiography. Serum ALP levels increased temporarily at 4–10 months postoperatively, and had normalized by 18 months postoperatively. Conversely, serum iOC and urinary DPD/Cre levels were within normal ranges throughout the follow-up period (Fig. 3).

Discussion

The etiology of HO formation is primarily categorized as neurogenic or traumatic. Neurogenic HO is commonly seen subsequent to traumatic brain or spinal-cord injuries, while traumatic HO typically occurs due to injury, burns, or hip-joint surgery [1–4,6]. Because the excision of immature HO is associated with high morbidity, due to recurrence and bleeding, allowing for maturation of the area of HO is important. Although the maturity of the HO was determined in the current patient by the lack of growth and marginal sharpening of HO on serial radiography, and by decreased uptake on serial bone scans, exact assessment may be difficult. The recommended interval after onset to allow for suitable maturation is 6 months for neurogenic HO and 12–18 months for traumatic HO [6,7]. In contrast, suitable periods for the maturation of HO in patients who have had long-term sedation with artificial ventilation remain unclear. However, two possible pathogenic processes seem to have been involved in our patient. One possible etiology is that sedation induced a pathogenic condition resembling neurogenic HO. The other is that long-term ventilation may cause changes in local tissue PO2 and pH, which could subsequently result in HO formation [8,9].

Mysiw et al. [10] showed that serum osteocalcin level was not a valuable adjunct in confirming a diagnosis of neurogenic HO after severe traumatic brain injury. However, some differences exist between the items assessed in our study and theirs. We assessed serum iOC, whereas Mysiw et al. [10] used serum osteocalcin. Serum iOC is more specific for bone formation than serum osteocalcin, as serum osteocalcin comprises accumulated heterogeneous fragments possibly produced as a result of catabolic breakdown in bones [11,12]. Another difference lies in items evaluated. The report by Mysiw et al. [10] was an observational study examining the utility of OC for diagnosis, while our longitudinal data show changes useful for assessing the maturation of HO. The increased bone metabolic activity induced by fracture healing has already been described [13–15]. Akesson et al. [16] showed that increases in osteocalcin level were more pronounced than increases in serum ALP after fracture. Ohishi et al. [17] showed that the bone resorption marker, urinary DPD/Cre, increased more promptly than osteocalcin level after fracture. We therefore considered that iOC (which is more specific than osteocalcin) and urinary DPD/Cre might be useful as markers of HO maturation, although no previous reports have described the use of urinary DPD/Cre and iOC levels during HO after long-term sedation.

In the current patient, a 179% increase in serum iOC and a 292% increase in urinary DPD/Cre above upper normal limits were found at the initial measurement, 3 months after the cessation of sedation. A similar but less pronounced increase in serum ALP was evident, at 62%. This increase in bone metabolic markers may have resulted from both the compulsory bed rest during long-term sedation, and the HO formation. Kim et al. [18] reported that DPD/Cre increased significantly and that osteocalcin tended to decrease during bed rest. Conversely, Wilkinson et al. [19] demonstrated that patients with HO displayed significant elevations in osteocalcin, but not in DPD/Cre. These findings suggest that increases in iOC may reflect increased bone formation activity in HO, while increases in DPD/Cre reflect high bone turnover due to bed rest. After the administration of disodium etidronate, the bone metabolic markers gradually settled. This decrease in bone metabolic markers may have been the result of several mechanisms, including the natural course of HO maturation and changes accompanying increased physical activity after the cessation of sedation. Disodium etidronate has been widely used in patients with HO to prevent the progression and recurrence of HO [20]. In animal studies and experimental models of HO, disodium etidronate has been demonstrated to reduce bone formation [21,22]. The decrease in bone metabolic

markers may, thus, have been accelerated by disodium etidronate.

We decided to perform surgical resection of the HOs at 11 months after the cessation of the long-term sedation, as the patient's serum ALP, serum iOC, and urinary DPD/Cre levels had decreased to around normal ranges, and the progression of HO on imaging had stopped at 10 months after this cessation. Histopathological examination of HO specimens identified lamellar bone with no cartilage. No recurrence of HO has been found over the past 4 years, and the postoperative improvements in ROM and the normalized serum iOC levels have been maintained.

In the current patient, determination of serum iOC, along with serum ALP, serial radiography, and serial bone scintigraphy, facilitated the preoperative monitoring of HO maturation and the postoperative monitoring of remission. To the best of our knowledge, this report is the first to show the utility of serum iOC in assessing heterotopic bone maturation.

There are few reports of HO caused by inhibition of the central nervous system, without injuries or lesions, in ventilated patients receiving long-term sedation, while the functional immobility caused by joint contracture is well known. The use of sedation has been increasing in intensive care units with recent improvements in advanced clinical care in various fields. Clinical care physicians should be aware of this potential complication, as HO may lead to limited ROM in patients undergoing artificial ventilation for long-term sedation.

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