CASE REPORT | OLGU SUNUMU

Severe hypocalcemia after oral ibandronate in a patient with metastatic breast cancer: a case report

Metastatik meme kanserli hastada oral ibandronat kullanımına bağlı ciddi hipokalsemi: Bir olgu sunumu

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Bone metastasis is a common finding in patients with metastatic breast cancer. In approximately 25% of breast cancers, bone is commonly the first area of metastasis. Pain, hypercalcemia and bone fractures are the most common complications of bone metastasis. Bisphosphonates effectively reduce and prevent skeletal related complications in breast cancer patients with bone metastases. Although hypocalcemia might occur during bisphosphonate therapy, symptomatic hypocalcemia after oral bisphosphonate therapy is rare and usually occurs several weeks after the initiation of the therapy. In this case report, we present a metastatic breast cancer patient with vitamin D deficiency who developed severe hypocalcemia in the early period following oral ibandronic acid treatment.

Key words: Bone metastasis; breast cancer; hypocalcemia; ibandronate.

Kemik metastazı metastatik meme kanserli hastalarda sık görülen bir bulgudur. Hastaların yaklaşık %25'inde ilk metastaz yeri kemiktir. Ağrı, hiperkalsemi ve kemik kırıkları, kemik metastazının en sık görülen komplikasyonlarıdır. Meme kanserine bağlı kemik metastazında iskelet sistemi ile ilişkili komplikasyonların engellenmesinde bifosfonatlar etkindir. Bifosfanat tedavisinin başlangıcında hipokalsemi görülebilmesine rağmen, oral bifosfanat tedavisinden sonra semptomlu hipokalsemi nadir görülür ve genellikle tedavi başlangıcından haftalar sonra ortaya çıkar. Bu olgu bildirisinde, D vitamini eksikliği olan ve oral ibandronik asit tedavisi ile erken dönemde ciddi hipokalsemi gelişen, metastatik meme kanser tanılı bir hasta sunulmuştur.

Anahtar sözcükler: Kemik metastazı; meme kanseri; hipokalsemi, ibandronat.

Worldwide, breast cancer accounts for 30% of all cancers in women.[1] Approximately 70% of patients with metastatic breast cancer develop bone metastases and approximately ¼ of breast cancers metastasize to bone first.[2-4] In the treatment of breast cancer-associated bone metastasis, bisphosphonates have proven to be effective in preventing skeletal related complications such as pathologic bone fractures and compression of the medulla spinalis. Bisphosphonates reduce bone resorption by binding to hydroxyapatite crystals in bone. It is recommended that bisphosphonate therapy should begin at radiological confirmation of bone metastasis, even if the patient has no symptoms. Bisphosphonates are also commonly used as adjuvant treatment to relieve bone pain in patients with metastatic bone disease.[5] The most important side effects of bisphosphonates include hypocalcemia, elevated levels of parathyroid hormone, skin rashes, irritation of the upper gastrointestinal tract,

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esophageal ulceration, fever, transient leukopenia, acute phase reaction, bone pain, eye inflammation, nephrotic syndrome and osteonecrosis of the jaw. [6] However, oral bisphosphonate-induced hypocalcemia is a very rare condition. In this case report, we present a vitamin D deficient patient diagnosed with metastatic breast cancer that developed severe hypocalcemia in the early period following oral ibandronic acid therapy.

CASE REPORT

Forty-seven-year-old female attended our emergency department with progressive fatigue for 1 month and joint pain spreading to all joints, as well as numbness and tingling around the mouth for the last two days. Her past medical history revealed that she had a left mastectomy for breast carcinoma and received adjuvant chemotherapy in 2005, and she had been on chemotherapy for recurrent metastatic breast cancer since January 2012. She had been taking 50 mg 1x1 oral ibandronic acid for bone metastasis over the last 40 days. In her physical examination, her general state of health was fair; body temperature 36.9 °C; blood pressure 120/80 mmHg; pulse 155/min and respiratory rate 20/min. On neurological examination, patient was conscious, cooperative, well oriented in time, place and person. Her pupillary was isochoric, her direct and indirect light reflexes were positive. Motor examination was normal. Sensory and cerebellar system examination was natural. Test for Chvostek's sign, and Trousseau's sign was positive. The cardiovascular system examination of the patient showed tachycardia. Other system examinations were natural. The patient's blood and biochemical parameters were as follows: hemoglobin 10.3 g/dl; calcium 3.8 mg/dl (corrected calcium level was 4.3 mg/dl); magnesium 1.4 mg/dl; phosphorus 0.7 mg/dl; albumin 3.3 g/dl; parathyroid hormone 290 pg/ml (15-65 pg/ml), and 25 OH VitD3 3 ng/ml. Transaminase, alkaline phosphatase, gamma glutamyl transferase, total bilirubin, BUN (Blood urea nitrogen) and creatinine levels were within normal limits. The electrocardiographic evaluation of patient revealed prolonged QT interval. As the patient had symptoms associated with hypocalcemia, as well as vitamin D deficiency, she

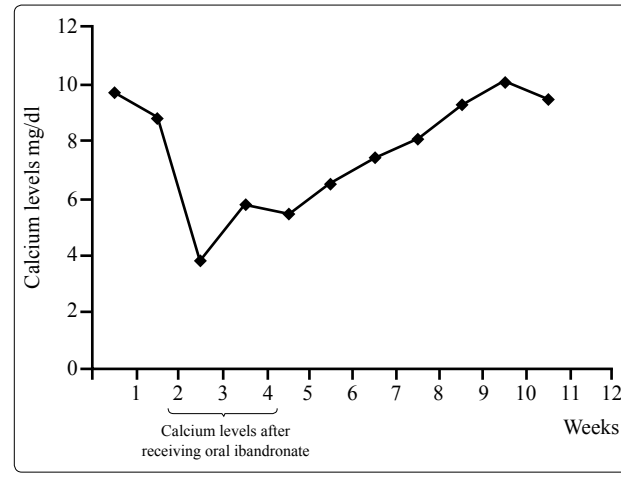

Fig. 1. Changes in the serum calcium levels.

was treated with intravenous calcium replacement, and was started on daily VitD3. In the meantime, oral ibandronic acid therapy was suspended. The follow-up assessments showed that patient's hypocalcemia was corrected and VitD3 levels became normal. Figure 1 shows the changes in the serum calcium levels. As the patient had bone metastasis, zoledronic acid therapy was also included in the regimen. The treatment was continued with VitD3 replacement, calcium, and zoledronic acid therapy. Regular follow-up controls of the patient receiving zoledronic acid therapy for eight months show that her calcium levels remain within the normal range.

DISCUSSION

Approximately 70% of patients with advanced breast cancer experience bone metastases.[2-4] Pain, bone fractures and hypercalcemia are the most frequent complications of bone metastases. Bisphosphonates are effectively used to reduce skeletal complications related to bone metastasis, and to treat malignancy-associated hypercalcemia.[7] They are synthetic analogs of pyrophosphate that inhibit bone resorption binding to hydroxyapatite crystals in the bone matrix. In addition, bisphosphonates reduce the release of bone-derived growth factors such as IL-6, IL-11, TGF -b, IGF-1, PTHrP, VEGF, which helps reduce the frequency and severity of skeletal related complications.

Bisphosphonates are generally well-tolerated drugs. Although hypocalcemia can be seen during

bisphosphonate therapy. Symptomatic hypocalcaemia is uncommon after oral bisphosphonate treatment and usually occurs several weeks after the initiation of the therapy.[8,11]

A phase III randomized, placebo-controlled study showed the efficacy of intravenous ibandronate versus placebo in reducing the incidence of skeletal complications in patients with breast cancer and bone metastases.[9] Our patient diagnosed with breast cancer was started on oral 50 mg 1x1 ibandronic acid treatment due to bone metastasis. Initially the patient was normocalcemic, but the symptoms of hypocalcemia emerged on the day 40 of the oral ibandronic acid therapy. The possible cause of the emergence of hypocalcemia might be ibandronic acid induced PTH inhibiting bone resorption. As ibandronic acid inhibits osteoclastic activity, bone resorption was reduced. Although serum PTH levels were elevated, serum calcium levels remained low. In addition, we thought that accompanying bone changes associated with vitamin D deficiency might be have played a significant role in the incidence of symptomatic hypocalcemia in such a short period of time. The basic mechanism of 1.25-hydroxyvitamin D3 action is to provide the amount of serum calcium and phosphorus levels to maintain bone mineralization. It provides this mechanism through the suppression of PTH. Deficiency in vitamin D3 causes secondary hyperparathyroidism.[10] It was reported in the relevant literature that symptomatic hypocalcaemia and hypomagnesemia occurred in 8% of patients with various malignancies treated with bisphosphonates despite prophylactic administration of vitamin D and calcium supplements.[11] As the patient with metastatic breast cancer was found to be deficient in vitamin D3 and she presented cardiac side effects associated with hypocalcaemia, she was begun on intravenous calcium replacement and vitamin D3 replacement. When finally oral ibandronate therapy was discontinued, the follow-up controls of the patient have showed that her serum calcium and vitamin D3 levels are now maintained within the normal range.

In summary, severe hypocalcemia can be seen in patientswith metastasis during bifosfonate therapy. We think that hypocalcemia can be prevented by closely monitoring the serum calcium and vitamin D3 levels, and starting calcium and 1.25-hydroxyvitamin D3 replacement in case of deficiency in patients taking biphosphonate therapy for metastatic cancer.

REFERENCES

1. Downing A, Prakash K, Gilthorpe MS, Mikeljevic JS, Forman D. Socioeconomic background in relation to stage at diagnosis, treatment and survival in women with breast cancer. Br J Cancer 2007;96(5):836-40. CrossRef
2. Coleman RE, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer 1987;55(1):61-6. CrossRef
3. Perrone MA, Musolino A, Michiara M, Di Blasio B, Bella M, Franciosi V, et al. Early detection of recurrences in the follow-up of primary breast cancer in an asymptomatic or symptomatic phase. Tumori 2004;90(3):276-9.
4. Coleman RE, Seaman JJ. The role of zoledronic acid in cancer: clinical studies in the treatment and prevention of bone metastases. Semin Oncol 2001;28(2 Suppl 6):11-6. CrossRef
5. Aapro M, Abrahamsson PA, Body JJ, Coleman RE, Colomer R, Costa L, et al. Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel. Ann Oncol 2008;19(3):420-32. CrossRef
6. Diel IJ, Bergner R, Grötz KA. Adverse effects of bisphosphonates: current issues. J Support Oncol 2007;5(10):475-82.
7. Dental management of patients receiving oral bisphosphonate therapy. Expert panel recommendations of American Dental Association Council on Scientific Affairs; 2006.
8. Gómez Font R, Martínez García ML, Olmos Martínez JM. Osteochemonecrosis of the jaws due to bisphosphonate treatments. Update. Med Oral Patol Oral Cir Bucal 2008;13(5):E318-24.
9. Body JJ, Diel IJ, Lichinitser MR, Kreuser ED, Dornoff W, Gorbunova VA, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 2003;14(9):1399-405. CrossRef
10. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 2005;294(18):2336-41. CrossRef
11. Reid IR. Emerging issues with bisphosphonates. Rheum Dis Clin North Am 2006;32(4):691-702. CrossRef