Novel treatment (new drug/intervention; established drug/procedure in new situation)

Treatment of hypertrophic osteoarthropathy in the case of pulmonary metastasis secondary-to-nasopharyngeal carcinoma with zoledronic acid: an enlightening experience

Nikhil Sonthalia, Kabita Mukherjee, Avishek Saha, Arunansu Talukdar

Department of General Medicine, Medical College and Hospital, Kolkata, West Bengal, India

Correspondence to Dr Arunansu Talukdar, arka_talukdar@yahoo.com

Summary

We describe a case of 23-year-old man, who presented with painful hypertrophic pulmonary osteoarthropathy involving bilateral upper and lower extremities, resulting from intrathoracic metastasis. The patient had a history of undifferentiated nasopharyngeal carcinoma which was treated successfully 2 years ago. The painful osteoarthropathy had made the patient incapacitated. A single dose of 4 mg of intravenous zoledronic acid (ZA) was given which resulted in complete resolution of pain along with reduction of swelling. There was no recurrence on follow-up. Bisphosphonates by their action on bone metabolism might alleviate the symptoms and its use should be encouraged in cancer patients with debilitating arthropathies. This article aims at highlighting the role of bisphosphonates, particularly ZA in managing patients with hypertrophic osteoarthropathy (HOA) and sharing our experience with this drug because of the rarity of the condition and lack of sufficient data in the medical literature.

BACKGROUND

Sometimes palliation is the main stay of treatment for cancer patients and alleviating pain becomes most challenging for the physicians. Hypertrophic osteoarthropathy is such a painful condition occurring mainly in patients of primary lung cancer, paraneoplastic syndromes and rarely in some other conditions like intrathoracic metastasis from extrapulmonary tumours, cystic fibrosis, right-to-left cardiac shunts, liver cirrhosis, etc where treatment options are unrewarding. Pain in this condition is resistant to conventional analgesic medications. In this regard bisphosphonates, particularly zoledronic acid (ZA), have demonstrated their utility in reducing pain, decreasing incidence of pathological fractures, effectively treating hypercalcemia of malignancy and other muscular-skeletal disorders associated with malignancy.¹ Intravenous bisphosphonates enter the bone rapidly and inhibit osteoclastic bone resorption. Compared to its predecessor molecule pamidronate, ZA is 40–850 times more potent in preclinical models of bone resorption.²

Intravenous use of pamidronate has been previously implicated as a modality of treatment for HOA but ZA is very rarely used in this condition because of lack of supporting data and long-term trials.³ ZA was developed on the basis of the hypothesis that a more potent inhibitor of osteoclast-mediated bone resorption would have greater clinical activity.⁴ When compared with pamidronate, it has been shown that ZA provides a higher response rate and longer duration of action.⁵ To our knowledge there are only 12 cases of bisphosphonates being used for treatment in HOA reported in the medical literature with very little document about the effectiveness of ZA as a single agent in this condition despite tumour progression.⁶ Here we report a case of HOA secondary-to-pulmonary metastasis from undifferentiated nasopharyngeal carcinoma (NPC)

treated with a single dose of intravenous ZA resulting in complete resolution of symptoms without recurrence at 2 months of follow-up.

CASE PRESENTATION

A 23-year-old man, non-smoker, presented with the history of fever, multiple joint pains mainly involving the bilateral wrist, ankle, knee and elbow joints, associated with swelling of the involved joints and cough with weight loss for last 6 months. Patient had a significant history of undifferentiated NPC (WHO type 3), with clinical staging of T2BN0M0, which was treated 2 years ago, with chemotherapy and radiotherapy. A response evaluation, 1-year post-treatment, showed no histopathological and radiological evidence of recurrence of NPC. On presentation, the fever was low-grade intermittent associated with productive cough marked by occasional episodes of haemoptysis. Painful extremities had made the patient almost bedridden for last 3 months as he had difficulty in performing activities of daily living. There was no history of Raynauds or any diurnal variation of joint pain. Patient had significant weight loss of over 10% in the last 6 months.

On examination he had mild pallor with grade 4 clubbing as evident by loss of Lovibond's angle and tender swelling of bilateral wrist, ankle and elbow and knee joints (figure 1). On systemic examination there were features of mild left-sided pleural effusion. There was no evidence of any nasopharyngeal mass lesion on ear, nose and tongue evaluation. Other systemic examinations were essentially normal.

INVESTIGATIONS

Routine blood tests revealed haemoglobin 9 g%, total leucocyte count (TLC) 14 200/mm³, erythrocyte sedimentation

Figure 1 Bilateral upper-limb and lower-limb digits of the patient showing clubbing associated with wrist and ankle swelling suggestive of hypertrophic osteoarthropathy. There is grade 4 clubbing clearly visible in the inset.

rate 80 at the end of first hour, C reactive protein 40 mg/dl ($n < 3$ mg/dl). Liver function test showed hypoalbuminaemia (2.6 g/dl), and serum uric acid, calcium, phosphate, sodium and potassium were within normal limits. Mantoux test showed 6 mm of induration and sputum for acid-fast bacilli was negative.

CT imaging and endoscopic examination of nasopharyngeal space were normal. Routine chest radiograph showed emphysematous lung field with an irregular soft tissue opacity at left lower lung field. A contrast-enhanced CT of thorax was done for further evaluation of this mass, which revealed an irregular soft tissue lesion at left lower zone with bilateral pleural effusion and left hilar lymphadenopathy. CT-guided biopsy from the lesion showed features of poorly differentiated carcinoma, compatible with NPC. Radiographs of bilateral wrist and ankle joints were obtained which showed evidences of subperiosteal new bone formation, a feature consistent with HOA (figure 2). A bone scan using technetium Tc

99m polyphosphate was done to corroborate the radiograph findings of extremities which showed features of 'hungry appendicular skeleton' demonstrated by increased cortical uptake in bilateral lower extremities, wrist, forearm and ankle joints and also increased linear cortical activity (figure 3). These features were compatible with hypertrophic osteoarthropathy.

DIFFERENTIAL DIAGNOSIS

- Paraneoplastic syndrome secondary to NPC
- Chronic fibro-caseous tuberculosis
- Pulmonary metastasis from NPC
- Bone metastasis

TREATMENT

The primary NPC was treated with concurrent chemoradiation 2 years ago. At this time, after investigating we planned for chemotherapy for the pulmonary metastasis as advised by the oncology team. But the patient elected no further chemo and/or radiotherapy. The pain was initially being managed with non-steroidal anti-inflammatory drugs, low-dose steroids and tramadol but the results proved to be fruitless. So we decided to give single intravenous infusion of 4 mg of ZA over 15 min.

OUTCOME AND FOLLOW-UP

Patient showed significant relief from pain within 24 h of ZA infusion.

By the end of day 3 there was marked relief from pain and swelling. After 1 week of the treatment, there was complete resolution of joint sign and symptoms. At 1-month follow-up a repeat bone scan showed a resolution of subperiosteal bone formation, which was noticed, on previous scan (figure 4). Patient elected no further chemo and/or radiotherapy and is on symptomatic management there after.

DISCUSSION

Hypertrophic osteoarthropathy may be a primary entity (pachydermoperiostosis) or a secondary condition associated with lung cancer, which accounts for 80% of secondary cases. The incidence of HOA in primary lung cancer

Figure 2 Aggressive-appearing periosteal reaction is seen around distal radius, ulna and around distal tibia, fibula on a skeletal bone survey.

Figure 3 Whole body bone scan done before treatment. It is showing diffuse increased uptake in the bilateral lower extremities, wrist and forearms along with increase linear cortical activity.

ranges from 1% to 10% with pulmonary metastasis being a rare cause for this condition.⁷ HOA is characterised by clubbing of the digits, painful swelling of the distal extremities, increased connective tissue deposition, vascular proliferation and new periosteal bone formation. Joint symptoms range from mild-to-severe arthralgia's that usually involves the metacarpal, wrist, elbow, knee and ankle joints as seen in our case.⁸ Our patient developed HOA following pulmonary

Figure 4 Whole body bone scan 1 month after the administration of zoledronic acid shows resolution of previously increased cortical uptake.

metastasis from NPC. Yacoub *et al* described three cases of HOA resulting from pulmonary metastasis in extrathoracic malignancy. Their review of the literature suggested that metastasis from osteosarcoma accounts for 30% of cases, from fibrosarcoma for 17%, from nasopharyngeal tumours for 19.1%, from uterine tumours for 12.7% and from tumours of other regions for 21.2% of cases.⁹ There was a suggestion made that fibrous tumours and tumours with more fibrous stroma tends to develop HOA more than others as fibrous stroma may be a factor stimulating reflex mechanism for osteoarthropathy.

Bisphosphonates are chemically stable derivative of inorganic pyrophosphate, which have high affinity for bone due to binding of hydroxyapatite crystals and incorporating into sites of active bone remodelling. Since the first reported case of pamidronate being used in HOA in 1997, bisphosphonates have emerged as a new hope in treating malignancy-related skeletal pain.¹⁰ Literature search revealed a total of 12 cases of HOA treated with bisphosphonates being reported including a single case series comprising of three cases. Among the 12 patients, 9 were successfully treated with pamidronate, 2 with ZA and 1 with residronate.^{11–13} ZA is a highly potent nitrogen-containing bisphosphonate and inhibits osteoclast-mediated bone resorption. King *et al* reported a case of HOA-related limb pain that resulted from bronchogenic carcinoma which was completely resolved following a single intravenous infusion of ZA 4 mg over 15 min.¹² Our patient also responded to a single dose of 4 mg intravenous ZA infusion. The pain substantially reduced within 3 days, being completely resolved within 7 days and requiring a minimal dose of non-steroidal anti-inflammatory drugs when needed. In another report Thompson *et al*¹⁴ demonstrated control of HOA-related pain in a metastatic melanoma patient but this was in conjunction with significant tumour response to combination chemotherapy. Our patient's pain responded only to ZA despite the progression of his systemic illness. The pathogenesis of HOA still remains unclear with several mechanisms being proposed. Vascular endothelial growth factor, platelet-derived growth factor, prostaglandin E, other cytokines and platelets may play a role in causing the periostitis and digital changes in HOA. The nitrogen-containing bisphosphonates like ZA promote osteoclast apoptosis by inhibiting the activity of farnesyl pyrophosphate synthase and thus relieves pain in these conditions. They also act by inhibiting osteocyte apoptosis and targeting monocytes. In addition, bisphosphonates may also have antitumour, anti-inflammatory, antiangiogenic effects and reduce vascular endothelial growth factor in patients with metastatic solid tumours.¹⁵

HOA-associated pain can be disabling and disheartening for the patients and their caretakers. Though there have been several case reports favouring the efficacy of bisphosphonates in relieving pain associated with this condition, data from randomised clinical trial are lacking. ZA as a more potent bisphosphonate may provide greater and longer benefit, as was seen in our patient. Multicentric randomised control trails are required to further define the role of ZA in treatment of HOA-associated pain, given the rarity of the disease. Further case reports, in this aspect should be contemplated to provide some insight and encouragement in the pain management in these patients, which is very challenging for the physician.

Learning points

- ▶ Hypertrophic osteoarthropathy is a painful condition of joints and extremities associated mainly with intrathoracic malignancies, paraneoplastic syndromes and rarely in some other conditions like cystic fibrosis, left-to-right shunts and liver cirrhosis, which usually incapacitates the patients.
- ▶ Pulmonary metastasis from extrathoracic primary malignancy, though rare, can also result in hypertrophic pulmonary osteoarthropathy.
- ▶ Pain in this condition is resistant to conventional analgesic medications including non-steroidal anti-inflammatory drugs, tramadol, steroids, etc.
- ▶ Bisphosphonates by their inhibition of osteoclastic bone resorption, antitumour and antiangiogenic effects have been found to be effective in reducing pain and swelling in HOA.
- ▶ A single dose of 4 mg zoledronic acid intravenous infusion acts faster is more effective and provide long-lasting pain relief in hypertrophic osteoarthropathy than pamidronate and should be encouraged to be used in this condition irrespective of the primary disease causing it.

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Competing interests None.

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REFERENCES

1. **Diel IJ**, Solomayer EF, Costa SD, *et al.* Reduction in metastases in breast cancer with adjuvant clodronate treatment. *N Engl J Med* 1998;**339**:357–63.
2. **Rosen LS**, Gordon D, Kaminski M, *et al.* Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double blind, comparative trial. *Cancer J* 2001;**7**:377–87.
3. **Suzuma T**, Sakurai T, Yoshimura G, *et al.* Pamidronate-induced remission of pain associated with hypertrophic pulmonary osteoarthropathy in chemoendocrine therapy-refractory inoperable metastatic breast carcinoma. *Anticancer Drugs* 2001;**12**:731–4.
4. **Product information for Zometa (zoledronic acid) injection**. Novartis Pharmaceuticals Corporations. East Hanover, NJ 07936. August 2004.
5. **Li EC**, Davis LE. Zoledronic acid: a new parenteral bisphosphonate. *Clin Ther* 2003;**25**:2669–708.
6. **Richa D**, Herbert SD. Hypertrophic osteoarthropathy treatment & management. <http://emedicine.medscape.com/article/333735-treatment> (accessed 5 June 2012).
7. **Sampe T**, McCluskie RA. Generalized hypertrophic osteoarthropathy in association with bronchial carcinoma: a review, based on 24 cases. *BMJ* 1955;**1**:754–9.
8. **Silveira LH**, Martinez-Lavin M, Pineda C, *et al.* Vascular endothelial growth factor and hypertrophic osteoarthropathy. *Clin Exp Rheumatol* 2000;**18**:57–62.
9. **Yacoub MH**, Simon G, Ohnsorge J. Hypertrophic pulmonary osteoarthropathy in association with pulmonary metastases from extra thoracic tumors. *Thorax* 1967;**22**:226–31.
10. **Speden D**, Nicklason F, Francis H, *et al.* The use of pamidronate in hypertrophic pulmonary osteoarthropathy (HPOA). *Aust N Z J Med* 1997;**27**:307–10.
11. **Jayakar BA**, Abelson AG, Yao Q. Treatment of hypertrophic osteoarthropathy with zoledronic acid: case report and review of the literature. *Semin Arthritis Rheum* 2011;**41**:291–6.
12. **King MM**, Nelson DA. Hypertrophic osteoarthropathy effectively treated with zoledronic acid. *Clin Lung Cancer* 2008;**9**:179–82.
13. **Amital H**, Applbaum YH, Vasiliev L, *et al.* Hypertrophic pulmonary osteoarthropathy: control of pain and symptoms with pamidronate. *Clin Rheumatol* 2004;**23**:330–2.
14. **Thompson MA**, Warner NB, Hwu WJ. Hypertrophic osteoarthropathy associated with metastatic melanoma. *Melanoma Res* 2005;**15**:559–61.
15. **Wood J**, Borjeon K, Ruetz S, *et al.* Novel antiangiogenic effects of the bisphosphonate compound zoledronic acid. *J Pharmacol Exp Ther* 2002;**302**:1055–61.

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