Case Report

Journal of Bone Biology and Osteoporosis

Bone Histomorphometric Findings in Ankylosing Spondylitis: A Case Report

Kondo N^{1*}, Yamamoto N^{2,3}, Watanabe K¹ and Endo N¹

¹Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan

²Niigata Rehabilitation Hospital, Niigata, Japan

³Niigata Bone Institute, Niigata, Japan

***Correspondence:** Naoki Kondo, Division of Orthopedic Surgery, Department of Regenerative and Transplant Medicine, Niigata University Graduate School of Medical and Dental Sciences, 1-757, Asahimachi-dori, Chuo-Ku, Niigata, 951-8510, Japan, Tel: +81-25-227-2272; Fax: +81-25-227-0782; E-mail: naokikondo1214@gmail.com

Received date: November 12, 2018; Accepted date: December 17, 2018; Published date: December 22, 2018

Abstract

There is minimal information on bone Histomorphometric characteristics in ankylosing spondylitis. We here report a case of a 36-year-old Japanese male that suffered from lumbago and could not gaze in the forward direction. Ultimately, a diagnosis of ankylosing spondylitis was made, and vertebroplasty was performed to correct the third lumbar spine. Histomorphometry of the iliac bone showed reduced bone volume parameters (bone volume, and trabecular thickness and width) than reference values. In addition, bone formation parameters (osteoid thickness and osteoblast surface per bone surface) and bone resorption parameters (eroded surface per bone surface and osteoclast number per bone surface) were also lower than reference values, indicating low bone turnover. By contrast, there was not a clear trend in bone resorption markers: bone-specific alkaline phosphatase (17 U/l) was normal, TRACP-5b (136 mU/dl) was slightly lower, urinary N-terminal telopeptide (45.3 nmol BCE/mmol Cr) was normal, and deoxypyridinoline (9.1 nM/mM Cre) was higher than reference values. However, there was deficiency in 25-hydroxy vitamin D (25-OH-D; 14.4 ng/ml). This case highlights the rare possibility of performing bone histomorphometry, and indicates that a low bone volume and low bone turnover (in both bone formation and resorption) are characteristics of ankylosing spondylitis, although bone formation markers (bone-specific alkaline phosphatase) and bone mineral density are within the normal range. The possibility of a serum 25-OH-D deficient status in ankylosing spondylitis should be further considered.

Keywords: Ankylosing spondylitis, Bone histomorphometry, Iliac bone biopsy, Low bone turnover

Abbreviations: AS: Ankylosing Spondylitis; BMD: Bone Mineral Density; L3: Lumbar 3; CT: Computed Tomography; CRP: C-reactive Protein; Ca: Calcium; iP: inorganic Phosphorus; TRACP-5b: Tartrate-resistant Acid Phosphatase 5b; uNTx: urinary N-terminal Telopeptide; dPD: deoxypyridinoline; 25-OH-D: serum 25-hydroxy-vitamin D; WBC: white blood cell; RBC: Red Blood Cell; ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor; MMP-3: Matrix Metalloproteinase-3; CCP: Cyclic Citrullinated Peptide; BAP: Bone-specific Alkaline Phosphatase; PTH: Parathyroid Hormone; ucOC: undercarboxylated Osteocalcin; NTx: N-terminal Telopeptide; TP: Total Protein; Alb: Albumin; CK: Creatinine Kinase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; ALP: Alkaline Phosphatase; gamma-GTP; BUN: Blood Urea Nitrogen; Cre: Creatinine; UA: Uric Acid; Ca: Calcium; iP: inorganic Phosphorus; BV/TV: Bone Volume; Tb.Th: Trabecular Bone Thickness; W.Th: Trabecular Width; OV/TV: Osteoid Volume per Tissue Volume; OV/BV: Osteoid Volume per Bone Volume; OS/BS: Osteoid Surface per Bone Surface; O.Th:

Osteoid Thickness; Ob.S/BS: Osteoblast Surface per Bone Surface; ES/BS: Eroded Surface per Bone Surface; Oc.N/BS: Osteoclast Number per Bone Surface.

Introduction

Ankylosing spondylitis (AS) is an inflammatory rheumatic disease that mainly affects the axial spine [1]. In general, AS patients tend to show a relatively low bone mineral density (BMD), and osteopenia and osteoporosis are reported to be the main complications, which are associated with a higher disease burden [2-4]. However, there are few reports on bone histomorphometric findings in AS [5,6]. In previous reports for histomorphometric findings of the iliac bone in AS patients, osteoid parameters were lower than the reference values but bone resorption parameters did not demonstrate the clear trend (normal or low) [5,6].

We here present a case of AS that required lumbar 3 (L3) vertebroplasty to correct the patient's inability to gaze in the forward direction. Histomorphometry of the iliac bone was successfully performed during surgery, allowing us to provide a rare report of the bone histomorphometric findings associated with AS.

Case Presentation

A 36-year-old male visited our clinic with a chief complaint of lumbago and inability to gaze in the forward direction. He reported beginning to feel pain in his neck and lumbar area as of 33 years old, which gradually turned to stiffness in his trunk, resulting in limited motion. He was forced to quit his job at 33 years old owing to worsening of his symptoms. X-ray and computed tomography findings of the sacroiliac joint revealed typical bamboo spine and sacroiliac joint arthritis with ankylosis (Figure 1). In addition, his spinal X-ray findings showed syndesmophytes in the cervical and lumbosacral regions (Figure 2). These findings met the modified New York diagnostic criteria (1984) [7], leading to a certain diagnosis of AS.

Laboratory findings showed a high C-reactive protein (CRP) level (1.76 mg/dl) and slightly elevated serum matrix metalloproteinase-3 (87 ng/ml) level (Table 1). Human leukocyte antigen was positive for B27. BMD of his left hip (femoral neck) was 0.940 g/cm² (T-score: 0.6). Rheumatoid factor and anti-cyclic citrullinated peptide antibodies were negative, and serum calcium (Ca) and inorganic phosphorus (iP) were within the normal limits.

Figure 1: Plain X-ray finding and computed tomography (CT) findings of the bilateral sacroiliac joints. (A) Plain X-ray of the antero-posterior view of the lumbosacral region. Bamboo spines are clearly observed. Black triangles show that the bilateral sacroiliac joints are completely ankylosing. (B) CT of the frontal view and (C) axial view of the bilateral sacroiliac joints. Asterisks show the ankylosed sacroiliac joint.

Figure 2: Spinal X-ray findings. (A) Lateral view of the cervical spine. Syndesmophytes are observed in the anterior longitudinal ligament (white arrowheads). (B) Lateral view of the total spine. Syndesmophytes are observed in the anterior longitudinal ligament at the lumbosacral (L1 through sacrum) level. Posterior lordosis is remarkable in the thoracic spine and the lumbar anterior lordosis is decreased.

Table 1: Laboratory findings.

Item	Unit	Present Case	Reference value	Item	Unit	Present Case	Reference value
WBC	/ μ l	7000	3300-8600	TP	g/dl	7.7	6.6-8.1
Neutrophil	%	49.7	41.0-75.0	Alb	g/dl	4.4	4.1-5.1
Lymphocyte	%	39.3	21.0-51.0	CK	U/l	73	59-248
Eosinophil	%	3.6	8.4	AST	U/l	18	13-30
Basophil	%	0.7	1.8	ALT	U/l	23	10.0-42
Monocytes	%	6.7	3.0-8.0	LDH	U/l	158	124-222
RBC	$\times 10^4/\mu$ l	522	435-555	ALP	U/l	336	106-322
Plt	$\times 10^4/\mu$ l	27.7	15.8-34.8	γ -GTP	U/l	40	13-64
CRP	mg/dl	1.76	0.14	BUN	mg/dl	9	8.0-20
ESR	mm/hr	9	2.0-10	Cre	mg/dl	0.7	0.65-1.0
RF	IU/ml	6.6	0.0-15.0	UA	mg/dl	4.2	3.7-7.8
MMP-3	ng/ml	87	36.9-121	Ca	mg/dl	9.5	8.8-10.1
anti-CCP antibody	U/ml	0.6	4.5	iP	mg/dl	3	2.5-4.6
Bone metabolism related markers	Unit	Present Case	Reference value				
BAP	U/l	17	13.0-33.9				
TRACP-5b	mU/dl	136	170-590				
Intact PTH	pg/ml	37	10.0-65				
ucOC	ng.ml	2.85	<4.5				
Urinary NTx	nmol BCE/ mmol Cr	45.3	13.0-66.2				
deoxypyridinoline	nM/mM Cre	9.1	2.1-5.4				
25-OH-D	ng/ml	14.4	30				

WBC: white blood cell; RBC: red blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; MMP-3: matrix metalloproteinase-3; CCP: cyclic citrullinated peptide; TRACP-5b: tartrate-resistant acid phosphatase 5b, BAP: bone-specific alkaline phosphatase; PTH: parathyroid hormone; ucOC: undercarboxylated osteocalcin; NTx: N-terminal telopeptide; 25-OH-D: 25-hydroxy vitamin D; TP: total protein; Alb: albumin; CK: creatinine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; gamma-GTP; BUN: blood urea nitrogen; Cre: creatinine; UA: uric acid; iP: inorganic phosphorus.

The bone metabolism markers intact parathyroid hormone and undercarboxylated osteocalcin were normal, and the bone formation marker bone-specific alkaline phosphatase was also in the normal range. There was no clear trend in bone resorption markers: tartrate-resistant acid phosphatase 5b (TRACP-5b) was slightly lower than the normal range (170-590 mU/dl), and urinary N-terminal telopeptide (uNTx) was within the normal range (13.0-66.2 nmol BCE/mmol Cr), whereas deoxypyridinoline (dPD) was higher than the normal range (2.1-5.4 nM/mM Cre). In addition, serum 25-hydroxy-vitamin D (25-OH-D) was in a deficient state (Table 1).

vertebral body (Figure 3). During surgery, the iliac bone was subjected to Villaneuva bone staining for bone histomorphometric analysis.

The bone mineral density of his left hip (femoral neck) was 0.940 g/cm² (T-score: 0.6).

Bone histomorphometric analysis showed that both bone formation and bone resorption parameters were lower and bone resorption parameters were also lower than those of aged-control reference values, suggesting a low bone turnover rate (Table 2, Figure 4).

Vertebroplasty was performed to correct the L3

The reference values were based on a previous report [8].

Figure 3: L3 corrected wedge osteotomy and spinal instrumentation. (A) Preoperative lateral view of X-ray of the total spinal column. (B) Postoperative lateral view of X-ray of the total spinal column. (C) Postoperative AP-view X-ray of the lumbar spine. (D) Postoperative lateral view X-ray of the lumbar spine. L3 showed a wedge-shaped osteotomy, which was corrected to an extension position and fixed with instrumentation. *In situ* autologous iliac bone graft was also performed.

Figure 4: Non-decalcified Villaneuva bone staining findings of the iliac bone. (A) Cancellous bone tissue (white arrow) between cortices (black arrows) appears loose. (B) Trabecular bones are sparsely detected in the cancellous bone region. (C) Osteoids (black arrows) attached to the trabecular surface are thin. Scale bar: (A) 5 mm, (B) 500µm, and (C) 200µm.

Postoperatively, the patient's lumbar pain improved. However, pain around the cervical region and at the upper thoracic level persisted. After screening, 6 mg/week of methotrexate was administered. However, inflammatory markers were still upregulated (CRP, 3.68 mg/dl and erythrocyte sedimentation rate, 25 mm/h) at 6 months after surgery, suggesting that the inflammation due to AS

remained.

The BMD of the left femoral neck was 0.857 g/cm² (T-score: 0.0) 2 years after surgery, and was 0.900 g/cm² (T-score: 0.3) 5 years after surgery, suggesting that the BMD had been preserved.

The patient was informed that data from the case could be submitted for publication, and he provided consent for the publication.

Table 2: Histomorphometric findings of the iliac bone.

	Parameter	Present Case	Reference Value [31-40 Male]
Bone volume	BV/TV	8.92	24.7
	Tb. Th	81.5	157
	W.Th	26.78	38.7
Osteoid	OV/TV	0.3	
	OV/BV	3.37	5
	OS/BS	27.83	30.2
	O.Th	4.87	11.2
	Ob.S/BS	1.81	6
Bone resorption	ES/BS	1.6	2.8
	Oc.N/BS	0.27	0.6

BV/TV: bone volume; Tb.Th: trabecular bone thickness; W.Th: trabecular width; OV/TV: osteoid volume per tissue volume; OV/BV: osteoid volume per bone volume; OS/BS: osteoid surface per bone surface; O.Th: osteoid thickness; Ob.S/BS: osteoblast surface per bone surface; ES/BS: eroded surface per bone surface; Oc.N/BS: osteoclast number per bone surface.

Discussion and Conclusion

The range of decreased BMD in AS patients has been reported at 19-62% [3]. We here present a very rare report of bone histomorphometry analysis for an AS patient.

In our case, involving a 36 years-old male, the duration of AS was 3 years prior to intervention. His BMD and bone formation markers were normal, whereas bone resorption markers did not show a clear trend because TRACP-5b was lower and others such as uNTx and dPD were not lower than the reference ranges. Kocygit et al. [4] reported that AS patients had significantly lower vitamin D levels compared to those of healthy controls (average 14.58 ng/ml for 68 AS patients vs. 20.20 ng/ml for 34 controls). In line with this finding, and other reports [9-11], the present patient with AS had a low vitamin D level of 14.4 ng/ml.

Bone histomorphometry can provide quantitative assessment of bone remodeling and structure, thereby offering information that is not available from other investigative approaches such as bone densitometry and assessment of biochemical markers of bone turnover. Accordingly, bone histomorphometry enables a more precise characterization of disease states and their response to treatment than can be obtained from qualitative examination of bone histology [12]. However, to our knowledge, there are only two previous reports of bone histomorphometry in AS.

Lee et al. [5] reported iliac bone histomorphometric findings for 10 subjects with AS, revealing a low bone volume and trabecular width in the majority of cases, but did not find an association of bone turnover. Our present findings support this previous study in that the osteoid thickness and osteoblast surface were strongly reduced; suggesting that bone formation was decreased.

Furthermore, Szejnfeld et al. [6] evaluated bone histology and histomorphometric changes for 16 white men with AS (mean age 34 ± 3 years, range 15-55 years), including 14 patients that presented with osteopenia, 10 with mineralization defects, and three with osteomalacia. They also found significantly lower values for trabecular bone mass and trabecular wall thickness than the control values. The bone osteoclast interface and the eroded surface were similar to those obtained from male controls. In addition, the mineral apposition rate and double-labeled osteoid staining intensity were significantly lower than those of the control group. Our case differs from their report [6] in that bone resorption was lower than the reference data, suggesting that bone resorption was inhibited.

However, this study is limited in that we were not able to perform staining to directly evaluate the mineral apposition rate.

This case contributes new data to the very limited information currently available on histomorphometric findings in AS patients. In addition, our data demonstrate a low bone turnover despite a normal hip BMD value in AS. This suggests that early treatment of osteoporosis is essential to prevent fragile fractures such as in the vertebrae, hip, and other sites.

A recent reviews about osteoporosis management in AS discussed the use of bisphosphonates for males and females not planning on future pregnancies as the first-line therapy [13]. In our case, once bone resorption will be

sufficiently upregulated, bisphosphonates will be required to manage osteoporosis.

Declarations

Ethics approval and consent to participate

Informed consent was provided by the patient.

Consent for publication

The patient was informed that data from the case could be submitted for publication, and he provided consent for the publication.

Availability of data and material

All data generated in this work are available from the corresponding author upon reasonable request.

Competing interests

The authors have no conflict of interest to declare.

Funding

No funding was received for this work.

Authors' contributions

Data collection and manuscript writing was performed by NK, bone histomorphometric part was performed by NY, spine surgery under informed consent was performed by KW, the administration of drugs was performed by NK, and manuscript review was performed by NE.

Acknowledgements

We acknowledge Editage for English Language editing.

References

1. Dougados M, Baeten D. Spondyloarthritis. *Lancet*. 2011;377(9783):2127-2137. doi: [http://dx.doi.org/10.1016/S0140-6736\(11\)60071-8](http://dx.doi.org/10.1016/S0140-6736(11)60071-8)
2. Klingberg E, Lorentzon M, Mellstrom D, et al. Osteoporosis in ankylosing spondylitis - prevalence, risk factors and methods of assessment. *Arthritis Res Ther*. 2012;14(3):R108. doi: <http://dx.doi.org/10.1186/ar3833>
3. van der Weijden MAC, Claushuis TAM, Nazari T, Lems WF, Dijkmans BAC, van der Horst-Bruinsma IE. High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: a systematic review. *Clin Rheumatol*. 2012;31(11):1529-

1535. doi: <http://dx.doi.org/10.1007/s10067-012-2018-0>

4. Koçyiğit BF, Akyol A. Vitamin D levels in patients with ankylosing spondylitis: Is it related to disease activity? *Pak J Med Sci*. 2018;34(5). doi: <http://dx.doi.org/10.12669/pjms.345.15739>
5. Lee YSL, Schlotzhauer T, Ott SM, et al. Skeletal Status of Men with Early and Late Ankylosing Spondylitis *Am J Med*. 1997;103(3):233-241. doi: [http://dx.doi.org/10.1016/S0002-9343\(97\)00143-5](http://dx.doi.org/10.1016/S0002-9343(97)00143-5)
6. Szejnfeld VL, Monier-Faugere MC, Bogнар BJ, Ferraz MB, Malluche HH. Systemic osteopenia and mineralization defect in patients with ankylosing spondylitis. *J Rheumatol*. 1997;24(4):683-688. doi: <http://dx.doi.org/https://www.ncbi.nlm.nih.gov/pubmed/9101502>
7. Linden SVD, Valkenburg HA, Cats A. Evaluation of Diagnostic Criteria for Ankylosing Spondylitis. *Arthritis Rheum*. 1984;27(4):361-368. doi: <http://dx.doi.org/10.1002/art.1780270401>
8. Rehman MT, Hoyland JA, Denton J, Freemont AJ. Age related histomorphometric changes in bone in normal British men and women. *J Clin Pathol*. 1994;47(6):529-534. doi: <http://dx.doi.org/10.1136/jcp.47.6.529>
9. Mermerci Başkan B, Pekin Doğan Y, Sivas F, Bodur H, Özoran K. The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis. *Rheumatol Int*. 2010;30(3):375-381. doi: <http://dx.doi.org/10.1007/s00296-009-0975-7>
10. Erten S, Kucuksahin O, Sahin A, Altunoglu A, Akyol M, Koca C. Decreased Plasma Vitamin D Levels in Patients with Undifferentiated Spondyloarthritis and Ankylosing Spondylitis. *Int Med*. 2013;52(3):339-344. doi: <http://dx.doi.org/10.2169/internalmedicine.52.9047>
11. Lange U, Teichmann J, Strunk J, Müller-Ladner U, Schmidt KL. Association of 1.25 vitamin D3 deficiency, disease activity and low bone mass in ankylosing spondylitis. *Osteoporos Int*. 2005;16(12):1999-2004. doi: <http://dx.doi.org/10.1007/s00198-005-1990-5>
12. Skingle L, Compston J. Chapter 48. Bone Histomorphometry. In: Vitamin D (Third Edition). Cambridge, Massachusetts, Academic Press. 2011:845-859.
13. Hinze AM, Louie GH. Osteoporosis Management in Ankylosing Spondylitis. *Curr Treatm Opt Rheumatol*. 2016;2(4):271-282. doi: <http://dx.doi.org/10.1007/s40674-016-0055-6>

Copyright: © **Kondo et al.** This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.