Case Report

New bone-like tissue formation in calcific tendinopathy: A case report

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A B S T R A C T

Currently, the pathogenesis of nontraumatic heterotopic ossification (HO), e.g., bone-like tissue in calcific tendinopathy remains unclear. Here, we report a 75-year-old, right-handed Japanese woman who had been on hemodialysis for 3 years and was admitted to our hospital to evaluate pain and swelling of the right forearm. She worked as a cook, and her main job over the 3 most recent years had been the frequent and continuous shredding of cabbage. A radiograph showed the highly radiopaque material on the dorsal aspect of the right wrist and in the right shoulder. The biopsy of this radiopaque material revealed HO with marrow, as well as calcified material. Histomorphometric analysis of the HO identified a severe type of osteitis fibrosa with a fibrous tissue volume to total volume of 19.8% (>0.5% required for diagnosis) and an osteoid volume to bone volume of 20.0% (>15% required for diagnosis). We found more woven bone-like tissue than lamellar bone-like tissue. However, the intact parathyroid hormone level was 3-times the normal upper limit with 203 pg/mL, but histomorphometric analysis of the right iliac crest revealed normal bone structure. These findings indicate that the frequent and continuous shredding action with the right hand contributed to the nontraumatic HO localized on the dorsal aspect of the right wrist.

1. Introduction

Heterotopic ossification (HO) is a type of osteogenesis and can be defined as the presence of bone-like tissue at a location where it does not normally exist. HO most commonly results from tissue injury, including neurological injury, brain and spinal cord damage, orthopaedic surgery, and burns (Garland, 1991), all of which may lead to an abnormally heightened or prolonged inflammatory response. Recent studies identified cellular and molecular mechanisms that cause the genetic forms of HO (Xu et al., 2018). However, little information is available on the mechanisms that lead to formation of nontraumatic HO, including in calcific tendinopathy. Here, we present the histomorphometric analysis of a case of radiopaque material localized on the dorsal aspect of the right wrist and the right shoulder, and compare the findings with the histomorphometry of an iliac bone biopsy.

2. Case presentation

A 75-year-old, right-handed Japanese woman on hemodialysis was admitted to our hospital to evaluate pain and swelling of the right forearm. The patient began maintenance hemodialysis at the age of 72; however, the primary kidney disease was unknown. At age 74 years, without any trauma or spinal cord injury she developed pain and swelling of the right forearm, which worsened by the month. Six months later, a radiograph and computed tomography showed a well-circumscribed, radiopaque mass on the dorsal aspect of the right wrist.

Abbreviations: ALP, alkaline phosphatase; BAP, bone alkaline phosphatase; BFR/BV, bone formation rate per unit of bone volume; BMPs, bone morphogenetic proteins; BV/TV, trabecular bone volume to total volume; CKD-MBD, chronic kidney disease-mineral and bone disorder; ES/BS, eroded surface to bone surface; Fb.V/TV, fibrous tissue volume to total volume; HO, heterotopic ossification; N.Oc/BS, number of osteoclasts to bone surface; Ob.S/BS, osteoblasts surface to bone surface; O.Th, osteoid thickness; Ov.BV, osteoid volume to bone volume; Ov.TV, osteoid volume to tissue volume; PTH, parathyroid hormone; Tb.Th, trabecular thickness; W.Th, trabecular unit wall thickness.

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and in the right shoulder (Fig. 1A and B). The patient was admitted to our hospital for further examination. She worked as a cook, and her main job over the 3 most recent years had been the frequent and continuous shredding of cabbage at that time. The patient was being prescribed lanthanum carbonate hydrate (1.5 g/d) to treat hyperphosphatemia and cinacalcet hydrochloride (25 mg/d) to treat hyperparathyroidism. However, she was not prescribed a vitamin D3 derivative.

On admission, the patient was 154 cm tall and weighed 43 kg. Blood laboratory levels are shown in Table 1.

Bone scintigraphy with $^{99m}$Tc-labeled methylene diphosphonate showed intense uptake in the affected right wrist, as well as in the right shoulder (Fig. 1C).

A computed tomography detected only a few calcifications of the abdominal aorta.

3. Surgical histology of the highly radiopaque material

A biopsy was taken of the highly radiopaque material around the extensor tendons of the right wrist. Histological examination revealed a mixture of calcified material and cancellous bone-like tissue in the muscle (Fig. 2A). Histomorphometric analysis of the bone-like tissue was performed at the Ito Bone Science Institute (Niigata, Japan) (Table 2).

4. Histomorphometric analysis of the bone-like tissue (HO)

Tetracycline double labeling was performed with 200 mg/day doxycycline (with a schedule of 3 days on, 4 days off, 3 days on, 13 days off). Histomorphometric analysis showed bone-like tissue accompanied by bone marrow tissue and blood vessels but did not confirm the existence of cortical bone. Osteoclasts, seen as large cells with multiple nuclei, were located next to gray calcified material with an irregular structure. Near the osteoclasts, osteoblasts with a single nucleus were seen in a line covering purple-colored osteoid. The osteoid continued on to mineralized mature bone-like tissue (Fig. 2B). This tissue consisted of lamellar bone-like tissue and nonlamellar woven bone-like tissue, whereby the latter was the predominant type (Fig. 2C). The ratio of trabecular bone volume to total bone volume (BV/TV) was higher than the age-matched reference range of iliac crest bone reported by Recker et al. (Recker et al., 1988) (44%; age-matched reference range: 19.6 ±
Bone-like tissue was classified as a severe type of osteitis fibrosa-like lesion because the Fb.V/TV was 19.8% (>0.5% required for diagnosis) and the OV/BV was 20.0% (>15% required for diagnosis) according to Sherrard’s classification of renal osteodystrophy (Sherrard et al., 1993). However, the patient’s intact-PTH was 203 pg/mL. This value was not consistent with hyperparathyroidism because intact-PTH of hyperparathyroidism patients may be more than 2–9 times the upper limit of normal.

5. Histomorphometric analysis of iliac bone

Five months after analyzing the bone-like tissue, we performed a histomorphometric analysis of the iliac bone to evaluate the relation between the HO and systemic skeletal bone. Tetracycline double labeling was performed with 200 mg/day doxycycline (with a schedule of 3

Table 1
Laboratory data.

|                         | First admission | Reference range |
|-------------------------|-----------------|-----------------|
| BAP (µg/L)              | 26.2            | 3.7–20.9        |
| 25O-hydroxyvitamin D (nmol/L) | 16.8            | >20             |
| 1,25-Dihydroxyvitamin D (pg/mL) | 8.2             | 20–60           |
| Osteocalcin (ng/mL)     | 120             | 8.4–33.1        |
| Intact PTH (pg/mL)      | 203             | 15–65           |
| Total protein (g/dL)    | 6.1             | 6.9–8.4         |
| Albumin (g/dL)          | 2.7             | 3.9–5.2         |
| Calcium (mg/dL)         | 8.9             | 8.7–10.1        |
| Phosphate (mg/dL)       | 3.4             | 2.8–4.6         |
| Alkaline phosphatase (U/L) | 415         | 117–350         |
| Immunoglobulin G (mg/dL) | 1245           | 870–1700        |
| Immunoglobulin A (mg/dL) | 182.1         | 110–410         |
| Immunoglobulin M (mg/dL) | 65.3           | 35–220          |
| Hemolytic unit of complement 50% (CH50/mL) | 51 | 30–50 |

Abbreviations: anti-ds DNA antibody, anti-double-stranded DNA antibody; BAP, bone alkaline phosphatase; PTH, parathyroid hormone.
days on, 11 days off, 3 days on, 19 days off), and cancellous bone was assessed by histomorphometry (Table 2). BV/TV, Tb.Th, and trabecular unit wall thickness (W.Th) were within the age-matched reference ranges. The osteoid marker OV/BV was 3.3%, and the Fb.V/TV was 0%. The N.Oc/BS was 0.41 N/mm, and the Ob.S/BS was 11.4%. Double labelling by tetracycline showed a bone formation rate per unit of bone volume (BFR/BV) of 24.1% per year, indicating normal bone turnover. The bone morphometric diagnosis showed normal bone structure (Fig. 2D), with an Fb.V/TV of 0% (<0.5%) and OV/BV of 3.3% (<15%) according to Sherrard’s classification of renal osteodystrophy (Sherrard et al., 1993).

6. Diagnosis

The patient was diagnosed with nontraumatic HO localized to the dorsal aspect of the right wrist. Frequent and continuous shredding of cabbage with the right hand was considered to contribute to the localized formation of new bone-like tissue in this patient because iliac bone biopsy showed normal bone structure.

7. Discussion

HO is divided into hereditary forms—fibrodysplasia ossificans progressiva and progressive osseous heteroplasia—and acquired, nongenetic forms. Acquired nongenetic HO most commonly results from tissue injury, including orthopaedic procedures and local injury (Garland, 1991). Its etiology remains unknown, although reports have become more common of calcific tendinopathy associated with repetitive trauma or movements (Arora and Arora, 2015; Tamam et al., 2011). In addition, the shoulder and hip are the sites most commonly affected by calcific tendinopathy (Sandstrom, 1938). Typically, the acquired nongenetic mineralization is limited to one joint or the area of one joint,
although multiple calcific lesions may occur in various metabolic disorders and systemic diseases (e.g., calcium pyrophosphate dehydrate crystal deposition disease, gout, kidney failure, connective tissue disease, and psoriatic arthritis) (Touraine et al., 2014).

Cofan et al. reported that deposits of calcium in the soft tissues near major joints, such as the hip, shoulder, and elbow joints occur with a prevalence of 0.5 to 3% among dialysis patients (Cofan et al., 1999). Hiramatsu et al. reported a case of the detection of HO in radiopaque masses in the soft tissues around both hips; histological analysis of the HO showed the formation of cancellous bone-like tissue, more of which was woven mineralized bone-like tissue than lamellar bone-like tissue (Hiramatsu et al., 2013). The patient was diagnosed with an osteitis fibrosa-like lesion because the fibrous volume was increased and iliac bone biopsy showed the presence of osteitis fibrosa. The authors concluded that secondary hyperparathyroidism may have contributed to the development and progression of uremic tumoral calcinosis and HO, as well as to osteitis fibrosa of the iliac bone (Hiramatsu et al., 2013).

The patient presented here had calcification lesions and HO in the right wrist and shoulder due to repetitive microtrauma. The histomorphometric analysis of iliac bone revealed normal bone structure according to the classification of Sherrard et al. (Sherrard et al., 1993), and a radiograph detected only a few calcifications of the abdominal aorta. We hypothesize that in this patient the HO was likely caused by a combination of the continuous repetition of the same motion (i.e., shredding) and an underlying systemic illness including abnormalities in mineral metabolism due to CKD.

Currently, a broad spectrum of cell populations has been reported to contribute to HO, whereby mesenchymal cell populations play the most important role (Xu et al., 2018; Kan and Kessler, 2014). However, the basic pathways of bone formation in HO remain unclear.

Calcific tendinopathy, or calcium hydroxyapatite crystal deposition disease (Wainner and Hasz, 1998), refers to the deposition of
Osteogenesis with marrow

The mechanism of the development of heterotopic bone-like lesion arising from the deposition of calcium

Muscle or Tendon

The deposition of calcium

Osteogenesis with marrow

Woven bone + Lamellar bone

Macrophages or Monocyte

Intruction of osteoclast

Osteoid formation

Instruction of the osteoblasts from mesenchymal system cells

Table 2
Histomorphometric analysis of the heterotopic bone-like tissue and right iliac crest bone.

| Parameter                        | Ratio or abbreviation | Unit   | Measured value (bone-like tissue) | Measured value (iliac bone) | Normal range |
|----------------------------------|-----------------------|--------|-----------------------------------|----------------------------|--------------|
| Bone volume                      | BV/TV                 | %      | 44.4                              | 13.8                       | 19.56 ± 5.62 |
| Trabecular thickness             | Tb.Th                 | μm     | 126                               | 101.9                      | 131.3 ± 28.1 |
| Wall thickness                   | W.Th                  | μm     | NM                                | 31.7                       | 28.29 ± 3.74 |
| Osteoid                          | OV/TV                 | %      | 8.88                              | 0.45                       | 0.36 ± 0.31  |
| Osteoid                          | OV/BV                 | %      | 20                                | 2.3                        | 1.2 ± 0.87   |
| Osteoid surface                  | OS/BS                 | %      | 68.1                              | 25.1                       | 14.0 ± 6.64  |
| Osteoid thickness                | O.Th                  | μm     | 18.9                              | 6.84                       | 8.31 ± 1.99  |
| Osteoblast surface               | Ob.a/BS               | %      | 38.7                              | 11.4                       | 3.66 ± 1.69  |
| Resorption                       | ES/BS                 | %      | 31.9                              | 20                         | 0            |
| Osteoclast number                | N.Oc/BS               | N.mm   | 2.8                               | 0.41                       | 0            |
| Osteoclast number                | N.Oc/TV               | N.mm2  | NM                                | 1.1                        | 0            |
| Fibrous volume                   | Fb.V/TV               | %      | 19.8                              | 0                          | 0            |
| Mineralization apposition rate   | MAR                   | μm/day | NM                                | 0.46                       | 0.477 ± 0.078|
| Mineralization lag time          | Mt                    | day    | NM                                | 50                         | 0            |
| Double labeled surface           | dLS/BS                | %      | NM                                | 4.12                       | 0            |
| Single labeled surface           | sLS/BS                | %      | NM                                | 6.24                       | 0            |
| Bone formation rate              | BFR/BS                | mm3/mmol2/year | 0.012 | 0.010 ± 0.008               | 0            |
| Bone formation rate              | BFR/BV                | %/year | NM                                | 24.1                       | 16.2 ± 12.5  |
| Activation frequency             | Ac.f                  | N/year | NM                                | 0.39                       | 0            |

NM, no measurement.

The newly developed bone-like tissue is not a part of the skeletal system and does not have the lamellar bone structure that is formed by load. Therefore, woven bone is predominant (Fig. 3). Continued stimulation through repetitive movements causes the newly developing bone-like tissue to further enlarge via positive bone remodeling mechanisms, so bone formation exceeds bone resorption. Further investigations in larger numbers of patients are required to confirm our hypothesis.

Based on the results of the bone histomorphometric analysis, we recommended that this patient take a break from shredding cabbage, and reduce the excessive load on his right hand. After one year, there was no improvement, but no further deterioration.

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