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Hypercalcemia of Malignancy Induced by Parathyroid Hormone-related Protein in a Patient with Medullary Thyroid Carcinoma

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We present the case of a 50-year-old male patient presenting with a mass lesion in the neck region and diarrhea. Histological examination of the excisional biopsy specimen revealed medullary thyroid carcinoma. In the laboratory examination of the patient marked hypercalcemia was detected along with a low parathyroid hormone (PTH) levels (<1 pg/ml, (normal range: 10-69 pg/ml). PTH-related protein (PTHrP) level was elevated (8.5 pmol/L, normal range: <1.3 pmol/L). An extensive metastasis screening found metastatic lesions in the liver while no bone metastasis was discovered. The patient died shortly after induction of chemotherapy due to respiratory failure. To the best of our knowledge, this is the first reported case of a PTHrP-producing medullary carcinoma of the thyroid associated with humoral hypercalcemia of malignancy.

Key Words: Humoral hypercalcemia of malignancy, parathyroid hormone-related protein, medullary thyroid carcinoma

Paratiroid Hormon İlişkili Proteine Bağlı Malin Hiperkalsemiyle Başvuran Meduller Tiroid Karsinomu Olgusu

Burada boyunda kitle ve diyare ile başvuran 50 yaşında bir erkek hastayı sunduk. Kitleden alınan eksizyonel biopsi örneğinin histolojik incelemesinde meduller tiroid karsinomu saptandı. Gelişindeki laboratuvar tetkiklerinde belirgin hiperkalsemi saptanan hastanın serum paratiroid hormon (PTH) düzeyi <1 pg/ml (normal: 10-69), PTH-ilişkili protein (PTHrP) düzeyi ise 8.5 pmol/L (normal: <1.3) bulundu, ayrıca karaciğerde metastaz saptandı, kemik metastazı tespit edilmedi. Kemoterapi başlanan hastanın durumu progressif olarak kötüleşti ve solunum yetmezliği nedeniyle kaybedildi. Olgumuz literatürde PTHrP üretimine bağlı malign humoral hiperkalseminin nedeni olarak bildirilen ilk meduller tiroid karsinomu olgusudur.

Anahtar Kelimeler: Malign humoral hiperkalsemi, paratiroid hormon ilişkili protein, meduller tiroid karsinomu

Hypercalcemia being detected in 10-40% of patients with malignancy is the most commonly encountered paraneoplastic syndrome. Malignancy associated hypercalcemia can be divided into two syndromes, humoral hypercalcemia of malignancy and local osteolytic hypercalcemia. Humoral hypercalcemia of malignancy is mediated by certain humoral factors secreted into the circulation by tumor cells.[1] Parathyroid hormone-related protein (PTHrP) is the most common etiological agent in the setting of humoral hypercalcemia and has been shown to be secreted from many types of solid tumors including squamous cell lung carcinoma, head and neck cancer, renal cell carcinoma, breast cancer and hematologic malignancies.[2]

Medullary thyroid carcinoma (MTC) originates from calcitonin secreting parafollicular C cells and constitutes 5-10% of all thyroid cancers. It can produce several hormones and peptides because of its neuroendocrinological origin.[3] MTC often presents as a nodular thyroid enlargement accompanied by cervical lymphadenopathies and sometimes

paraneoplastic syndrome can also be present in the initial clinical presentation. In this report a patient with metastatic thyroid carcinoma presenting with malignant hypercalcemia is described.

CASE REPORT

A 50-year-old male patient presented with complaints of a mass lesion in the neck region which progressively increased in size over the past 2 months, weight loss, sweating and diarrhea. His medical history was not significant except for a diagnosis of goiter made 4 years previously. No diagnosis of thyroid disease was present in the family members. In physical examination a 6 cm in diameter painless mass located in the left thyroid lobule was detected along with multiple cervical lymphadenopathies on the right side. The liver was palpable 8 cm below the right costal margin.

Laboratory data are shown in Table 1. It was noted that in the setting of profound hypercalcemia PTH level was low while the PTHrP level was significantly above normal. The biopsy taken from the mass lesion revealed alternating round and spindle shaped monomorphic tumor cells having neuroendocrinological features and staining positive for calcitonin which was consistent with the diagnosis of medullary thyroid carcinoma (Figure 1-2). Abdominal CT scan showed extensive hypodense lesions in the right lobe of the liver. Metastasis was found in the biopsy specimen taken from the liver. Indium^{111} marked somatostatin scintigraphy did not reveal any bone metastasis. Screening for multiple endocrine neoplasm (MEN) syndromes by determining urinary catecholamine levels and computerized adrenal tomography was performed and no findings suggestive of pheochromocytoma were found. RET protooncogene analysis for familial MTC was also negative.

Figure 1. Hematoxylin eosin stain of the biopsy specimen showing infiltration of tumor cells (×100).

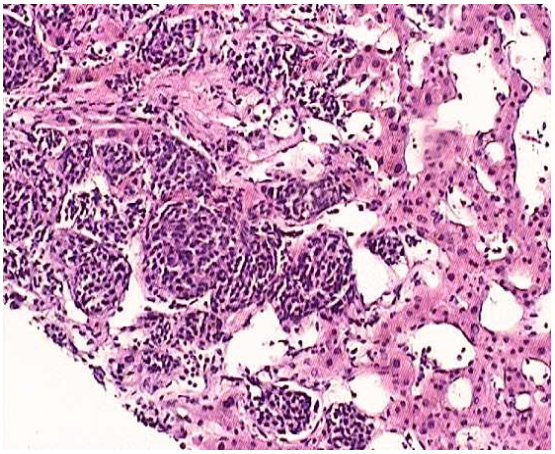
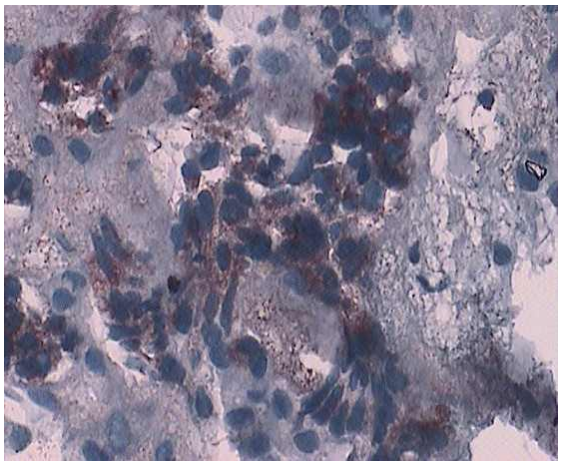


Table 1. Laboratory data on admission (Abnormal values are shown in bold character and normal range of each parameter is in parenthesis).

Complete blood count			Electrolytes		
WBC	6200/mm^3		Na	138 mmol/L	(135-148)
RBC	3.57 × 10^6/µL		K	3.7 mmol/L	(3.5-5.5)
Hb	**11.6 g/dL**		**Ca**	**13.5 mmol/L**	(8.5-10.5)
Hct	**38%**		**P**	**1.5 mmol/L**	(2.3-4.7)
Plt	171000/µL				
Blood chemistry			Hormonal data		
Urea	40 mg/dL	(10-50)	**PTH**	**<1 pg/ml**	(10-69)
Creatinine	1.1 mg/dL	(0-1.5)	**PTH-rP**	**8.5 pmol/L**	(<1.3)
AST	**88 IU/L**	(5-34)	**Calcitonin**	**>500 pg/ml**	(0-30)
ALT	**92 IU/L**	(0-55)	25(OH)vitD	15 ng/ml	(15-55)
LDH	**504 IU/L**	(125-243)	**1.25(OH)$_2$vitD**	**102 pg/ml**	(19-67)
ALP	**260 IU/L**	(40-150)			
GGT	**554 IU/L**	(30-63)	Tumor markers		
Total bilirubin	**2.46 mg/dL**	(0-1)	**CEA**	**385.3 ng/ml**	(0-5)
Direct bilirubin	**1.35 mg/dL**	(0-0.5)	AFP	3.4 U/L	(0.2-7)
İndirect bilirubin	**1.11 mg/dL**	(0.1-1)	CA 12.5	32 U/L	(0-35)
Total protein	6.9 g/dL	(6.4-8.3)			
Albumin	3.7	(3.5-5)			
Amilase	49 U/L	(5-125)			
PT	13.5 sn	(10-14)			
aPTT	26.3 sn	(26-40)			

Figure 2. Monomorphic tumor cells with alternating spindle and round formation staining positive for calcitonin (×400).



The diagnosis of medullary thyroid carcinoma and paraneoplastic hypercalcemia associated with PTHrP secretion was made and chemotherapy with cisplatin and DTIC was started. The patient died on the 8th day of hospitalization due to respiratory failure.

DISCUSSION

Because of its neuroendocrine origin medullary thyroid carcinoma can express several genes either not normally expressed or expressed in minute amounts in C cells. Among the proteins coded by these genes are somatostatin, CRH, ACTH, proopiomelanocortin, beta-endorphin, beta-MSH, VIP, gastrin releasing peptide, neurotensin, substance P, prostaglandin E2 and F2α, kinins, serotonin, histaminase, neuron-specific enolase, dopa decarboxylase, CEA and chromogranin A.[3] Some of these products can give rise to certain clinical states and paraneoplastic syndromes. Serotonin, prostaglandins and histaminase are held responsible for diarrhea and flushing seen in some MTC cases.[4] Most common paraneoplastic syndrome seen in the setting of MTC is the Cushing syndrome due to secretion of ACTH and CRH from the tumor cells.[5]

Humoral hypercalcemia of malignancy is defined as hypercalcemia found in patients with cancer without the presence of bone metastasis and hyperparathyroidism. The factors playing role in the pathogenesis are IL-1, IL-6, prostaglandins, TGF-alpha and -beta, PDGF and TNF-alpha.[2] These factors at the same time are thought to play role in osteolytic hypercalcemia.[6] PTHrP is the leading cause of humoral hypercalcemia and secreted from several tumors. PTHrP has 70% homology to the first 13 amino acids of the N-terminal portion of PTH and this homology enables PTHrP to bind PTH receptors and mimic the effect of PTH. It is also being secreted from other body tissues and plays role in cartilage and bone growth and calcium metabolism. In healthy individuals PTHrP levels are extremely low and it is thought to show its effect as an endocrine and autocrine regulator of calcium.[2]

Nakashima et al. have studied PTHrP expression in anaplastic, squamous and follicular cell type thyroid tumors and showed that while normal thyroid epithelium does not express PTHrP, almost all tumors cells show expression.[7] They also postulated that PTHrP expression correlates with the malignt growth pattern of the tumoral tissue and malignant alteration of thyroid epithelial cells. In the literature two cases of anaplastic thyroid carcinoma [8,9] and two cases of papillary thyroid carcinoma [10] presenting with hypercalcemia and shown to produce PTHrP are present. In addition two more cases of squamous cell thyroid carcinoma presenting with hypercalcemia and leukocytosis have been published and it has been stated that hypercalcemia could have been the result of PTHrP or other humoral factors secreted from the tumor cells.[11,12]

In a small number of experimental trials PTHrP expression in MTC cells have been reported [13-15] but in the literature no clinical cases of MTC presenting with hypercalcemia associated with PTHrP secretion has been reported previously. In response to calcium lowering effect of calcitonin which is secreted in high amounts from the MTC, compensatory hyperparathyroidism makes calcium levels stay in the normal range.[16] Because the effect of calcitonin on serum calcium levels is much milder when compared to the potency of PTH; even in the presence of very high calcitonin levels in patients with MTC serum calcium levels remain normal or slightly below normal.[17,18] The appearance of clinically significant hypercalcemia is in direct correlation with the level of PTHrP gene expression and amount of synthesized PTHrP from the tumor cells.[19]

In our case, suppressed levels of PTH in the presence of hypercalcitoninemia and accompanying hypercalcemia suggested the diagnosis of humoral hypercalcemia. Measurement of high levels of PTHrP and negative screening for bone metastasis confirmed this diagnosis. The relatively low levels of 25-hydroxyvitamin D can be explained by the increased turnover of 25-hydroxyvitamin D to 1.25-dihydroxyvitamin D associated with stimulation of

1α-hidroxylase by high PTHrP levels. It is known that humoral hypercalcemia of malignancy is associated with poor outcome. Hence the clinical course of the patient rapidly deteriorated despite initiation of chemotherapy.

In conclusion, we report a case of MTC who presented with severe humoral hypercalcemia associated with PTHrP secretion from the tumor cells. To our knowledge, this is the first reported case of a PTHrP secreting metastatic medullary carcinoma of the thyroid with humoral hypercalcemia of malignancy.

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