CASE REPORT

Hyperphosphatemia in a patient with spinal cord injury who received etidronate for the treatment of heterotopic ossification

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INTRODUCTION: Heterotopic ossification (HO) is defined as ectopic bone formation around peripheral joints and in soft tissues. HO is a common complication of diseases of the central nervous system, such as spinal cord injury (SCI) and traumatic brain injury. HO is seen in up to 50% of patients with SCI and typically occurs in the first 12 weeks after onset of injury. Although no treatment method is proven to be curative, nonsteroidal anti-inflammatory drugs, irradiation of the involved body part and bisphosphonates are commonly used in the management of HO.

CASE PRESENTATION: Here we present a 27-year-old male patient with a T10 ASIA Impairment Scale (AIS) A SCI, who developed hyperphosphatemia as a complication of bisphosphonate therapy initiated for the treatment of HO during the 6th post-operative week. After cessation of etidronate use, phosphate levels gradually returned to normal over 2 weeks.

DISCUSSION: Hyperphosphatemia is a rare complication of etidronate use. It is speculated to result from increased renal tubular phosphate reabsorption and is usually asymptomatic. Although mostly asymptomatic, this complication must be kept in mind while administering etidronate to SCI patients and blood phosphate levels should be monitored in the early weeks of treatment.

Spinal Cord Series and Cases (2017) 3, 17032; doi:10.1038/scsandc.2017.32; published online 8 June 2017

INTRODUCTION

Heterotopic ossification (HO) is a common complication of diseases of the central nervous system, such as spinal cord injury (SCI) and traumatic brain injury.¹ Bisphosphonates are often used in the management of HO. Here we present a subject that developed hyperphosphatemia as a complication of etidronate treatment.

CASE PRESENTATION

A 27-year-old male patient with a history of T8-T12 vertebral fractures and SCI after a motor vehicle collision was transferred to our clinic for inpatient rehabilitation. Subject had T10 ASIA Impairment Scale (AIS) A paraplegia. His initial blood tests showed no abnormality. The patient was started on subcutaneous low-molecular weight heparin treatment as a prophylaxis for deep vein thrombosis. He did not have a history of renal pathology and emptied his bladder using intermittent catheterization. During the 6th post-operative week, the patient developed swelling in his right lower extremity. Passive hip range of motion was normal. A lower extremity venous Doppler ultrasonography, which was ordered to rule out deep vein thrombosis revealed no pathological finding. Cold packs were applied to reduce swelling. Repeat blood biochemistry showed increased levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (ALT: 83 U l⁻¹, ALP: 216 U l⁻¹). X-rays of the thigh were normal. Magnetic resonance imaging of the thigh revealed diffuse soft tissue edema extending from the acetabulum to the anterior region of the thigh and a mass lesion, which was 13 × 6 cm in diameter with indefinite borders in the proximal thigh region (Figure 1). A three-phase bone scintigraphy was ordered. The lesion that was continuous with acetabulum showed increased uptake in all three phases, while the mass lesion showed increased uptake in blood flow and

blood pool phases (Figure 2). These findings were interpreted to be compatible with HO, which had not yet completely matured. Etidronate therapy was initiated, starting with a dose of 20 mg kg⁻¹ per week for 2 weeks, and then planned to continue as 10 mg kg⁻¹ per week for 10 more weeks. Four days after the first dose of etidronate, bloodwork revealed a decrease in ALP levels. Blood phosphate levels, which were normal before the use of etidronate, were found to be increased to 6.2 mg dl⁻¹ (normal value < 4.5 mg dl⁻¹). Dietary phosphate restriction and anti-phosphate medication in addition to daily blood monitoring were ordered, while the patient was monitored for symptoms related to hyperphosphatemia. On the following days, phosphate levels further increased to 7.7 mg dl⁻¹, while parathormone (PTH) and urine calcium (Ca) levels were found to be 5.14 pg ml⁻¹ and 305 mg/24-h, respectively. Blood albumin and Ca levels were within normal limits. Phosphate levels did not respond to these treatment strategies and etidronate therapy was terminated after a consultation with nephrology. Hydration and phosphate binding medication was continued for 2 more weeks. ALP, Ca, P and PTH levels returned to normal limits and the swelling in the right lower extremity disappeared. Symptoms did not reappear during follow-up.

DISCUSSION

HO is defined as ectopic bone formation around peripheral joints and in soft tissues. HO is a common complication of diseases of the central nervous system, such as SCI and traumatic brain injury.¹ It usually involves large joints distal to the neurologic lesion. The hip is reported to be the most commonly involved joint.² Differential diagnosis of HO includes infections, deep vein thrombosis, hematoma and neoplasms.

Figure 1. Magnetic resonance, (a) coronal and (b) transverse plane images show diffuse soft tissue edema extending from the acetabulum to the anterior region of the thigh and also a mass lesion, which was 13×6 cm in diameter with indefinite borders, located in proximal thigh (arrow).

HO is seen in up to 50% of patients with SCI and typically occurs in the first 12 weeks after disease onset.¹ Most cases are asymptomatic while up to 20% are reported to become symptomatic. Most common symptoms are pain, erythema, increased warmth and low-grade fever. In subjects with a complete SCI, pain may be minimal or absent and tissue swelling may be the only symptom. Most common risk factors for the development of HO in patients with spinal cord injuries are male sex, cervical or thoracic injury rather than lumbar injury, pressure sores, pneumoniae, tracheostomy, penetrating trauma to the thorax, severe neurological damage (complete vs incomplete injury), presence of spasticity and smoking.² Microtraumas, hemorrhage and increased tissue pressures were also reported to play a role in HO.³ Frequent subcutaneous injections have also been reported as a risk factor for the development of HO.⁴ Our patient had a complete thoracic SCI, and received multiple soft tissue injections for the prophylaxis of deep vein thrombosis; this may have facilitated the development of lower extremity HO.

HO becomes asymptomatic as the newly formed bone matures but gradual limitation of joint range of motion in these patients threatens rehabilitation goals such as mobilization and performing activities of daily living. Response to surgical treatment is usually temporary and recurrence rates are high, which make diagnosis and early treatment, as well as recognizing and preventing risk factors all the more important.

Although no treatment method is proven to be curative, nonsteroidal anti-inflammatory drugs, irradiation of the involved body part and bisphosphonates are commonly used in the management of HO. Bisphosphonates such as pamidronate are also used to decrease recurrence rates after surgical treatment.¹

Bisphosphonates inhibit osteoclast activity and increase apoptosis, and are used in diseases such as osteoporosis, HO, Paget's disease, reflex sympathetic dystrophy and malignant hypercalcemia in which there is increased bone turnover. They exert their effects by mimicking the pyrophosphate molecule by binding hydroxyapatite.⁵ Etidronate is a simple, nitrogen-containing bisphosphonate. It slows down bone turnover and decreases bone mineralization. This demineralizing effect limits its use in the treatment of osteoporosis but increases its therapeutic efficacy in diseases that cause abnormal bone deposition such as HO. Aminobisphosphonates also exert their effects by down-regulating proinflammatory cytokines and therefore decreasing inflammation.⁶

Hyperphosphatemia is a rare complication of etidronate use. It is speculated to result from increased renal tubular phosphate reabsorption and is usually asymptomatic. Most cases of hyperphosphatemia were reported in patients receiving etidronate for the treatment of Paget's disease.^{7,8} Walton *et al.*⁷ reported on 11 patients with Paget's disease who received 20 mg kg⁻¹ etidronate and whose blood phosphate levels

Figure 2. Three-phase bone scintigraphy. First pass, blood pool and bone phase image showing the lesion in right thigh that was continuous with acetabulum, which showed increased uptake in all three phases.

reached peak values during the second to third weeks of treatment. Subjects' blood phosphate levels returned to normal after the termination of etidronate therapy. Similarly, our patient's phosphate levels returned to pre-treatment normal levels 2 weeks after discontinuation of etidronate treatment. Although most patients with hyperphosphatemia are asymptomatic, hypocalcemic symptoms such as muscle cramps, tetany, perioral numbness and tingling, bone pain, pruritus and rash are occasionally seen. These symptoms are more commonly seen in cases with acute elevations in phosphate levels. Because our patient developed hyperphosphatemia in a short period of time after the administration of etidronate and did not respond to phosphate restriction, we monitored his blood phosphate levels daily until his phosphate levels started to decrease, then checked blood phosphate levels every week until he was discharged from the hospital. In patients with clinical symptoms or with kidney disease, blood phosphate levels may need to be monitored more closely.

CONCLUSION

In our literature search, we could not find any mention of hyperphosphatemia as a complication of etidronate use for the treatment of HO. Although mostly asymptomatic, this complication must be kept in mind while administering etidronate to SCI

patients and blood phosphate levels should be monitored in the early weeks of treatment.

COMPETING INTERESTS

The authors declare no conflict of interest.

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