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Case Report

Refractory hypercalcemia due to hyperparathyroidism in a patient with metastatic parathyroid carcinoma

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ABSTRACT

Hypercalcemia caused by parathyroid carcinoma is an extremely rare malignancy, with resulting higher morbidity and mortality, and remains a difficult challenge for clinicians. We herein have demonstrated the case of a 74-year-old woman with metastatic parathyroid carcinoma, complicated with refractory hypercalcemia both at initial presentation and during disease progression. Initially, her calcium level responded poorly to conventional medical treatments such as hydration, loop diuretics, and bisphosphonates; her hypercalcemia was only resolved after en bloc resection of parathyroid tumor as well as metastasectomy. However, her disease progressed and her hypercalcemia showed only a transient response to cinacalcet in the setting of worsening hyperparathyroidism. Ultimately, the addition of denosumab appeared to provide effective and durable treatment benefits.

1. Introduction

Parathyroid carcinoma is an extremely rare malignancy without any recognized effective therapeutic strategy, and usually is responsible for less than 1% of cases of primary hyperparathyroidism (HPT) in the United States.[1] The majority of parathyroid carcinoma are hormonally functional, and thus most patients have hypercalcemia at presentation with associated symptoms such as bone pain, fracture, and renal impairment. The diagnosis of parathyroid carcinoma is often difficult to make since its clinical features are shared with benign causes of hyperparathyroidism. Imaging modalities such as 99mTc sestamibi scan and neck ultrasound can be used to localize the disease, but are less useful to assess malignant potential. En bloc resection of parathyroid tumor at the time of initial operation has been recommended and offers the best chance of cure. Progressive disease occurs in more than half of the patients with parathyroid carcinoma and surgical resection remains the primary intervention, since there are no other effective systemic therapies that facilitate to stop progression of the disease. However, reoperation rarely brings cure and is almost always followed by relapse. For those patients with advanced and inoperable disease, chemotherapy and external beam radiation treatment might be considered; the 5- and 10-year overall survival rates were 82.3% and 66%, respectively.[2] Herein, we have described a woman with metastatic parathyroid carcinoma, in whom refractory hypercalcemia was managed with novel agents.

2. Case report

2.1. Initial presentation

A 74-year-old Chinese woman was admitted to our hospital due to significant weight loss of 8 kg within a two-week period, accompanied by fatigue, poor appetite, and constipation. She had a medical history of hypertension and type 2 diabetes mellitus under regular follow-up and treatment. The patient reported severe nausea and sensation of heartburn lasting several days, also describing that she had not defecated for more than one week. She had taken probiotics to relieve her gastrointestinal upset.

Upon physical examination, the patient appeared to have general malaise, though her consciousness was clear and alert. Other vital signs were within normal range. Additionally, there were more wrinkles over the lips, her oral mucosa and tongue were dry, no palpable mass was found over the head and neck, breath sounds

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were symmetric and clear, her abdomen was soft and nontender with significantly decreased bowel movement, and the patient's four limbs were freely movable. Overall, the patient was dehydrated and constipated.

Subsequent laboratory studies revealed significant hypercalcemia with serum calcium level of 15.3 mg/dl [reference range: 8.4–10.6 mg/dl]. Furthermore, a markedly increased creatinine level of 3.78 mg/dl [reference range: 0.7–1.2 mg/dl] and a BUN of 81 mg/dl [reference range: 7–20 mg/dl] were also found. Otherwise, there was no apparent albumin/globulin reverse or anemia. Thereafter, a series of further testing was arranged, including tumor survey, because paraneoplastic hypercalcemia could not be ruled out. The patient's serum level of intact parathyroid hormone (iPTH) was found to be significantly elevated, up to 431.3 pg/ml [reference range: 15.0–63.8 pg/ml]. Both the thyroid and adrenal functions were within the reference range. Her tumor markers were checked, resulting in a CEA level of 2.5 ng/ml [reference range: 0.0–5.0 U/ml], CA-125 of 12.6 U/ml [reference range: 0.0–35.0 U/ml], CA15-3 of 35.7 U/ml [reference range: 0.0–32.4 U/ml], and CA-199 of 491.5 U/ml [reference range: 0.0–37.0 U/ml].

Meanwhile, we undertook aggressive hydration with calcium-lowering medications, including bisphosphonates, after making a preliminary diagnosis of hypercalcemia crisis with associated acute kidney injury and lethargy. However, the treatment manifested little or no apparent benefit. Urgent hemodialysis was thus applied to relieve the patient's illness, which was also ineffective when it was noted that her calcium and iPTH levels had increased to 17.4 mg/dl and 1073.7 pg/ml, respectively, even after the above therapies were applied.

Several imaging examinations were undertaken to provide a better overall assessment of the patient's disease. Computed tomography (CT) of the patient's chest showed right hilar lymphadenopathy as noted in Fig. 1. Sonography of the neck revealed a hypoechoic nodule size of 1.6 × 0.95 cm in the right retrothyroid region, compatible with parathyroid adenoma. Also, magnetic resonance imaging of the abdomen was negative for abnormal intra-abdominal lesions. 99mTc sestamibi scan was also performed due to the patient's primary hyperparathyroidism, which disclosed a focal uptake in the right upper thoracic region but was negative for parathyroid adenoma (Fig. 2).

Since the patient was diagnosed with ectopic parathyroid adenoma or carcinoma, surgical intervention was suggested after comprehensive review and thorough discussion in the multidisciplinary conference. The patient then underwent right superior parathyroidectomy, followed by thoracoscopic wedge resection of the right upper lobe of lung and radical mediastinal lymph node dissection several days later. Histopathology confirmed the diagnosis of parathyroid carcinoma with lung and mediastinal lymph node metastasis (Fig. 5). Immunostains showed diffuse positive for chromogranin A and synaptophysin, compatible with the presence of a neuroendocrine tumor. Postoperatively, the patient's PTH level decreased from 1160 to 237 pg/ml, and thereby her hypercalcemia had resolved.

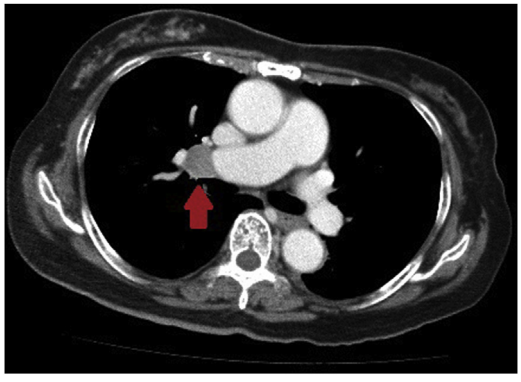

Fig. 1. CT images of chest at initial diagnosis.

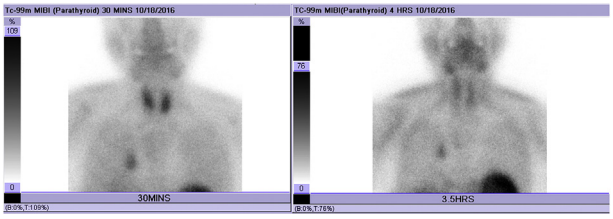

Fig. 2. 99mTc sestamibi scan: Negative for parathyroid adenoma but a focal uptake in the right upper thoracic region is noted.

However, disease progression with multiple lung metastasis developed two months later (Fig. 3a, b and c), accompanied by recurrence of hyperparathyroidism. Afterward, her hypercalcemia recurred on several occasions with only a limited and transient response to IV hydration, IV bisphosphonates (zoledronic acid 4 mg), and IV calcitonin. She was treated with chemotherapy, darcabazine 200 mg/m^2 and 5-Fluorouracil 1000 mg/m^2, every two weeks for three cycles, then shifted to etoposide 240 mg/m^2 and cisplatin 75 mg/m^2. After the patient responded poorly to chemotherapy, the patient received palliative radiotherapy to the lung and mediastinal metastases. With regard to the previous ineffective therapy for her hypercalcemia, a calcimimetic, cinacalcet (25 mg BID), had been used, which temporarily halted the upward trend of calcium level and thereafter stabilized her clinical condition. Denosumab 60 mg also seemed to play a role after her hypercalcemia became refractory to cinacalcet. Since then, the patient had a normal calcium level for several months until we reported her case here (Fig. 4).

3. Discussion

In this case, we comprehensively reviewed the clinical course and management of parathyroid carcinoma with associated hyperparathyroidism. Parathyroid carcinoma is a rare disease which currently lacks effective systemic therapy. En bloc surgical resection of the tumor and the ipsilateral thyroid lobe remains the only curative modality,[3,4] and both chemotherapy and radiotherapy rarely provide an encouraging response. Additionally, patients with parathyroid carcinoma usually struggle with and are frustrated by repeated recurrences. Nevertheless, parathyroid carcinoma itself is seldom the cause of mortality. Death is often due to intractable hypercalcemia, which causes severe complications such as cardiac arrhythmia, renal failure, and fracture. Therefore, resolving hypercalcemia is the urgent need for patients. In this case, we had tried virtually every kind of method typically employed to deal with refractory hypercalcemia, including aggressive hydration concurrent with loop diuretics, hemodialysis, and calcium-lowering agents such as bisphosphonate, calcitonin, cinacalcet and denosumab. For this patient, however, most of these options were either limited or only transiently effective except for denosumab, which seemed to be more promising in managing hypercalcemia.

Denosumab, a monoclonal antibody, inhibits osteoclast activity through the inhibition of receptor activator of nuclear factor *k*B ligand (RANKL). The effects of denosumab on skeletal-related events (SREs) were investigated in three large randomized trials: one in patients with breast cancer, one in patients with prostate cancer, and one in patients with multiple myeloma or solid tumors other than breast or prostate cancer. Therefore, it has been

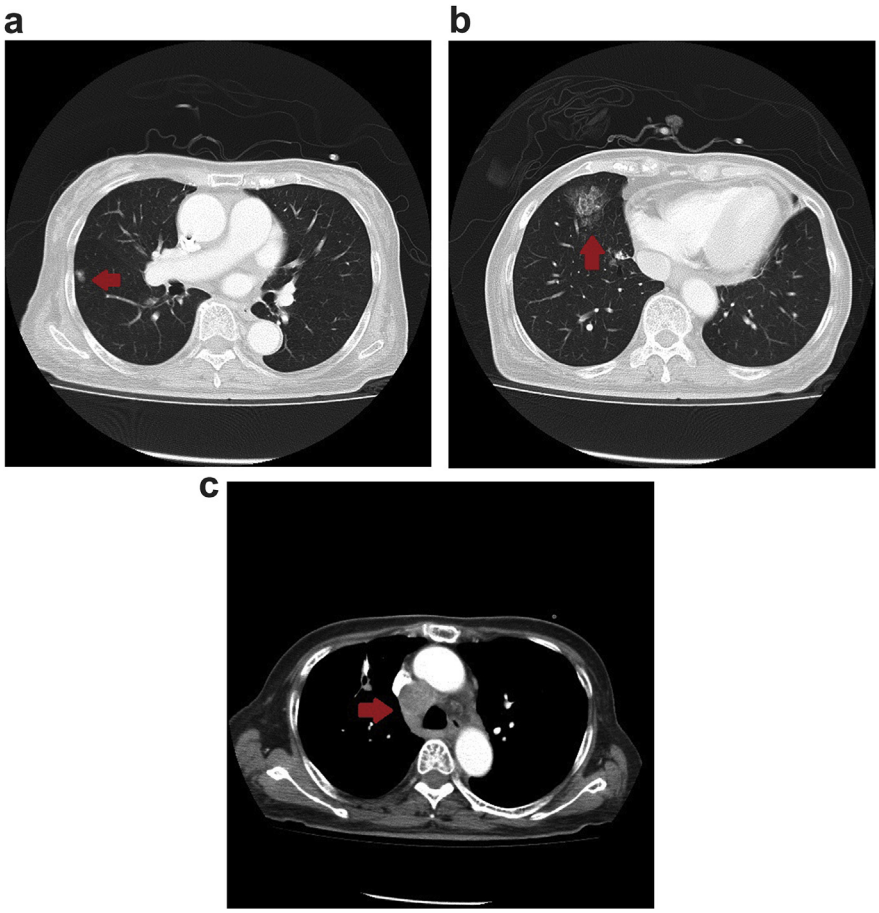

Fig. 3. CT images of chest after recurrence (a, b and c).

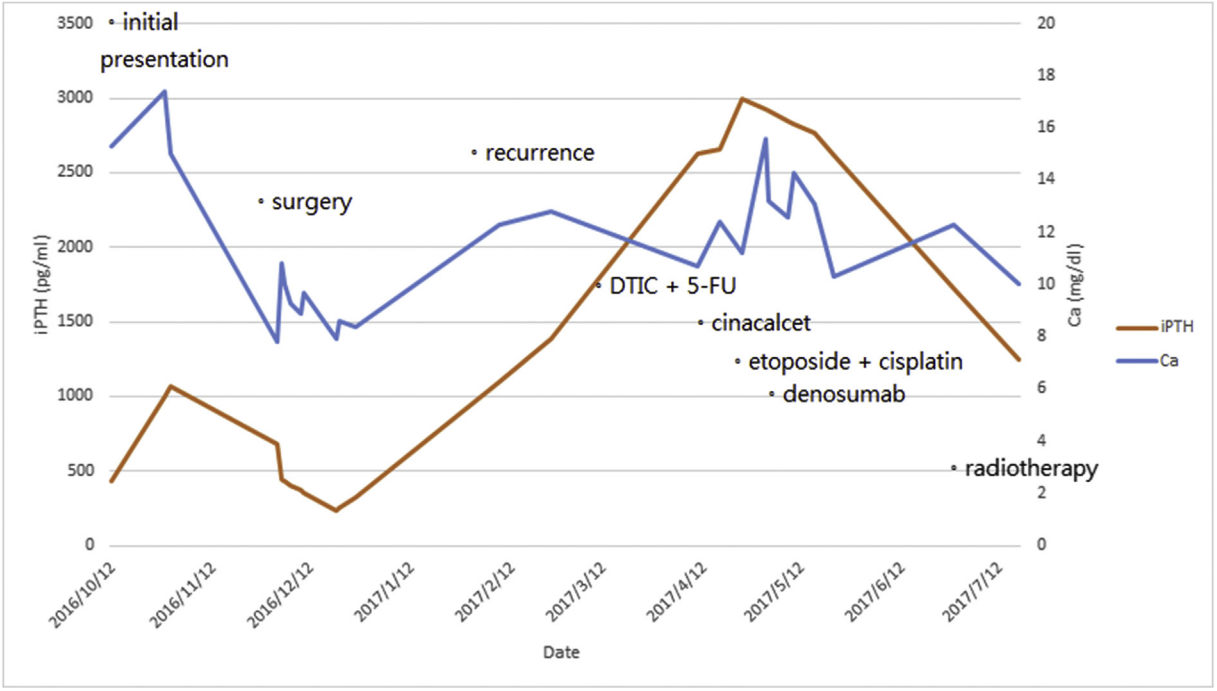

Fig. 4. Graphic illustration of the time course of Ca levels (continuous line, scale on the left axis), PTH levels (dotted line, scale on the right axis) in relation to the management.

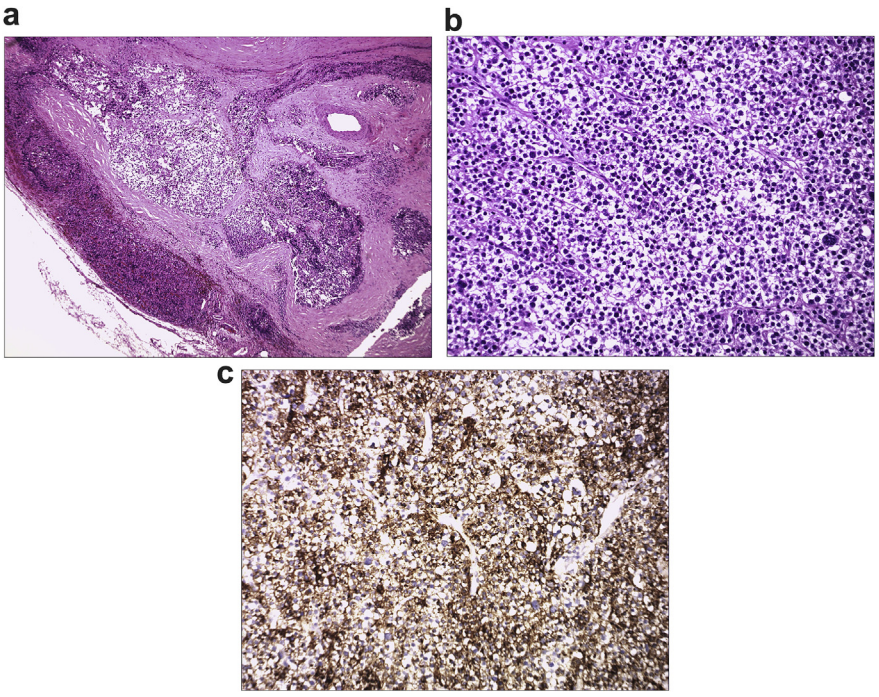

Fig. 5. Microscopic images of parathyroid carcinoma of parathyroid gland (a) and lung metastasis (b); immunohistochemical stain with PTH of lung metastasis (c).

approved for the prevention of skeletal-related events in malignancies with bone metastases.[5,6] It had been reported that a 39-year-old man with refractory hypercalcemia due to underlying parathyroid carcinoma was treated successfully by the anti-resorptive agent denosumab for an additional 16 months.[7] Our report also demonstrated the efficacy of denosumab in the management of hyperparathyroid-mediated hypercalcemia caused by parathyroid cancer.

The largest single-institution review of patients with parathyroid carcinoma was completed and published by Avital Harari et al.,[8] which showed that distant metastases or lymph node metastases were found to be associated with increased mortality, as well as an increase in recurrence. Moreover, even for this group of patients with aggressive disease, median overall survival could be around 10 years, given the slow-growing nature of parathyroid carcinoma. Therefore, careful management and avoidance of complications became the most important factor in treating these patients. Our report indicates that selective use of the novel agent denosumab may have a potential role for palliative treatment of hypercalcemia caused by parathyroid cancer.

Sources of funding

None.

Conflict of interest

The authors declare that they have no conflicts of interest.

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