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Histochemical observation of bony reversal lines in bisphosphonate-related osteonecrosis of the jaw

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Objective. To contrast the pattern of bony reversal linesin bisphosphonate osteonecrosis of the jaw with infected osteomyelitis derived acute osteonecrosis of the jaw.

Study Design. This study investigated the histochemical characteristics of reversal lines in 50 cases of BP-related osteonecrosis of the jaw (BRONJ) compared with non−BP-involved bones in 20 cases of chronic osteomyelitis of the jaws. Necrotic bones were stained by using the toluidine blue, Safranin O, Giemsa, van Gieson, and Masson's trichrome staining methods.

Results. All BP-involved bones in BRONJ were distinguishable from non−BP-involved bones in chronic osteomyelitis of the jaws by multiple thick, irregular, reversal lines, which were strongly stained with toluidine blue, Safranin O, and Giemsa solution. The reversal lines of BP-involved bones (average 31.2 ± 10.85 μm) were thicker than those of osteomyelitic bones (average 11.1 ± 3.76 μm), and they were closely associated with immature bony matrices containing collagenous materials positive for van Gieson and Masson's trichrome staining with statistical significance ($P = .0212$ in t test statistics). The immature reversal lines of BP-involved bones continuously appeared as thick non-birefringence lines between lamellate structures as observed under a polarizing microscope, whereas the reversal lines of non−BP-involved bones were gradually thinned as their mineralization advanced.

Conclusions. BP-involved bones had immature bony matrices outlined by thick reversal lines, which might be crucial to rapid osteonecrosis of BRONJ and also could be hallmarks for the differential diagnosis of BRONJ from chronic osteomyelitis of the jaws. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;■:1-9)

Bisphosphonates (BPs) are chemically stable analogues of pyrophosphate that bind strongly to the bone mineral hydroxyapatite. They have been widely used to treat diseases caused by excessive bone resorption.[1-3] Clinically available BPs can be divided into two subclasses on the basis of their structure and molecular mechanism of action. The simple, non−nitrogen-containing derivatives can be incorporated into nonhydrolyzable cytotoxic adenosine triphosphate analogues. The more potent nitrogen-containing BPs inhibit farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway.[4]

The main pharmacologic effect of BPs is the inhibition of bone resorption caused by decreased function of osteoclasts. Effects such as antiangiogenic properties,[5] inhibition of calcification in the treatment of malignant hypercalcemia and reduction in the joint inflammatory reaction in the treatment of arthritis, are secondary. Accordingly, BPs are used commonly for a variety of medical purposes, including prevention and treatment of osteoporosis,[6] prevention of bone metastases,[7] treatment of increased blood calcium levels associated with malignant disease, treatment of symptomatic Paget disease,[8,9] Gorham-Stout syndrome,[10,11] giant cell tumor of bone,[12] and treatment of avascular necrosis of the bone.[13]

Since the initial reported cases of BP-related osteonecrosis of the jaw (BRONJ),[14,15] numerous studies have tried to explain the pathogenic mechanism by which this atypical osteonecrosis develops.[16-19] The role of various factors, such as trauma induced by dental extractions or operations, damage to the peripheral vascular system, metabolism of BPs within the jaws, and infections by microbial pathogens is still poorly understood.[20]

The leading hypothesis for the pathogenesis of BRONJ suggests that BRONJ results from cessation of bone remodeling and turnover.

BPs are stable analogues of pyrophosphate characterized by a P-C-P structure and two side chains attached to

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Statement of Clinical Relevance

Bisphosphonates-involved bones had immature bony matrices outlined by thick reversal lines. These histologic findings could be hallmarks for the differential diagnosis of BRONJ from chronic osteomyelitis of the jaws.

Table I. Clinical data of 50 patients with BRONJ

No	*Gender*	*Age*	*Site*	*Stage*[*]	*Bisphosphonate*	*Routes/regimens*	*Duration*	*Surgical Intervention*	*Intervention*
1	F	78	Rt. Mx. Posterior	3	Alendronate	Oral, 70 mg weekly	More than 3 years	Saucerization	
2	F	67	Rt. Mn. Posterior	3	Alendronate	Oral, 10 mg daily	3 years	Saucerization	
3	F	76	Lt. Mx. Anterior/Rt. Mn. Posterior	3	Risedronate	Oral, 35 mg weekly	5 years	Resection	Both jaws
4	F	71	Lt. Mx. Posterior	2	Alendronate	Oral, 70 mg weekly	More than 3 year	Saucerization	
5	F	74	Rt. Mx. Posterior	3	Alendronate	Oral, 10 mg daily	More than 3 years	Resection	
6	M	66	Lt. Mn. Posterior	3	Alendronate	Oral, 10 mg daily	3 years	Saucerization	
7	F	78	Lt. Mx. Posterior	3	Zoledronate	Intravenous, 4 mg monthly	7 years	Saucerization	
8	F	65	Lt. Mn. Posterior	2	Alendronate	Oral, 10 mg daily	More than 3 years	Saucerization	
9	F	71	Lt. Mx. Posterior	3	Risedronate	Oral, 35 mg weekly	More than 3 years	Saucerization	Edentulous/Palate
10	F	76	Mn. Anterior	2	Alendronate	Oral, 70 mg weekly	More than 3 years	Saucerization	
11	F	81	Rt. Mn. Posterior	2	Risedronate	Oral, 35 mg weekly	More than 3 years	Saucerization	
12	F	76	Rt. Mn. Anterior	1	Risedronate	Oral, 35 mg weekly	More than 3 years	Curettage	
13	F	73	Lt. Mx. Posterior	3	Alendronate	Oral, 70 mg weekly	5 years	Decortication	Edentulous region
14	F	83	Lt. Mn. Body	2	Zoledronate	Intravenous, 4 mg monthly	4.5 years	Curettage	
15	F	77	Rt. Mx. Anterior	2	Risedronate	Oral, 35 mg weekly	More than 3 years	Curettage	
16	F	80	Lt. Mx. Posterior	3	Risedronate	Oral, 35 mg weekly	3 years	Curettage	
17	F	76	Rt. Mn. Posterior	3	Zoledronate	Intravenous, 4 mg monthly	More than 3 years	Saucerization	
18	F	72	Mn. Anterior	3	Risedronate	Oral, 5 mg daily	More than 3 years	Resection	
19	F	74	Lt. Mn. Posterior	3	Risedronate	Oral, 150 mg monthly	4 years	Saucerization	
20	F	80	Rt. Mn. Anterior	3	Alendronate	Oral, 70 mg weekly	More than 3 years	Saucerization	
21	F	75	Rt. Mn. Anterior	1	Alendronate	Oral, 10 mg daily	More than 3 years	Saucerization	
22	F	79	Rt. Mn. Posterior	3	Alendronate	Oral, 10 mg daily	7 years	Saucerization	
23	F	62	Rt. Mx. Sinus	2	Zoledronate	Intravenous, 4 mg monthly	More than 3 years	Decortication	
24	F	61	Mx. Sinus	3	Risedronate	Oral, 5 mg daily	More than 3 years	Decortication	
25	F	86	Rt. Mn. Posterior	3	Zoledronate	Intravenous, 4 mg monthly	7 years	Saucerization	
26	F	75	Rt. Mx. Anterior	2	Alendronate	Oral, 10 mg daily	5 years	Decortication	
27	F	83	Lt. Mn. Anterior	2	Alendronate	Oral, 70 mg weekly	More than 3 years	Saucerization	
28	F	69	Mx. Anterior	1	Alendronate	Oral, 70 mg weekly	More than 3 years	Saucerization	
29	F	53	Lt. Mn. Posterior	3	Pamidronate	Intravenous, 30 mg 3 months	3 years 9 months	Saucerization	
30	F	73	Rt. Mn. Anterior	3	Alendronate	Oral, 10 mg daily	More than 3 years	Saucerization	
31	M	60	Rt. Mn. Posterior	3	Alendronate	Oral, 10 mg daily	More than 3 years	Curettage	
32	F	68	Lt. Mn. Posterior	3	Alendronate	Oral, 10 mg daily	More than 3 years	Resection	
33	F	69	Mx. Anterior	2	Alendronate	Oral, 10 mg daily	More than 3 years	Curettage	
34	M	68	Lt. Mn. Posterior	2	Zoledronate	Intravenous, 4 mg monthly	More than 3 years	Saucerization	
35	M	41	Rt. Mx. Anterior	3	Pamidronate	Oral, 200 mg daily	3 years	Curettage	
36	F	71	Rt. Mx. Posterior/Lt. Mn. Posterior	3	Alendronate	Oral, 70 mg weekly	More than 3 years	Saucerization	Both jaws
37	F	65	Rt. Mx. Anterior	1	Alendronate	Oral, 70 mg weekly	More than 3 years	Curettage	
38	M	63	Lt. Mn. Posterior	2	Alendronate	Oral, 10 mg daily	4.5 years	Saucerization	
39	F	86	Lt. Mn. Posterior	3	Alendronate	Oral, 10 mg daily	More than 3 years	Saucerization	
40	F	60	Mn. Anterior	2	Alendronate	Oral, 10 mg daily	6 years	Saucerization	
41	F	64	Lt. Mn. Posterior	3	Pamidronate	Intravenous, 30 mg 3 months	More than 3 years	Resection	

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