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Case Report

Tumor induced osteomalacia secondary to anaplastic thyroid carcinoma: A case report and review of the literature

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ABSTRACT

Context: Tumor induced osteomalacia related to anaplastic thyroid cancer has never been reported.
Objective: We describe a case of tumor induced osteomalacia (TIO) in a patient with a fibroblast growth factor 23 (FGF-23) secreting anaplastic thyroid carcinoma. The current imaging modalities are reviewed.
Design and intervention: Clinical, biochemical, and radiological assessments were done, including computer tomography (CT) of the neck and skull to thigh positron emission tomography (PET)/CT. The patient underwent surgical tumor debulking three days after presentation due to airway compromise. Molecular studies of the resected tissue were performed using reverse transcriptase–polymerase chain reaction (RT-PCR) and gel electrophoresis for the phosphaturic mesenchymal tumor FGF-23.
Results: Resected tissue demonstrated features of anaplastic thyroid cancer with positive markers for FGF-23 protein, consistent with a FGF-23 secreting paraneoplastic tumor. The patient's metastatic burden rapidly progressed as demonstrated by a dramatic rise in serum FGF-23 levels and worsening hypophosphatemia in concert with progression of the metastatic lesions on PET/CT.
Conclusion: We believe that our patient's rapidly progressive anaplastic thyroid cancer was responsible for persistent hypophosphatemia and osteomalacia, substantiated by the finding of FGF-23 protein within the thyroid tumor cells. Our case indicates that anaplastic thyroid cancer can cause TIO.

1. Introduction

Tumor induced osteomalacia (TIO) is a rare phosphorus-wasting syndrome caused by tumors capable of secreting FGF-23 in a similar fashion as other FGF-23-mediated diseases, such as x-linked hypophosphatemia, autosomal recessive and autosomal dominant hypophosphatemia rickets. TIO is characterized by signs and symptoms of severe osteomalacia or rickets. Clinical features include bone and muscle pain, muscle weakness, skeletal deformities and recurrent fractures as well as microfractures of long bones (Drezner, 2008; Mammen and de Beur SM, 2008). Laboratory testing usually reveals low serum phosphorus, low or inappropriately normal range circulating concentration of 1,25-dihydroxyvitamin D (1,25$(OH)_2$D), high urine fractional excretion of phosphorus, normal serum calcium and normal 25-hydroxyvitamin D 25(OH)D levels. Successful surgical resection of the FGF-23 secreting tumor is curative, thus accurate localization of the tumor is of the utmost importance (Jonsson et al., 2003). The majority of the TIO cases previously reported in the literature have been caused by small mesenchymal tumors derived from bone (Fatani et al., 2013; Westerberg et al., 2012; Gandhi et al., 2012), soft tissue (Jiang et al., 2012), skin (Gardner et al., 2013) and cartilage (Hautmann et al., 2014). TIO has also been reported in association with malignant adenocarcinomas of the ovary (Lin et al., 2014), lung (Taylor et al., 1984), prostate (Lee et al., 2014), colon (Ryan and Reiss, 1984) and head/neck (Tarasova et al., 2013; Kominek et al., 2011; Luo et al., 2013; Mathis et al., 2013). To our knowledge, TIO induced by anaplastic thyroid cancer has not been reported previously.

2. Case report

A 59 year-old white man presented to the Mayo Clinic Florida emergency department with a 3-month history of rapidly progressive dysphagia to liquids and solids, cough and hoarseness. CT of the neck with contrast revealed a 7 cm infiltrating mass centered in the anteroinferior aspect of the neck that completely encased the left carotid artery, esophagus and trachea (Fig. 1). He was evaluated by an otolaryngologist who performed a core needle biopsy of the mass, which demonstrated findings of an undifferentiated malignant neoplasm. Due to extensive infiltration of vital structures, a complete resection of the tumor was not possible. The patient underwent debulking of the tumor, tracheotomy for airway management and gastrojejunostomy

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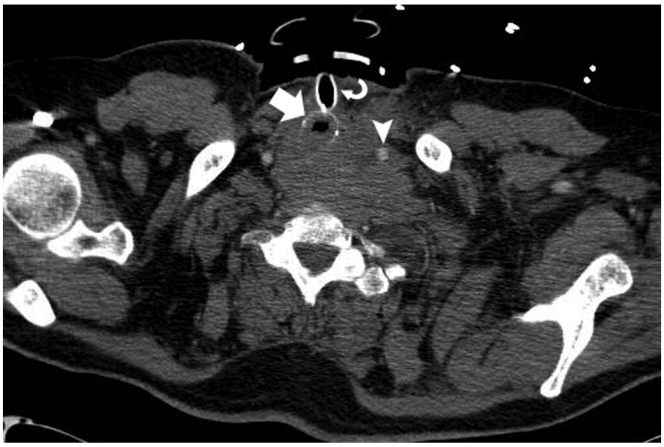

Fig. 1. Axial CT contrast-enhanced image at the level of the upper trachea demonstrates a large soft tissue density mass in the anterior neck centered to the left of midline, compatible with the patient's known history of anaplastic thyroid cancer. The mass completely encases the left carotid artery (arrowhead), trachea and esophagus and obliterates the left jugular vein. The tracheal ring (fat arrow) is partially destroyed with tumor infiltration into the tracheal lumen. A portion of the tracheostomy tube (curved arrow) is seen just superior to its tracheal entry site.

tube placement for enteral feeding. Final operative histopathology was consistent with anaplastic thyroid carcinoma.

His past medical history was significant for papillary thyroid cancer treated with right lobectomy in 1984. He underwent completion thyroidectomy in 1991 due to a recurrence. He developed vocal cord immobility after his first surgery. He appears to have mild post surgical hypoparathyroidism based on finding of low calcium with low normal PTH and high urine calcium. The patient was placed on hormone replacement therapy for expected hypothyroidism. The patient was unsure whether he underwent ^{131}I therapy at the time of his second surgery. His phosphorus level prior to presentation is unknown.

During his hospitalization, the patient required large amounts of daily phosphorus replacement due to persistent critically low serum phosphorus levels. Biochemical evaluation (Table 1) was also noteworthy for elevated 24 h urine phosphorus secretion, low serum 1,25$(OH)_2$D, and increased serum alkaline phosphatase activity. The serum 25(OH)D level was in the lower end of the reference range.

Laboratory findings are listed in Table 1. A skull-thigh PET/CT showed abnormal areas of hypermetabolism consistent with metastases in the lungs, mediastinum, liver and left greater trochanter. Repeat imaging one week later revealed progression in size and number of his lung and liver metastases (Fig. 2). Biopsy of these lesions was not feasible due to the decline of patient's health status.

The patient suffered a rapid decline in his overall condition and died of multiorgan failure one month after presentation. A repeat FGF-23 level at the time of his death had more than tripled from 2355 RU/mL to 7950 RU/mL.

Table 1
Results of laboratory tests.

	3/19	3/22	4/11	Normal range
Serum values				
Calcium (mg/dl)	8.8	8.6	8.8	(8.9–10.1)
Phosphorus (mg/dl)	0.7	0.9	0.9	(2.5–4.5)
ALP (IU/l)	128	146	649	(45–115)
Creatinine (mg/dl)	0.7	0.8	1.1	(0.8–1.3)
BUN (mg/dl)	7	11	28	(8–24)
Intact PTH (pg/ml)		16.1	9.9	(15–65)
1,25$(OH)_2$D (pg/ml)		17	<8	(18–78)
25$(OH)_2$D (ng/ml)		12.2	17.3	(>20)
TSH (mIU/L)	38.17	45.34	19.32	(0.3–5)
Free T4 (ng/dL)		1.1	0.8	(0.8–1.8)
TG (ng/ml)	13.4			(<0.1)[a]
TG Ab (Iu/mL)	<1.8			(<1.8)
iFGF-23 (RU/mL)		2355	7950	(<180)
Urine values				
Calcium (mg/24 h)		391	636	(25–300)
Phosphorus (mg/24 h)		1169	3591	(<1099)

ALP- total alkaline phosphatase; TG- thyroglobulin tumor marker; TG Ab- thyroglobulin antibody.
[a] Athyrotic individuals; iFGF 23- intact fibroblast growth factor 23.

3. Pathology and immunohistochemistry

Tissue obtained from the anterior left neck measuring 6.0 cm in maximum dimension was provided for pathological analysis. Dissection revealed a 3.5 cm gray/white tumor with adherent soft tissue and skeletal muscle. Histologically, a malignant epithelioid and spindle cell tumor was identified that was infiltrating the skeletal muscle and encasing the large vessel walls. The tumor was negative for cytokeratin, thyroglobulin and TTF-1, consistent with an anaplastic thyroid carcinoma. Tissue fragments obtained during surgical debulking were analyzed using reverse transcriptase polymerase chain reaction (RT-PCR) and gel electrophoresis for phosophaturic mesenchymal tumor FGF-23 gene on RNA extracted from paraffin imbedded tissue. The tissue was positive for the presence of FGF-23 by RT-PCR (Fig. 3). The FGF-23 gene revealed positive amplification results; all controls yielded appropriate results. Molecular analysis confirmed the expression of the gene within the neoplastic cells.

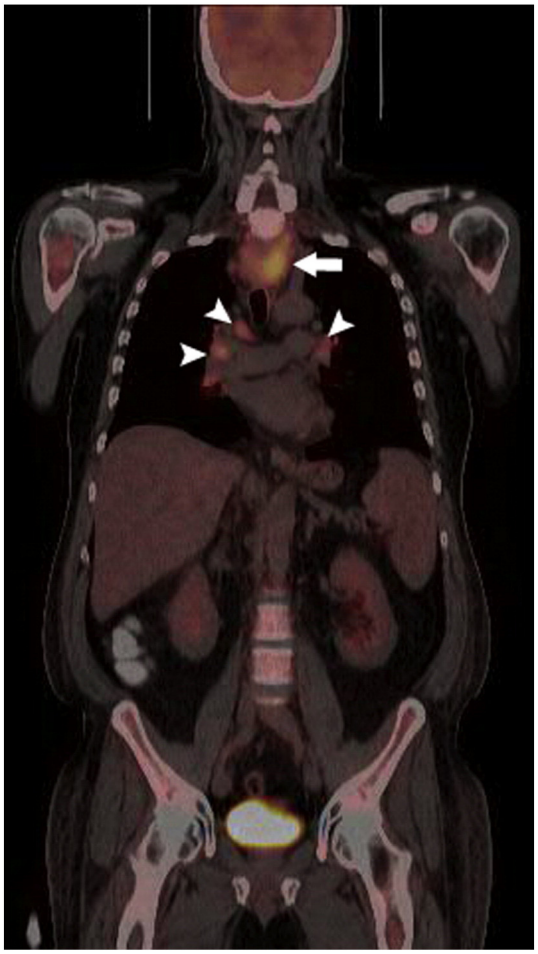

Fig. 2. Coronal fused PET/CT image demonstrates abnormal glucose hypermetabolism of a large superior mediastinal mass (arrow) corresponding the patient's known anaplastic thyroid cancer. There is abnormal hypermetabolism in the visualized mediastinal and bilateral hilar lymph nodes (arrowheads), compatible with metastatic disease.