Original Paper

A Case of Carcinoid Tumor-Associated Hypercalcemia

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Key Words

Carcinoid tumor • Hypercalcemia

Abstract

Hypercalcemia as a complication of carcinoid tumors is extremely rare. Accordingly, we report the case of a 55-year-old male with metastatic carcinoid tumor and hypercalcemia, which corrected when the patient was treated with octreotide for symptomatic relief of watery diarrhea. The etiology of the hypercalcemia is presumed to be a neoplastic expression of fibroblast growth factor-23, which was found to be inappropriately high-to-normal when other factors such as parathyroid hormone, calcitonin and vitamin D were appropriately low or low-to-normal.

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Carcinoid tumors, when metastatic to liver or when arising outside the gut, classically cause the carcinoid syndrome, with profuse watery diarrhea, flushing, and hypotension. Hypercalcemia has only very rarely been associated with carcinoid tumors. Accordingly, we report an unusual case of carcinoid tumor associated with hypercalcemia, and propose an unusual mechanism for the tumor-related hypercalcemia based on a detailed workup.

Case Presentation

A 55-year-old white male was referred to the University of Missouri-Columbia Hospital for diagnosis and management of weight loss of 30 pounds and severe diarrhea of 1–2 years' duration, and progressive debilitation due to orthostatic dizziness. He reported 8–10 watery stools occurring at any time of day

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Fig. 1. **a** Cytology. Needle-core biopsy of the liver mass showing normal liver (top) and carcinoid tumor (nodules). The tumor is made up of monotonous small cells with eccentric bland and ‘salt-and-pepper’ nuclei, and slightly granular eosinophilic cytoplasm. **b** Chromogranin. **c** Synaptophysin. The trabeculae and nests of carcinoid tumor stain positively with the neuroendocrine markers chromogranin and synaptophysin.

Fig. 2. Octreotide scan. An area of increased uptake is visible within a loop of small bowel immediately anterior to the left renal inferior pole.

and night. He also had nausea and anorexia, but denied vomiting, hematemesis, hematochezia, melena, and abdominal pain. Personal habits included longstanding cigarette smoking; he denied use of alcohol and recreational drugs, and his past medical history was notable only for longstanding gastro-esophageal reflux disease. Evaluation of his symptoms at the outside medical facility included an abdominal CT scan which demonstrated multiple nodular liver densities suggestive of metastases, and a colonoscopy which yielded several benign hyperplastic polyps.

The patient appeared thin and ill, but was afebrile. His blood pressure was 96/66 mm Hg, with orthostatic tachycardia, dry mucous membranes, and decreased skin turgor. The remainder of the physical examination was normal, with no hyperpigmentation, unusual skin lesions, lymphadenopathy, or appreciable hepatosplenomegaly. His chest was clear to auscultation and his heart sounds were normal S1 and S2, without murmur, S3 or S4. The serum chemistry profile revealed hyponatremia (130 mmol/l), hypokalemia (2.0 mmol/l), creatinine (1.67 mg/dl), phosphate was low (2.6 mg/dl) and calcium elevated at 11.2 mg/dl (8.6–10.2 mg/dl), with normal albumin and total protein. His serum chromogranin A level was elevated at 620 ng/ml (normal: 0–95 ng/ml).

The initial management consisted of aggressive intravenous hydration with improvement in azotemia and blood pressure, but no improvement in serum calcium. Profuse watery diarrhea persisted and was evaluated extensively, with negative test results for fecal leukocytes, ova and parasites, *Clostridium difficile* toxins, celiac antibody panel, and urinary 5-hydroxyindoleacetic acid (5-HIAA). Upper and lower endoscopies demonstrated no mucosal lesions or strictures. A CT-guided biopsy of his liver lesions demonstrated carcinoid tumor staining positive for chromogranin A, synaptophysin, and CK7 (fig. 1). Subsequently, a whole body octreotide scan showed an uptake consistent with carcinoid tumor primarily involving the small bowel (fig. 2) with extension to the mesentery, and multifocal hepatic metastases.

Workup of the patient’s persistent hypercalcemia was generally negative: parathyroid hormone (PTH) was appropriately suppressed (11.1 pg/ml; normal: 15–65 pg/ml), PTH-related peptide <2 pmol/l

Table 1. Effects of octreotide treatment on the serum calcium levels in a patient with carcinoid syndrome

	Before octreotide administration	1 day after octreotide treatment	3 days after octreotide treatment
Serum calcium (normal = 8.6–10.2 mg/dl)	12.0 mg/dl	10.5 mg/dl	9.5 mg/dl

(normal: 0–4 pmol/l), 25-hydroxy vitamin D [calcidiol] normal at 31 ng/ml (normal range: 30–80 ng/ml), and 1,25-dihydroxy vitamin D [calcitriol] normal at 38 pg/ml (normal range: 15–75 pg/ml). Serum and urine protein electrophoreses demonstrated no M-spike. However, the fibroblast growth factor-23 (FGF-23) was borderline elevated at 172 relative U/ml (normal: <180 U/ml). Following the diagnosis of metastatic carcinoid tumor, therapeutic trial of octreotide resulted in an improvement in the frequency and volume of diarrhea and normalization of serum calcium (table 1).

Discussion

Carcinoid tumors are neuroendocrine-derived neoplasms originating most frequently in the gastrointestinal tract (54.5%) and lungs, and occasionally in other locations such as the kidneys [1]. The incidence of carcinoid tumors is estimated at 4.7 per 100,000 persons [2]. The small bowel is the most frequently involved segment of the gut (44.7% of total cases). Clinical manifestations of carcinoid tumors vary, depending on the site of origin and the presence of metastases. When originating in the small bowel, as in this reported case, abdominal pain, diarrhea, and intestinal obstruction predominate [3]. In general, the mechanism of diarrhea is secretory, due to the production of serotonin and other amines synthesized and secreted by the carcinoid cells. Since bioactive amines secreted by gut carcinoids enter the portal circulation, they are largely metabolized by the liver prior to entering the systemic circulation. Therefore, the presence of diarrhea generally heralds the presence of liver metastases, which can release the bioactive amines directly into the systemic circulation. In addition to diarrhea, other typical symptoms of the carcinoid syndrome are cutaneous flushing, bronchospasm, and right-sided heart disease [4]. Hypercalcemia has been reported in association with carcinoid tumors in a total of 16 cases since 1966 [5–8]. Putative explanations for the hypercalcemia have included the production of PTHrp by tumor cells; direct osteolysis by bone metastases; co-existent primary hyperparathyroidism, as part of a multiple endocrine neoplasia syndrome; and elevated calcitonin levels. None of these factors explained the hypercalcemia associated with the carcinoid tumor in the current reported case. However, FGF-23 was in the high-to-normal range despite a low level of serum phosphate. Thus, the most likely candidate to explain the elevated calcium was an inappropriately high FGF-23 level.

The current report represents the 17th case of hypercalcemia due to a carcinoid tumor [9]. The production of PTHrp by the carcinoid tissue is by far the most commonly reported link between hypercalcemia and neuroendocrine tumors. PTHrp is a polypeptide sharing structural homology with the N-terminus of PTH. Like PTH, PTHrp has been shown to augment bone resorption, increase renal calcium reabsorption, and promote phosphorus excretion [10–12]. PTHrp has been strongly associated with hypercalcemia complicating cancers of squamous cells (e.g. the lung, kidney, bladder, breast, and head and neck) and in some non-Hodgkin lymphomas [12]. In this reported case, the undetectable serum level of PTHrp effectively excludes that mechanism of disease from further consideration.

Direct osteolysis caused by carcinoid tumors metastatic to bone is an extremely rare event and apparently more common in atypical carcinoids than in typical ones. The mechanism of hypercalcemia in such cases is presumed to be direct bone disruption and release of calcium, though a humoral etiology cannot be entirely ruled out. A reduction in tumor burden by chemotherapy in such cases has resulted in the normalization of serum calcium [13]. However, there was no evidence of bone metastasis on the octreotide scan in our patient.

The association of carcinoid tumor with MEN 1 syndrome is very rare, with only one reported case in Japan and one in Israel. In these cases, diarrhea did not dominate the clinical presentation, in contrast with the current case, and hypercalcemia was linked to hyperparathyroidism in a straightforward fashion, with inappropriately elevated serum PTH and concurrent hypercalcemia. In one of the cases, the carcinoid tumor secreted gastrin [14, 15].

Excess production of calcitonin was suggested previously in light of the common embryological background of the carcinoid tissue and the parafollicular cells (C-cells) of the thyroid. Hypothetically, hypercalcitoninemia could result in increased PTH secretion, but the resolution of hypercalcemia with persistent hypercalcitoninemia has largely rendered this concept moot. In the current case, the normal PTH weights against this etiology for hypercalcemia [16].

We posit that the most likely factor to explain the hypercalcemia in the current case of carcinoid was the increased tumor production of FGF-23, a phosphaturic hormone that normally buffers rising phosphate levels in early renal failure [17]. Indeed, the serum FGF-23 was borderline elevated despite low serum phosphate levels suggesting dysregulation of its production, likely via the carcinoid tumor. FGF-23, which is a normal osteocyte product, is now known to be an important phosphatonin, augmenting renal phosphate excretion by decreasing the expression of type 2a sodium-dependent phosphate co-transporters in proximal tubular cells [17]. FGF-23 also inhibits the activation of vitamin D, by decreasing the expression of renal 1- α -hydroxylase. An overexpression of FGF-23 is now known to be associated with and possibly causative of autosomal-dominant and X-linked hypophosphatemic rickets and oncogenic osteomalacia [9]. A heightened expression of FGF-23 is observed progressively as chronic renal failure evolves, buffering against hyperphosphatemia and mineralization of vascular and soft tissues [17]. As measured by enzyme-linked immunosorbent assay (ELISA), increased serum FGF-23 has been associated with humoral hypercalcemia of several different malignancies, possibly including carcinoid tumors [9]. In most instances, increased PTHrp was also observed, and the serum FGF-23 did not correlate with either serum phosphorus or calcitriol (1,25-dihydroxy vitamin D). The precise role of FGF-23 in the pathogenesis of tumor-related hypercalcemia has not been clearly established. It is possible that an elevated FGF-23 level is a true paraneoplastic product of tumor cells, or alternatively is produced by normal cells in response to tumor-related PTHrp-mediated hypercalcemia. If FGF-23 is a true paraneoplastic cell product, it is conceivable that FGF-23-induced hypophosphatemia stimulates an increased PTHrp production because of its simultaneous inhibition of calcitriol synthesis. Further work examining FGF-23 and PTHrp derived from cultured tumor cell lines may help to clarify what is presently a clinical conundrum as to the sequence of instigating and adaptive events [9, 18].

Based on the information detailed in the current case report, we postulate a new mechanism of hypercalcemia, characterized by the neoplastic production of FGF-23, which may mimic some of the effects of PTH and/or PTHrp. In the current case, it is presumed that the administration of octreotide caused a reduced expression of FGF-23 by the patient's carcinoid tumors, but at this point, this is only speculative. It will be of interest to examine cultured tumor cell lines for the presence of FGF-23 in this and similar cases, when the standard detailed workup of malignancy-associated hypercalcemia is otherwise unrevealing.

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Disclosure Statement

The authors have nothing to disclose.

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