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CASE REPORT

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Severe hypercalcemia due to metastatic pancreatic neuroendocrine tumor: a case report

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Abstract

Background Hypercalcemia of malignancy, as a paraneoplastic syndrome, is the most common metabolic disorder that accounts for 30% of malignancies and usually has a poor prognosis. Neuroendocrine tumors are uncommon and arise from neuroendocrine cells throughout the body. Actually, paraneoplastic hypercalcemia in neuroendocrine tumors is unusual and mostly associated with parathyroid hormone-related protein (PTHrP) secretion.

Case presentation We report a 51-year-old Iranian man who presented with nausea, vomiting, and significant weight loss for 1 month. Laboratory data revealed calcium of 26 mg/dl, accompanied by low level of PTH. Octreotide scan revealed a large donut-shaped octreotide avid lesion in the epigastric region at the right side of the mid-abdomen, with multiple varying size foci of abnormally increased radiotracer uptake in the epigastric region and both lobes of the liver. Endoscopic ultrasonography demonstrated a large heterogeneous mass lesion with irregular outline and good demarcation in the body of the pancreas with diffuse foci of calcification. Percutaneous biopsy of the liver mass demonstrated a well-differentiated neuroendocrine tumor (low grade) confirmed by immunohistochemistry with strongly positive chromogranin and synaptophysin stain. Hypercalcemia was treated with hydration, few sessions of hemodialysis, calcitonin, and denosumab injection. However, the patient developed symptomatic hypocalcemia. Oncology consultation led to prescription of long-acting octreotide 30 mg monthly and everolimus daily.

Conclusion Pancreatic neuroendocrine tumor could lead to malignant hypercalcemia; secretion of PTHrP is the most common cause, and signs and symptoms are usually milder than paraneoplastic syndrome due to hematologic and solid tumor. Generally, survival is better; however, its treatment is challenging, and primary debulking surgery is often required. A team approach to management is important at all points.

Keywords Hypercalcemia, Neuroendocrine tumor, Pancreas, PTHrP

Background

Paraneoplastic syndromes (PNSs) are various clinical states affecting different systems, which represent with clinical symptom and signs associated with malignancies. PNS is the result of tumor-mediated bioactive substance or immune-mediated production that does not connect with the origin of the tumor or certain organ. PNS could happen before, simultaneously, or after the diagnosis of tumor and could affect the tumor management. Also, PNS could affect the quality of life and prognosis [1, 2].

Hypercalcemia of malignancy as a PNS is the most common metabolic disorder that affects up to 30% of advanced malignancies and usually has a poor prognosis [3, 4]. It occurs through four mechanisms: (1) parathyroid

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Given that primary hyperparathyroidism could be apart from multiple endocrine neoplasia type 1 and type 2, it is important to rule it out before paraneoplastic hypercalcemia syndrome is diagnosed, especially in patients with hypercalcemia simultaneous with NET [23, 24]. Although it is unusual, in patients who present with hypercalcemia due to NET, it would be better to consider ectopic production of PTH whenever high PTH levels are present with no parathyroid-related cause. It is worth recognizing, because it could prevent unnecessary parathyroidectomy or neck exploration [13].

Paraneoplastic hypercalcemia due to PTHrP secretion of NET, in contrast to other malignancies producing PTHrP, is associated with better survival (up to 125 months) [25]. Management of paraneoplastic hypercalcemia is challenging. It is suggested that a multidisciplinary team should control the clinical manifestations and tumor growth. Sometimes control of hypercalcemia requires anti-tumor agents and operative resection of the primary source of the tumor, in addition to the routine treatment of hypercalcemia [26].

In the literature, we found some cases of NET-induced hypercalcemia with variable management strategies. Elisa *et al.* presented a 45-year-old man with hypercalcemia due to pancreatic NET that was treated with distal pancreatectomy and analogous somatostatin. After the operation, due to progression of disease and liver metastasis, everolimus was prescribed for the patient. Then, due to persistent hypercalcemia, management was continued with zoledronic acid and denusumab, which caused jaw osteonecrosis and was stopped. Ultimately, 20 mg prednisolone was administered to the patient, which stabilized the calcium level, but despite the stability of the calcium level, the patient expired [17].

Also, we found another case with well-differentiated bronchial tumor, which presented with lung mass and hypercalcemia of 14.4 mg/dl, PTH of 4.7 pg/ml, and PTHrP of 109 ng/ml that was treated with 4 mg zolendronic acid every 28 days; then, lobectomy was done, which led to normalized calcium level and decreased PTHrP [17].

According to the 2017 World Health Organization (WHO) classification based on ki67 proliferation and mitotic rate, well-differentiated G1–G3 neoplasm, without invasion to the artery of the celiac axis or superior mesenteric artery, is considered as the operable neoplasm. In addition, tumors larger than 2 cm are candidates for surgery; however, tumors between 1–2 cm in low-risk lesions may be considered for surgery rather than surveillance [27]. In the case of pancreatic NETs, the risk of operation rather than the progression or recurrence should be carefully considered [28].

Our patient's tumor was 51 mm × 37 mm with advanced vascular invasion and liver metastasis and so consensus was hemipancreatectomy and liver transplantation, but the patient and his family refused.

There are several medical treatment plans for symptomatic patients who are not candidates for surgery. Chemotherapy based on temozolomide or capecitabin is considered for functional tumor, but they do not have long-standing effect on hypercalcemia [29–31]. The analog of somatostatin, such as octreotide or lanreotide, is considered for decreased tumor burden, not only in resectable lesion, but also in metastatic lesion, to decrease both symptoms and tumor growth [32–34]. However, this medical treatment sometimes is not sufficient and efficacy decreases over time as result of tachyphylaxis [25].

Our patient's hypercalcemia was difficult to control because the first presentation was malignant hypercalcemia, and the origin of the tumor was unknown at presentation (we did not have enough time to search for it). He was treated with octreotide 30 mg monthly and everolimus 10 mg daily, but the effect of treatment did not last long and 6 months later, the patient returned with severe hypercalcemia. Moreover, treatment with denosumab in the case of vitamin D deficiency lead to symptomatic hypocalcemia.

Similar to our patient, Noura *et al.* presented a case of malignant hypercalcemia due to high production of PTHrP from pancreatic NET, which resulted in symptomatic hypocalcemia after treatment with denosumab in the case of low-normal vitamin D levels [35].

A recent investigation showed that tyrosine kinase inhibitor drugs, such as sunitinib, could decrease the calcium level in some cases [36, 37].

The limitation of this study was lack of accessibility to assess PTHrP, and 1,25 dihydroxyvitamin D.

Conclusion

Pancreatic NET could lead to malignant hypercalcemia; before the diagnosis, we should rule out multiple endocrine neoplasia (MEN) type 1. Secretion of PTHrP is the most common cause, and signs and symptoms are usually milder than paraneoplastic syndrome due to hematologic and solid tumor. Generally, survival is better; however, its treatment is challenging, and primary debulking surgery is often required. A team approach to management is important at all points.

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