Anaplastic Thyroid Carcinoma with Humoral Hypercalcemia of Malignancy (HHM): An Autopsy Case Report

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Abstract. An 84-year-old woman was admitted to our hospital for the examination and treatment of painful right thyroid swelling on August 2, 2002. Thyroid ultrasonography showed a mass of about 6 cm in diameter at the right thyroid lobe. Aspiration biopsy cytology (ABC) of her mass showed a thyroid carcinoma. Her neck mass was cold on ^{123}I scintigraphy and hot on both early- and delayed- phase ^{201}Tl scintigraphy. Whole body ^{67}Ga scintigraphy scan showed a strong hot accumulation in the area from the right thyroid lobe to the right lateral lobe. Multiple lung tumors were observed from chest computed tomography (CT) scans. She was diagnosed as having an anaplastic thyroid carcinoma with metastatic lung tumors. As her thyroid carcinoma was inoperable, percutaneous injection therapy of lipiodol and ethanol (lip-PEIT) against the primary thyroid carcinoma was performed twice a week. However, the thyroid carcinoma gradually enlarged and oppressed her trachea. Two months after the initiation of lip-PEIT, parathyroid hormone-related protein (PTHrP)-dependent hypercalcemia was diagnosed because serum levels of calcium, phosphate and intact-PTHrP were 2.72 mmol/l (10.9 mg/dl), 0.71 mmol/l (2.2 mg/dl), 3.2 pmol/l, respectively. The hypercalcemia was reduced by the use of pamidronate. After one week she died of an airway obstruction caused by the developing thyroid carcinoma. Carcinoma cells with a mixed papillary and squamoid pattern were positively stained immunohistochemically by anti-PTHrP(1-34) antisera. Herein, we report a rare autopsy case of a PTHrP-producing thyroid carcinoma.

Key words: Thyroid carcinoma, HHM, PTHrP, Lip-PEIT

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HYPERCALCEMIA in malignancy usually has a rapid onset and can cause confusion, stupor, nausea, vomiting, and dehydration. The incidence of hypercalcemia in malignancy is 15 cases per 100,000 person-years [1]. Malignancy-associated hypercalcemia is classified into two groups: one is humoral hypercalcemia of malignancy (HHM), which is induced by humoral factors, and the other is local osteolytic hypercalcemia (LOH), which is induced by cytokines such as interleukin-1 α (IL-1 α), IL-6, tumor necrosis factor- α (TNF- α), and transforming growth factor- α (TGF- α) [1, 2]. In the former, parathyroid hormone-related peptides (PTHrP) are purified from a squamous cell

carcinoma cell line and are measurable in the serum of patients with various malignancies including renal cell carcinomas, adult T-cell leukemia/lymphoma, multiple myeloma, B cell lymphoma, breast carcinoma, etc. [3, 4].

Anaplastic thyroid carcinoma constitutes about 1.6% of all thyroid carcinomas, usually occurs after the age of 60 years, and is approximately two times more common in women than in men [5]. This carcinoma is highly malignant, nonencapsulated, extends widely, and has a poor prognosis [6–11]. In several anaplastic thyroid carcinoma cell lines, many cytokines such as granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), IL-1 α , IL-6, and TGF- α are produced [12–15]. However, only four cases, including the present one, with a PTHrP-producing thyroid carcinoma have ever been reported to the best of our knowledge [15, 16]. Here, we report a rare autopsy case of a patient with anaplastic thyroid carcinoma with HHM.

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Case report

An 84-year-old woman entered our hospital complaining of a painful right thyroid swelling in July, 2002. For examination and treatment of the swelling, she was admitted to our hospital on August 2, 2002. She had apoplexy at the age of 70 and a right femoral neck fracture at the age of 84. Her physical examinations were as follows: height 147.4 cm, body weight 41.3 kg, body temperature 36.2°C, blood pressure 138/72 mmHg, and pulse rate 78/minute. There were no abnormal findings on her heart, lungs or abdomen. A large and painful mass from the right thyroid lobe to

the lateral neck and right cervical lymph node swelling were palpable. Laboratory data showed mild anemia and a slight elevation of CRP and thyroglobulin (Tg) (Table 1).

Thyroid ultrasonography showed a low echoic mass of $60.6 \times 37.3 \times 26.3 \text{ mm}^3$ in the right thyroid lobe and bilateral cervical lymph node swellings (Fig. 1). Aspiration biopsy cytology (ABC) of her mass showed Papanicolaou V, which was suspected as being a thyroid papillary carcinoma because of its intranuclear cytoplasmic inclusion.

Her neck mass on T1- and T2-weighted magnetic resonance (MR) images showed low- and high-intensity,

Table 1. Laboratory data on admission

WBC	5200/ μl	BUN	18 mg/dl	TSH	2.4 $\mu\text{IU/ml}$
RBC	$371 \times 10^4/\mu\text{l}$	Cr	0.8 mg/dl	T3	125 ng/dl
Hb	11.7 g/dl			T4	10.6 $\mu\text{g/dl}$
Ht	35.6%	TP	6.8 g/dl	Tg	249 ng/dl (<30)*
Plt	$18.4 \times 10^4/\mu\text{l}$	Albumin	4.2 g/dl		
				TGPA	10>
CRP	1.2 mg/dl	T.Bil	0.4 mg/dl	MCPA	10>
ESR	70 mm/hr	GOT	15 IU/l		
		GPT	8 IU/l		
BS	106 mg/dl	Alp	327 IU/l		
Na	143 mEq/l	Amy	66 IU/l		
K	3.7 mEq/l	LDH	184 IU/l		
Cl	103 mEq/l				
Ca	2.47 mmol/l (2.20–2.62)*	T-cho	208 mg/dl		
Pi	1.1 mmol/l (0.81–1.45)	Trig	66 mg/dl		

Abbreviations: Tg, thyroglobulin; TGPA, anti-thyroglobulin particle agglutination; MCPA, anti-thyroid microsomal particle agglutination.

*Numbers in parentheses indicate the normal range.

Fig. 1. Thyroid ultrasonography

Thyroid ultrasonography showed a low echoic mass of $60.6 \times 37.3 \times 26.3 \text{ mm}^3$ in the right thyroid lobe and bilateral cervical lymph node swellings (A, B).

respectively. The right mass oppressed the common carotid artery and internal jugular vein and shifted the trachea to the left (Fig. 2A–C). It was cold on ^{123}I scintigraphy (Fig. 3A) and hot on early-(Fig. 3B) and delayed-(Fig. 3C) phases of ^{201}Tl scintigraphy. Whole body ^{67}Ga scintigraphy scan showed a strong hot accumulation in the area from the right thyroid lobe to the right lateral neck and a hot accumulation in the chest region (Fig. 3D). Multiple lung tumors were observed from the chest computed tomography (CT) scans. Cranial MR images showed no tumors. Based on the above findings, she was diagnosed as having an anaplastic thyroid carcinoma with metastatic lung tumors.

As she was elderly, she and her family refused to get chemotherapy or radiation treatments, or to undergo an operation for thyroid carcinoma. We therefore started percutaneous injection therapy of a mixed solution of lipiodol and ethanol (v/v = 1/1) (lip-PEIT). From August 26 to October 18, lip-PEIT was performed twice a week (13 times, total volume was 4.26 ml) against the primary thyroid carcinoma. TSH suppression therapy [17, 18] was also started because we suspected that her anaplastic carcinoma had transformed from a papillary carcinoma based on the elevated Tg levels in her blood and cytology. However, the thyroid carcinoma in her neck gradually enlarged and oppressed her trachea. Although bone $^{99\text{m}}\text{Tc}$ scintigraphy showed hot spots at the neck of her right thigh bone, right frontal sinus and pelvic cavity, x-ray and CT at each position showed no masses (Figure not shown). On a whole body ^{67}Ga scintigraphy scan on October 5, 2002, the hot accumulation from the right thyroid lobe to the right lateral neck was stronger than before and new metastatic lesions appeared in the lungs, liver and pelvic cavity.

Although the specific symptoms of hypercalcemia had not appeared, HHM was diagnosed because elevated serum levels of calcium (2.72 mmol/l (10.9 mg/dl)) and intact-PTHrP (3.2 pmol/l) (immunoradiometric assay (IRMA), Mitsubishi, Tokyo, Japan) and a decline of serum phosphate levels (2.2 mg/dl) were found on October 28, 2002 (Table 2). As the treatment for hypercalcemia, we selected bisphosphonate [1]. Hypercalcemia was reduced to (2.12 mmol/l (8.5 mg/dl)) by an intravenous injection of 30 mg of pamidronate. After one week she died of an airway obstruction caused by the developing thyroid carcinoma.

Table 2. Laboratory data on Oct. 29, 2002

Ca	2.72 mmol/l
Pi	0.71 mmol/l
Albumin	3 g/dl
Ca ²⁺	2.68 mEq/l (2.24–2.58)*
Intact-PTH	7 pg/ml (14–66)
Intact-PTHrP	3.2 pmol/l (<1.1)
1 α -25(OH) ₂ VD	26 pg/ml (27.5–68.7)
Calcinonine	23 pg/ml (15–86)

*Numbers in parentheses indicate the normal range.

Autopsy

Most of the tumor tissue in her neck consisted of anaplastic cancer nests, including carcinoma cells with large and atypical nuclei (Fig. 4A). A papillary pattern beside the trachea (Fig. 4B) and a squamoid pattern in its surroundings were observed. Osteoclast-like polymorphic and giant cells were spotted. Little necrosis was spotted in the tumor tissue. The invasion of carcinoma cells into lymphatic vessels and blood vessels was severe. Metastasis of the thyroid carcinoma was found in the lung, liver, spleen, small intestine, kidney and skin around the thoracic area.

Immunohistochemical staining of PTHrP using a $\times 1000$ dilution of anti-PTHrP(1-34) rabbit serum (Yanaihara Institute Inc., Shizuoka, Japan) showed that specimens of the resected tumors of the thyroid (Fig. 4C), liver, kidney, spleen, skin and small intestine (data not shown) were all positively stained to the same degree. The membrane and cytoplasm of the carcinoma cells were stained by anti-PTHrP(1-34) antisera.

Immunohistochemical staining of p53 using a $\times 100$ dilution of mouse p53 monoclonal antibody (DO-7, Novocastra Laboratories Ltd., Newcastle upon Tyne, UK) showed that species of the resected tumor of the thyroid were negatively stained.

Discussion

We have reported a rare case of a patient with anaplastic thyroid carcinoma with HHM diagnosed through an autopsy.

An anaplastic thyroid carcinoma is diagnosed using various images, such as ultrasonography, scintigraphy, and histopathological findings. In the present case, cytology of the thyroid tumor showed the suspected

Fig. 2. Neck MR image

Her neck mass showed low- and high- intensity on T1- (A) and T2- (B, C) weighted MR images, respectively. The right mass oppressed the common carotid artery and internal jugular vein and shifted the trachea to the left.

Fig. 3. Thyroid ^{123}I and ^{201}Tl scintigraphy and whole body ^{67}Ga scintigraphy scan

Her right neck mass was cold on ^{123}I scintigraphy (A) and strongly hot in early phase ^{201}Tl scintigraphy (B) and decreased in washing-out in the delayed phase (C). Whole body ^{67}Ga scintigraphy scan showed a strong hot accumulation in the area from the left thyroid lobe to the lateral neck and hot accumulation in the chest region. Multiple lung tumors were observed from chest CT scans (D).

Fig. 4. Pathology of the thyroid carcinoma

Most of the tumor tissue in her neck consisted of anaplastic cancer nests, including carcinoma cells with large and atypical nuclei (A). A papillary pattern beside the trachea (B) and a squamoid pattern in its surroundings were observed. Osteoclast-like polymorphic and giant cells were spotted. The membrane and cytoplasm of the carcinoma cells were stained by anti-PTHrP(1-34) antisera (C).

papillary carcinoma because intranuclear cytoplasmic inclusion was observed. However, some images showed anaplastic thyroid carcinoma. The pathological findings show that the thyroid tumor in the present case is mainly an anaplastic carcinoma associated with papillary carcinoma, suggesting the occurrence of an anaplastic transformation of a differentiated thyroid carcinoma [19–21].

Mutations of the p53 tumor suppressor gene play a major role in the development of many carcinomas, namely in the colon, breast and bladder [22–24]. The activation of the p53 gene is a late event associated with the most advanced stages of tumor progression [19, 21, 25–27]. Furthermore, overexpression of p53 plays a role as a prognostic factor of human thyroid

carcinoma [28]. In literature, the incidence of p53 alterations in poorly differentiated and anaplastic carcinomas of the thyroid is reported to be 22–86% [19, 29–31]. However, the present case did not show such findings of p53 overexpression.

Our patient's thyroid carcinoma was inoperable, and she was elderly and she and her family refused to allow chemotherapy or radiation treatment, or to undergo an operation. Therefore, we chose local percutaneous injection therapy in the neck for her thyroid carcinoma.

PEIT has been established as being effective for thyroid cysts and functioning nodules [32, 33], as well as for thyroid carcinomas [34]. Furthermore, lip-PEIT was reported to be more effective than ethanol (PEIT) alone for solid thyroid tumors, including carcinomas

Table 3. Some cases of patients with thyroid carcinoma and HHM

	Age	Sex	Histology	Ca (mmol/l)	Intact-PTHrP	PTHrP-C	PTHrP (1–87)	Authors and References
1	60	F	PC	2.79	138 pg/ml (<20)*			Ito <i>et al.</i> (16)
2	58	F	PC	2.54–2.84	284 pg/ml (<20)			Ito <i>et al.</i> (16)
3	67	F	Anap.	3.44		164 pmol/l (13.8–55.3)*	4.02 pmol/l (<1.1)*	Yazawa <i>et al.</i> (15)
4	84	F	Anap.	2.72	3.2 pmol/l (<1.1)			Present case

Abbreviations: PC, papillary carcinoma; Anap., anaplastic carcinoma.

*Numbers in parentheses indicate the normal range.

[33]. However, the pathological findings in the present case suggest that lip-PEIT may not be effective for large thyroid carcinomas. Although the strategies to diagnose and treat the anaplastic carcinomas have been progressing, the prognosis of anaplastic thyroid carcinomas is still rather poor [6–11, 35, 36].

As serum calcium levels were high and serum phosphate levels were low in the present case, primary hyperparathyroidism and HHM were initially suspected. Blood levels of intact-PTH and 1α -25(OH)₂ VD were low, while PTHrP was high in sera. At this point in time, there were no signs of a metastatic bone tumor of the thyroid carcinoma. She was diagnosed as having HHM. Her laboratory data corresponded to the report that PTHrP has essentially the same actions as PTH through common receptors for PTH/PTHrP to elevate plasma calcium [37]. Based on the report that the receptor binding and activation domains of PTHrP are

contained within the first 34 amino acids [38], we underwent an immunohistochemical staining of the primary thyroid carcinoma and metastatic tumors at several sites using anti-PTHrP(1–34) antisera. The findings of the immunohistochemical stain in the present case confirmed that thyroid carcinoma cells produced PTHrP. Pathological findings of the PTHrP staining of the primary and metastatic thyroid carcinoma suggest that HHM may involve the increasing of PTHrP-producing cells, but not the thyroid carcinoma's transforming to anaplastic carcinoma. To the best of our knowledge, HHM caused by a thyroid carcinoma has been reported in only 4 cases, including present case (Table 3).

Thus, we have reported a rare autopsy case of a patient with a PTHrP-producing anaplastic thyroid carcinoma.

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