

Letter to the Editor (Case report)

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Vitamin D-resistant osteomalacia after 10 years of haemodialysis in a patient with rheumatoid arthritis

Rheumatology key message

- Higher disease activity of rheumatoid arthritis in a patient on hemodialysis can contribute to the vitamin D-resistant osteomalacia.

DEAR EDITOR, Higher disease activity of RA in a patient on haemodialysis can contribute to the vitamin D-resistant osteomalacia. Mineral abnormalities related to renal osteodystrophy are common in patients on long-term haemodialysis [1]. The gold standard for diagnosing renal osteodystrophy is bone histomorphometric analysis [2]. Intractable bone lesions in haemodialysis patients are diverse and multifactorial, but detailed evaluation by bone biopsy can help determine the best treatment. Osteomalacia is a common bone disease in haemodialysis patients with vitamin D deficiency [3, 4]; however, few reports have been published on the pathogenesis of vitamin D-resistant osteomalacia in these patients. Here, we describe a case of vitamin D-resistant osteomalacia due to higher disease activity of RA in a patient on haemodialysis.

A 61-year-old Japanese woman who had been on haemodialysis for 10 years was admitted to our hospital for further examination of generalized bone pain. She developed RA at the age of 30 but had no family history of RA. At age 51 years, IgA nephropathy was diagnosed by kidney biopsy and maintenance dialysis was started. Since diagnosis, her RA had been treated only with nonsteroidal anti-inflammatory drugs, but at age 58 years the RA disease activity gradually worsened and the TNF- α inhibitor etanercept was started at a dose of 50 mg weekly. Disease activity did not subsequently decrease, so prednisolone (5 mg/day) was added. Secondary hyperparathyroidism was diagnosed and normalized by treatment with the active vitamin D₃ derivative alfacalcidol (0.5 μ g/day) and cinacalcet hydrochloride (25 mg/day), but the bone pain did not subside. The bone pain suddenly became severe without any precipitating cause (Supplementary Fig. S1, available at *Rheumatology* online), so the patient was admitted to our hospital for further evaluation.

Blood levels of relevant factors were as follows: calcium, 8.5 mg/dl; phosphate, 5.6 mg/dl; alkaline phosphatase, 511 IU/ml (ref, 117 to 350 IU/ml); intact parathyroid hormone, 102 pg/ml (ref, 25 to 117 pg/ml); 1,25-dihydroxy

vitamin D₃, 45.6 pg/ml (ref, 20 to 60 pg/ml); CRP, 2.3 mg/dl (ref, <0.14 mg/dl); rheumatoid factor, 2 IU/ml (ref, <10 IU/ml); and anti-cyclic citrullinated peptide antibody, 72 U/ml (ref, <4.5 U/ml). The Disease Activity Score with CRP was 4.5. Bone scintigraphy with ^{99m}Tc-labelled methylene diphosphonate showed intense uptake in multiple regions; these findings are characteristic of systemic bone disease including osteomalacia (Supplementary Fig. S2, available at *Rheumatology* online).

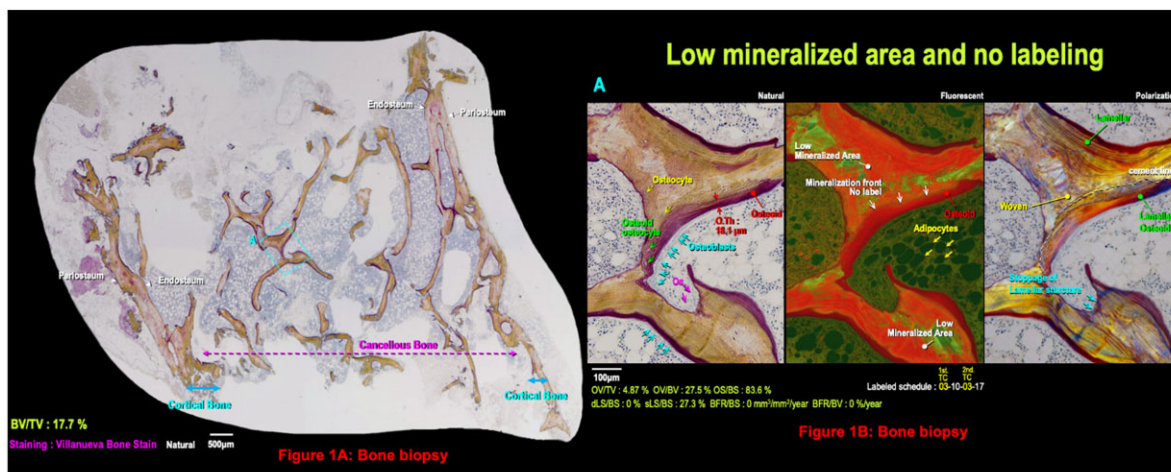
Histomorphometric analysis of the right iliac bone was performed at the Ito Bone Science Institute (Niigata, Japan) according to the previously described method [3, 4]. Tetracycline double labelling was performed with 200 mg/day doxycycline (with a schedule of 3 days on, 10 days off, 3 days on, 17 days off). In cancellous bone (Supplementary Fig. S3, available at *Rheumatology* online), all osteoid markers were higher than the age-matched reference range described by Recker *et al.* [5]. No binding of tetracycline was detected after double labelling (Fig. 1A and B). Osteomalacia was diagnosed according to Sherrard's classification of renal osteodystrophy [6] because the fibrous tissue volume to total volume ratio was 0.03% (<0.5% required for diagnosis) and the osteoid volume to total bone volume of mineralized and unmineralized bone ratio was 27.5% (>15% required for diagnosis).

Because the patient's serum 1,25(OH)₂ D₃ level was maintained within the reference range by administration of an active vitamin D₃ derivative, poor control of the RA disease activity was considered to be the most likely cause of the vitamin D-resistant osteomalacia. Therefore, etanercept was discontinued and treatment was started with the anti-IL-6 inhibitor tocilizumab at a dose of 162 mg every other week. The disease activity of RA subsided and was maintained in long-term remission. After 12 months, the severe bone pain subsided and ALP turned gradually to within the reference range. At the time of writing this article, the patient continues to do well (Supplementary Fig. S1, available at *Rheumatology* online).

Osteomalacia is a metabolic bone disease characterized by defective mineralization of the osteoid matrix and accumulation of unmineralized bone. The causes of osteomalacia include abnormal vitamin D metabolism, abnormal mineralization, and hypophosphataemia. In dialysis patients, osteomalacia was reported to occur because of aluminium toxicity and vitamin D deficiency [3, 4]. To our knowledge, only one article has reported on the relationship between RA and osteomalacia, and the authors suggested that poor dietary intake may be a causative factor [7]. This paper was published in the 1980s, and we are not aware of any subsequent reports of osteomalacia in dialysis patients with RA.

In conclusion, we describe a patient with RA on long-term haemodialysis in whom osteomalacia was determined

Fig. 1 Bone biopsy



(A) Low-power field: in cancellous bone, the bone volume, trabecular thickness and trabecular connectivity were within the age-matched reference range. Thinning and porosis of the cortical bone was the main finding, but extension of the bone marrow cavity into the cortical bone was also observed. (B) High-power field of cancellous bone: the figure shows an enlargement of the square area. Natural microscopy: the dark blue colour indicates the osteoid area. The ratio of fibrous tissue volume to total volume was 0.03% (<0.5% required for diagnosis). Fluorescent microscopy: the red color indicates the osteoid area; the orange color, the area with low mineralization; and the yellow-green color, the mineralized area. The ratio of osteoid volume to total bone volume of mineralized and unmineralized bone was 27.5% (>15% required for diagnosis). The result of tetracycline double labeling was negative. Polarization microscopy: the mixture of lamellar bone and woven bone is shown.

as the cause of bone lesions, despite adequate administration of an active vitamin D₃ derivative. The clinical course of this case indicated that the inflammatory factors associated with RA contributed to the vitamin D-resistant osteomalacia because, after treatment with a TNF- α to an IL-6 inhibitor, the bone pain and ALP levels improved and RA disease activity subsided.

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Data availability statement

All data generated or analysed during this study are included in this published article.

Supplementary data

Supplementary data are available at *Rheumatology* online .

Masaki Hatano^{1,*}, Izuru Kitajima¹, Masaki Nakamura¹, Kazuya Isawa¹, Tatsuya Suwabe^{2,3}, Junichi Hoshino^{2,3}, Naoki Sawa^{2,3}, Seizo Yamamoto¹ and Yoshifumi Ubara^{2,3,*}

¹Department of Orthopaedic Surgery, ²Department of Nephrology and Rheumatology and ³Okinaka Memorial Institute for Medical Research

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Correspondence to: Masaki Hatano, Department of Orthopaedic Surgery, Toranomon Hospital Kajigaya, 1-3-1, Takatsu, Kawasaki, Kanagawa 212-0015, Japan. E-mail: hm0523jp@yahoo.co.jp

*Masaki Hatano and Yoshifumi Ubara contributed equally to this paper.

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