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Case Report

A rare complication of prolonged bisphosphonate treatment: The osteonecrosis of jaw in a patient with metastatic prostate cancer

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Abstract. Bisphosphonates are frequently used for the treatment of bone metastases. We described a 71 years old male with the previous diagnosis of bone metastatic prostate cancer and who underwent hormonotherapy combined with zolendronic acid treatment during 7.5 years and presented the complaints of severe jaw pain and inability of chewing. It was determined that the findings of increased PSA with osteonecrotic area on jaw at radiological imaging. He was urgently diagnosed with the diagnosis of osteonecrosis of jaw related to the long-term zolendronic acid treatment. Bisphosphonate treatment was stopped, and he was treated with conservative treatment, and the disorder was improved by this management. This unclear disorder is required more detailed studies on the terms of ethiology, treatment style, follow-up at the treatment period, and management of complications with the aim of applying these agents more safely.

Key words: Prostate cancer, bone metastasis, Bisphosphonate treatment, jaw osteonecrosis

1. Introduction

Bisphosphonates are frequently used for the treatment of bone metastases. The application of intravenous bisphosphonates has been shown to reduce skeletal complications from bone metastases from a variety of solid tumors including prostate cancer (1-3). Although these agents are commonly well tolerated and currently widely used in the setting of hormone-refractory prostate cancer, they rarely induce clinically significant side effects. In addition, recent reports have suggested an increased risk of osteonecrosis of the jaw (ONJ) as a potentially serious complication related to the long-term use of intravenous bisphosphonate treatment (4-6). In this study, we presented a case of ONJ, which occurred as a result of long-term intravenous bisphosphonate treatment in a patient with the diagnosis of bone metastatic prostate cancer.

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2. Case report

In February 2005, a 71 years old man with a PSA value >1000 ng/dL and severe lumbar and hip pain was referred to our out-patient clinic for prostate biopsy. The prostate was bilaterally and diffusely firm on digital rectal examination. The prostate biopsy revealed a histopathological diagnosis of prostate adenocarcinoma with a Gleason score of 4+5= 9/10. The whole body bone scintigraphy showed that there were multiple bone metastases in the vertebrae, especially in lumbar vertebrae and medial sacral region. Subsequent radiological analyses detected no additional distant metastatic findings. As a result of the investigations, the patient was diagnosed with bone metastatic prostate cancer, stage T2cN0M1b, and the combined treatment of hormonatherapy [goserelin acetate (Zoladex® Astra Zeneca LA 10.8mg depot) + bicalutamide (Casodex® Astra Zeneca) 50 mg] and zolendronic acid was initiated. One vial of zoledronic acid (Zometa®, Novartis) that contained 4 mg zoledronic acid was diluted in 100 mL saline and intravenously infused in a duration of 15 minutes. This treatment was administered once every 4 weeks on a regular basis.

At 6th month control of the treatment, it was seen that PSA decreased in the level of 1.48ng/dL (normal, 0-4ng/dL), and an improvement was

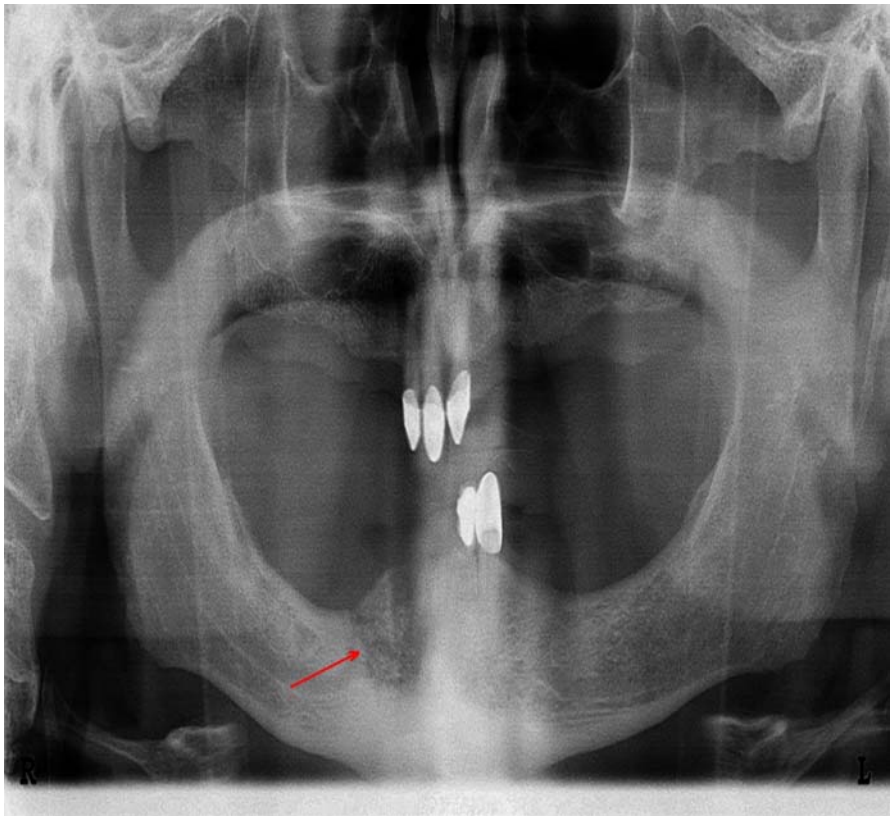

Fig. 1. The demonstration of osteonecrotic area on the jaw that occured as a result of prolonged intravenous bisphosphonate treatment in a patient with the diagnosis of bone metastatic prostate cancer.

observed in the complaints, mainly in lumbo-sacral pain. This combined treatment was contiuned with hormotherapy manipulations during approximately 7.5 years. In this period, the PSA and admission complaints were under control, and the patient could comfortably perform daily activities with this combined treatment.

In October 2012, the patient applied to our clinic with the complaints of severe jaw pain that was resistant to analgesics and inability of chewing. The analyses showed that an increase of PSA to 6.5 ng/dL with no additional metastatic findings on radiological examinations except for jaw radiography. The radiological imaging of jaw demonstrated a necrotic area on mandible that was more radiolucent than the adjacent bone structures (Figure 1). As a result of long-term intravenous bisphosphonate treatment and the admission complaints, the diagnosis of ONJ related to the long-term zolendronic acid treatment was supposed. Thus, zolendronic acid treatment was immediately stopped, and the patient was consulted to the dental surgeon. The dental surgeon applied the conservative treatment (analgesic, anti-inflammatuar, antibiotic) and regularly followed the patient in accordance with us. At subsequent controls, it was seen that the complaints improved and the necrotic area of jaw resolved without the need for an additional, more invasive treatment.

3. Discussion

Bisphosphonates have been widely used in the past few years to prevent complications from skeletal metastases in solid tumors. Although full knowledge of their pharmacokinetics and pharmacodynamics has not been clearly defined yet, it was supposed that these compounds affect the bone metastatic tumors by a group of mechanisms. The direct effects of bisphosphonates on tumor are inhibition of tumor cell adhesion and invasion in bone, exhibition of cytostatic and proapoptotic effects on a variety of human tumor cell lines, anti-angiogenic properties and decreasing circulating levels of vascular endothelial growth factor (7,8). Subsequently, the indirect influences include alteration of the bone microenvironment by binding to exposed bone mineral around resorbing osteoclasts, inhibition of osteoclast function and bone resorption, inducing apoptosis in osteoclasts, inhibition of their genesis, and decreasing recruitment of osteoclastic precursors

to bone. All of these mechanisms influence the bone microenvironment those make it less suitable for tumor proliferation (9,10).

Although these agents are commonly well tolerated, some potential complications including osteonecrosis of the jaw (ONJ) can be occurred. Bisphosphonate-associated osteonecrosis is firstly described as a long-term complication of bisphosphonate treatment with the lesion of necrotic bone in the oral cavity of a patient receiving bisphosphonate treatment and who has not received radiotherapy to the head and neck (11). The disorder is usually painful, but sometimes the process can be asymptomatic. The osteonecrosis can develop spontaneously or after a dental intervention. Our case had the complaints of severe jaw pain that was resistant to analgesics and related inability of chewing with spontaneous development and acute onset without any dental intervention. The etiology of ONJ is still on debate. The disease is supposed to be caused by both local and systemic factors that increase the risk of thromboembolism. The lesions most commonly localized in the mandible. However, the ONJ in patients with cancer may be due to some factors including localization to the jaw, prolonged bisphosphonate therapy, and metastatic disease. Alterations in the bone microenvironment by bisphosphonates may play an important role in the pathogenesis of osteonecrosis. Furthermore, once local ischemia develops, the anti-angiogenic effects of bisphosphonates might block the healing period (12-14). On the other hand, there is no a standard consensus on the optimal duration for intravenous bisphosphonate treatment, the treatment style (continuous or intermittent), and a follow-up protocol to avoid the potential complications. Therefore, it is required prospective and randomized studies on these terms with the aim of applying these agents more safely.

The treatment of ONJ related to bisphosphonates is also still unclear similar to the ethiology. In these cases, conservative treatment, local debridement or surgery can be used as a treatment of choice, but conservative treatment and minor debridement may commonly be insufficient, thus most cases may require a major surgical intervention. However, no definitive standard of care has been set for this disorder, and no definitive consensus guidelines have been provided yet. Additionally, there is no agreement on the surgical or nonsurgical approach to this issue (15). In the present study, the symptoms and lesion on mandible were improved by conservative treatment without any requirement of a surgical intervention. We supposed that the success of conservative treatment might have been due to the early diagnosis and management of this disorder.

The clinicians who applied bisphosphonate treatment especially in metastatic prostate cancer patients must be take care on this potential complication and control the patients regarding the dental complications. Because, early detection and treatment of osteonecrosis is essential. Furthermore, more detailed and comprehensive studies are requried for the incidence, ethiopathogenesis and optimal management of this disorder.

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