

Bisphosphonate-related spindle cell carcinoma and osteonecrosis

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Abstract

A 48-year-old female with a complaint of persistent pain referred to the Imam Khomeini (Tehran, Iran) in 2018. Based on the radiographic findings, radiolucent lesion found in the right mandible and she had alendronate administration approximately for 10 years. Since the past 6 months, the lesion detected in the right mandible. According to the computed tomography scan, a large lytic destructive lesion with a soft-tissue component was seen at the right mandibular ramus. Microscopic examinations revealed the proliferation of anaplastic spindle-shaped cells arranged in interlacing bundles and whorled patterns. Nuclear polymorphism, scattered cells with hyperchromatic nuclei and increased mitotic activity were notable. Immunohistochemistry findings for tissue section composed of spindle cell proliferation revealed Ki67 (20% positive in hotspots), scattered positive right side incisional biopsy was done. The observation revealed hyperplastic and disorganized squamous epithelial lesion, suggestive of spindle squamous cell carcinoma and osteonecrosis in this patient.

Keywords: Bisphosphonate, osteonecrosis, spindle cell carcinoma, women

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INTRODUCTION

Osteoporosis is a metabolic bone disorder known as low bone mass and microarchitectural deterioration of bone tissue.^[1] Postmenopausal osteoporosis happens in case of the estrogen deficiency and increase bone turnover.^[1] Bisphosphonates are antiresorptive drugs prescribe for bone mineral density, and strength in patients suffering Paget's disease, bone metastases of multiple myeloma, and osteoporosis. Bisphosphonates are osteoclastic resorption inhibitors which widely used for the treatment of the bone-remodeling disturbances.^[2] Alendronate,

risedronate, pamidronate and ibandronate are potent nitrogen-containing bisphosphonates, which are the most common therapy in the management of the patients with osteoporosis.^[3] However, adverse effects such as esophageal ulcer, atypical femoral fracture, atrial fibrillation and bisphosphonate-related osteonecrosis of the jaw (BRONJ) were reported by bisphosphonate therapy.^[2] The BRONJ sometimes happens following dental extractions or oral bone surgery in patients taking bisphosphonate drugs.^[4] The etiology of the BRONJ is the subject of numerous scientific discussions for oral and maxillofacial surgeons.^[5]

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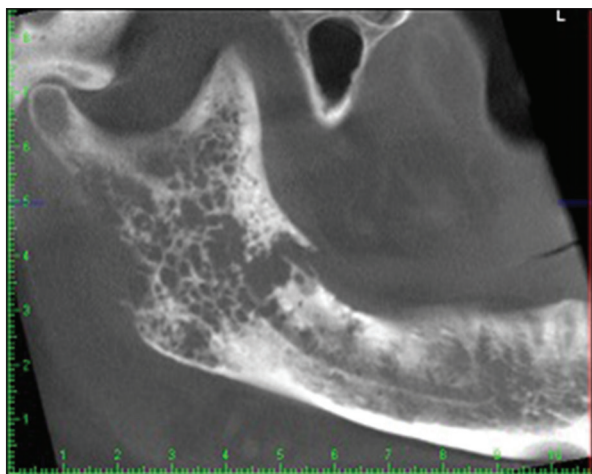


Figure 1: Spindle cell carcinoma involving the right mandibular ramus has destroyed the posterior border of the ramus, retromolar area and ramus

BRONJ is characteristic with high number of osteoclasts with active re-absorbed bone and obliteration of blood vessels.^[6] Dentoalveolar trauma was the predominant risk factor of the BRONJ.^[7] BRONJ incidence is much higher in female, especially postmenopausal osteoporosis exposed to bisphosphonate therapy for a long period (more than 3 years).^[4] Spindle cell carcinoma (SCC) is a rare biphasic head, neck and oral cavity tumor. It is a rare, highly malignant squamous cell carcinoma.^[8] The SCC increase aggressive carcinoma and metastasis incidence.^[8] A correct and timely immunohistochemistry (IHC) test is the key factor for tumor diagnosis.^[8] We present a case of spindle squamous cell carcinoma and osteonecrosis in a 48-year-old Iranian female who had bisphosphonate therapy background.

CASE REPORT

A 48-year-old female with right mandible lesion referred to the Imam Khomeini Hospital (Tehran, Iran) in 2018 with the chief complaint of pain in the right mandibular area for 6 months. Her medical history showed that she had osteoporosis and was taking alendronate approximately for 10 years. According to the computed tomography scan, a large lytic destructive lesion with a soft-tissue component was seen as the right mandibular ramus suggestive of a malignant tumor lesion or metastasis [Figure 1]. A 12 mm × 7 mm lymph node in the IB zone on the right side of the neck was detected. Salivary glands have normal appearance complete opacity of the right sphenoid sinus was noted suggesting of sinusitis. An incisional biopsy was performed under local anesthesia and the microscopic examinations revealed proliferation of anaplastic spindle-shaped cells arranged in interlacing bundles and whorled patterns. Nuclear polymorphism, scattered cells

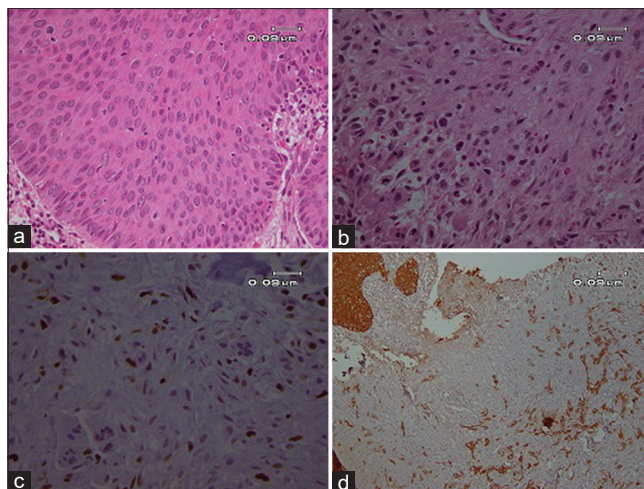


Figure 2: Microscopic features of the lesion, epithelial cells in the overlying oral epithelium show nuclear polymorphism and scattered hyperchromatic nuclei. Significant increased mitotic figures are noticeable (×400). (a) The transition of the epithelial cells to the mesenchymal cells is evident (×400). (b) Immunostaining of ki-67 reveals nuclear staining in more than 20% of the spindle cells (×400). (c) Spindle cells in the stroma show immunoreactivity for pan-cytokeratin. Staining of the overlying oral epithelium serves as internal control for the staining (×40) (d)

with hyperchromatic nuclei and increased mitotic activity were notable. Sections of overlying oral epithelium revealed nuclear polymorphism, hyperchromatic, increased nuclear-cytoplasmic ratio, increased mitotic activity and atypical mitotic figures throughout the entire thickness of the epithelium. A fragment of necrotic bone was seen beneath the oral epithelium. To determine the origin of the spindle cells and their relationship to the overlying oral epithelium with carcinoma *in situ*, IHC studies for pan-cytokeratin and ki-67 was performed. The spindle cells revealed more than 20% nuclear immunoreactivity for ki-67 (that indicates their high proliferative activity) and occasional cytoplasmic reactivity for pan-cytokeratin which shows they are originally epithelial cells. Based on histopathologic features and IHC studies, the diagnosis of spindle squamous cell carcinoma and osteonecrosis was suggested [Figure 2].

DISCUSSION

Osteonecrosis of the jaw is characterized by bone necrosis as a consequence of a wide variety of systemic and local factors that compromise bone blood flow.^[9] The appearance of the BRONJ is similar to osteonecrosis.^[9] The differential diagnosis of BRONJ is critical, and temporomandibular disorders, periodontitis and periapical pathology also contribute to the development of the BRONJ.^[10] Bisphosphonates are widely used for prevention and treatment of bone metastases.^[10] Bisphosphonates are effective in skeletal

disorders, including osteoporosis, Paget's disease, bone metastases and hypercalcemia.^[11] Even though direct mechanism for bone necrosis related to bisphosphonate is not fully elicited, they inhibit osteoclastic activity.^[11] The osteoclast inhibition interrupts bone resorption and weakens bone turnover remodeling and mechanical properties of the skeletal.^[12] Several factors such as periodontal disease, dental extraction, implant placement, oral infection, patient age and so on can increase the adverse effect of the bisphosphonates such as alendronate.^[13] Symptoms such as bone sequestrums, suppuration, mucosa or cutaneous fistula might appear in patients with a long background of the bisphosphonates administration and BRONJ.^[13] The appeared lesions will become a secondary infection or trauma site in soft tissue and bone levels.^[13] Following the infection, pain is also deniable.

SCC is a very rare and high-grade type of the SCC. Involvement is in lungs, kidneys and liver and usually affects people in 70–80 years old. Microscopically, the tumor is composed of two components: proliferative malignant spindle-shaped cells in the deep part and superficial epithelium that demonstrates carcinoma *in situ* or a well-differentiated SCC in the surface. Originally, the spindle cells are believed to be epithelial cells that have gone under the procedure of epithelial-mesenchymal transition. It means that they have lost some of their epithelioid features such as expression of E-cadherin and reveal some mesenchymal features such as cytoplasmic expression of vimentin with spindle-shaped neoplastic proliferation. It accounts for 3% of SCCs.^[8] SCC is a rare tumor in the oral cavity.^[8] The SCC of the oral cavity in a 65-year-old woman was reported by Parikh *et al.*^[14] Despite the direct mechanism for SCC is not fully elicited, but several cell biomarkers such as cadherins and cytokeratins decreases.^[14] The termination of bisphosphonate treatment leads to osteoclasts regeneration, increase bone turnover and biochemical markers of bone turnover. Furthermore, reducing bisphosphonate exposure decrease the incidence of the BRONJ.^[9] Based on the IHC reports, the cytokeratin positivity was significantly higher in SCC which was seen in our case.^[15] In addition, squamous cell areas of SCC had a higher mean positivity for cytokeratin. In addition, keratin expression decreases while vimentin expression increases in the spindle cells of SCC.^[15] Bisphosphonate decrease expression of the receptor activator of nuclear factor-kappa-B (NF- κ B) ligand (RANKL) and RANKL/RANK-mediated NF- κ B activation. NF- κ B has a mediatory role in bone remodeling. However, the direct mechanism is not fully elicited.^[16] This case report is the first report on the

incidence of the BRONJ with spindle squamous cell carcinoma and osteonecrosis in bisphosphonate-treated women. There are two mechanisms for the effect of the bisphosphonate, primary as osteoclastic inhibiting role on the cessation of bone remodeling and bone turnover and secondary bisphosphonate-induce inhibition of neoangiogenesis leads to loss of blood vessels in the jaws and avascular necrosis.^[17] A correlation reported between BRONJ in an osteoporosis patient, who simultaneously revealed an oral squamous cell carcinoma in an 84-year-old Caucasian female.^[18] There is no clear evidence supporting the role of bisphosphonate in the development of oral squamous cell carcinoma, but some cases of oral squamous cell carcinoma in patients taking bisphosphonate are reported in literature. It would be prudent to screen and monitor these patients for all adverse reactions that could interest the oral cavity.^[18] Based on the high rate of the osteoporosis and administration of the alendronate, this observation can be as coincidence, but the tumor observed in the necrosis site indicating for other possible mechanism(s). However, based on the reports, bisphosphonate therapy leads to the pseudoepitheliomatous hyperplasia which might relate to direct and indirect side effects of the bisphosphonate therapy.

CONCLUSION

Findings of the current report revealed the woman had BRONJ and following spindle squamous cell carcinoma and osteonecrosis. Hyperplastic and disorganized squamous epithelial lesion indicates spindle squamous cell carcinoma and osteonecrosis. Based on the high rate of the osteoporosis and administration of the alendronate, this observation can be as coincidence, but the tumor observed in the necrosis site indicating for other possible mechanism(s). However, based on the reports, bisphosphonate therapy leads to the pseudoepitheliomatous hyperplasia which might relate to direct and indirect side effects of the bisphosphonate therapy. It is suggested to minimize bisphosphonate therapy in patients needed the dental treatments have. Oral hygiene and antibiotic treatment should be confirmed on BRONJ patients.^[19] It seems, further researches needed in the prevention, risk reduction and treatment of the BRONJ for dental management option.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will

not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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