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Hyperthyroidism and Primary Thyroid Osteosarcoma with Lung Metastasis

Chih-Fan Chen[1], Yang-Fan Liu[2], and Pei-Wen Huang[3]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, [2]Division of Chest Surgery, Department of Surgery, [3]Department of Pathology, Hsinchu Mackay Memorial Hospital, Hsinchu City, Taiwan

Abstract

Primary thyroid osteosarcoma is a very rare primary malignancy of the thyroid gland. Only a dozen of cases were reported in published journals. We reported a case of a 83-year-old male who originally presented with diarrhea and weight loss. He had a history of hyperthyroidism and had been taking methimazole before thyroid ultrasound found a 3.5cm left nodular goiter with intrathoracic extension. Fine needle aspiration cytology reported negative for malignant cells. Three years later, the patient was admitted due to dyspnea and blood-tinged sputum. Chest X ray and CT scan found enlargement of the left thyroid lobe with calcification and thoracic extension, nodules in both lungs and trachea. He was immediately intubated and underwent surgical removal of intrathoracic goiter and right lung nodule. The pathology reported left intrathoracic thyroid osteosarcoma with lung metastasis. Removal of the tracheal nodule and tracheal stent implantation were performed via bronchoscopy. Palliative chemotherapy was prescribed and radiotherapy was planned. However, due to rapid progression of the residual tumor causing compression and obstruction of airway, he died of respiratory failure. The primary thyroid osteosarcoma is well-differentiated but with special characteristics of rapid tumor growth and coarse calcification. Urgent surgical intervention needs to be considered due to rapid progression, which determines the prognosis of thyroid osteosarcoma. (J Intern Med Taiwan 2021; 32: 56-62)

Key Words: Hyperthyroidism, Primary thyroid osteosarcoma, Lung metastasis

Introduction

Primary thyroid osteosarcoma is a very rare well-differentiated primary malignancy of the thyroid gland. Here we present the clinical features, biochemistry, imaging finding, and management of a patient with primary thyroid osteosarcoma.

Case Presentation

An 83-year-old male patient had history of duodenal ulcers, chronic kidney disease, and benign prostate hyperplasia post transurethral resection of the prostate (TURP). Due to persistent diarrhea and weight loss of 12 kilograms within one year, he visited our family medicine physician. Thyroid function tests detected suppressed thyroid stimulating hormone (TSH) < 0.0025 IU/ml (reference range 0.35-4.94 IU/ml) with elevated free T4 level 3.67 ng/dl (reference range 0.71-1.48 ng/dl), and TSH receptor antibody 43% (reference range <14%). Methimazole was prescribed for two years until he achieved euthyroid status. Thyroid ultrasonography found left

Reprint requests and correspondence：Dr. Chih-Fan Chen
Address：Division of Endocrinology and Metabolism, Department of Internal Medicine,Hsinchu Mackay Memorial Hospital, No. 690, Sec. 1, Guangfu Rd., East Dist., Hsinchu City, Taiwan

thyroid tumor more than 3.5 cm in size, with intrathoracic extension (Figure 1). Fine needle aspiration cytology twice reported negative for malignant cells. Tc99m thyroid scan revealed left thyroid gland was enlarged with uneven radioactivity distribution. Multinodular goiter on the left side was suspected (Figure 2). His thyroid disease was subsequently followed at the local clinic.

Three years later, the patient visited our outpatient pulmonary department because of hemoptysis. The chest X-ray and chest CT reported enlargement of the left thyroid lobe with calcification and thoracic extension, along with nodules in both lungs and trachea (Figure 3, 4). Dyspnea and stridor were noted for one day, and he was sent to ER. Arterial blood gas showed hypercapnic respiratory acidosis. Diagnosed with intrathoracic goiter with acute respiratory failure, he was immediately intubated with mechanical ventilator support.

Low TSH 0.1240 μIU/ml, normal free T4 1.15 ng/dl, and mildly elevated TSH receptor antibody 19% were found. Methimazole was prescribed for

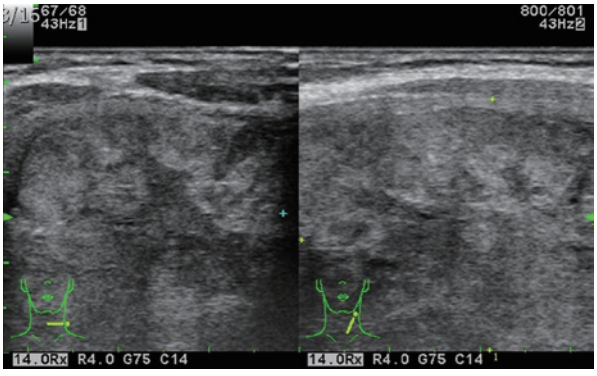


Figure 1. Thyroid ultrasonography showed a heterogenous left nodular goiter more than 3.5cm with intrathoracic extension.

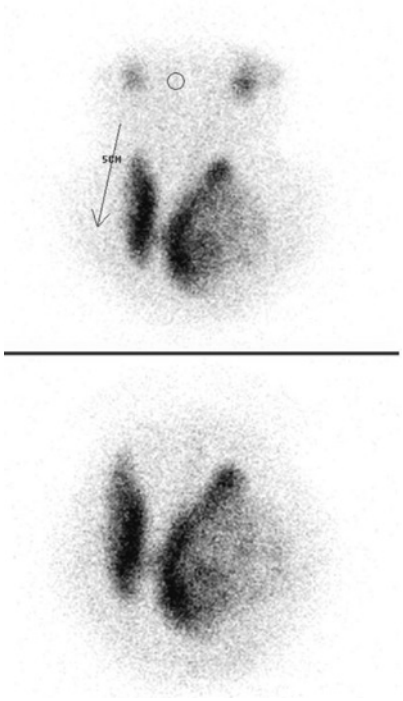


Figure 2. Tc99m thyroid scan revealed left thyroid nodular goiter with uneven radioactivity distribution.

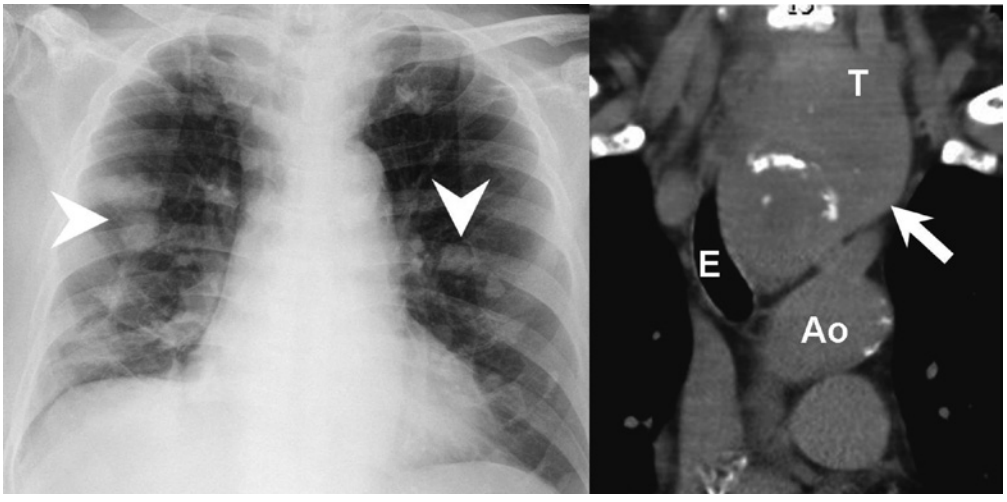


Figure 3 and 4. Chest X-ray and CT reported enlargement of left thyroid lobe with calcification and thoracic extension, plus multiple nodules in both lungs and trachea.

one month before he underwent surgical removal of intrathoracic goiter and lobulated tumor and the pulmonary nodule in the superior segment of right lower lung lobe. The pathology reported left intrathoracic thyroid osteosarcoma with right lower lung metastasis. Microscopically, the sections showed a fairly defined tumor composed of spindle or polyhedral neoplastic cells with nuclear atypia and frequent mitoses. Some scattering thyroid follicles were seen within the tumor. Areas with neoplastic cartilage and bone intimately associated with tumor cells were seen (Figure 5, 6). The tumor cells were positive for vimentin and CD99, and negative for CK, EMA, TTF-1, thyroglobulin and CD31. In the lung wedge resection tissue, a tumor mass with massive hemorrhage and necrosis was observed. The tumor cells were positive for vimentin and negative for CK and p63 (Figure 7). Immunostaining of thyroid osteosarcoma was negative for PAX8 (Figure 8).

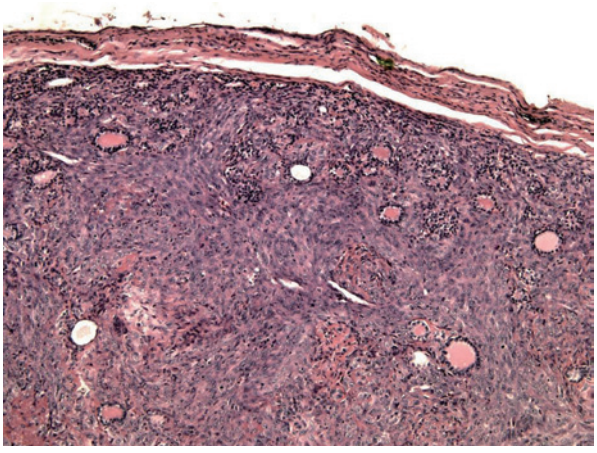


Figure 5. (100x) A fairly defined tumor composed of spindle or polyhedral neoplastic cells with nuclear atypia and mitoses.

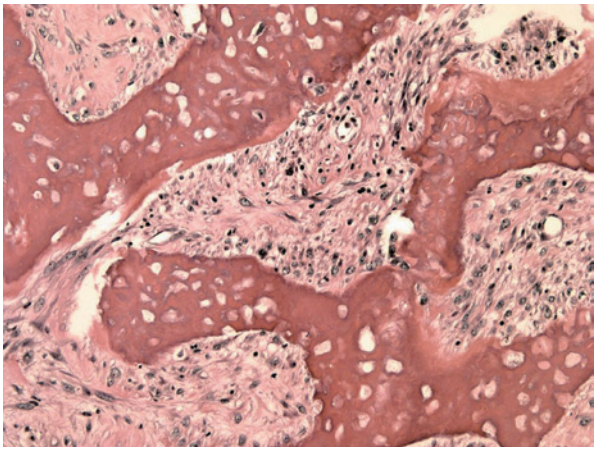
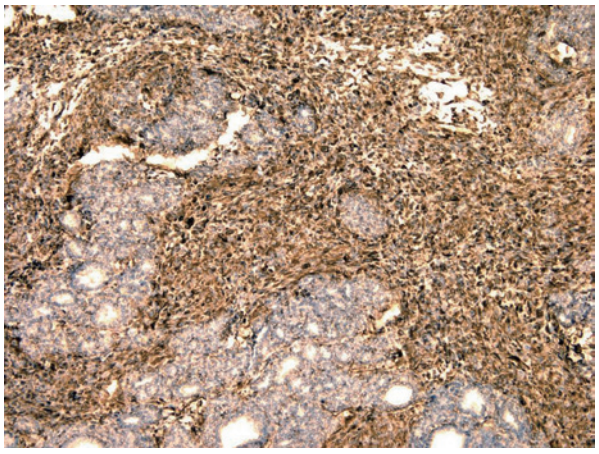


Figure 6. (200x4) Neoplastic cartilage and bone were observed .



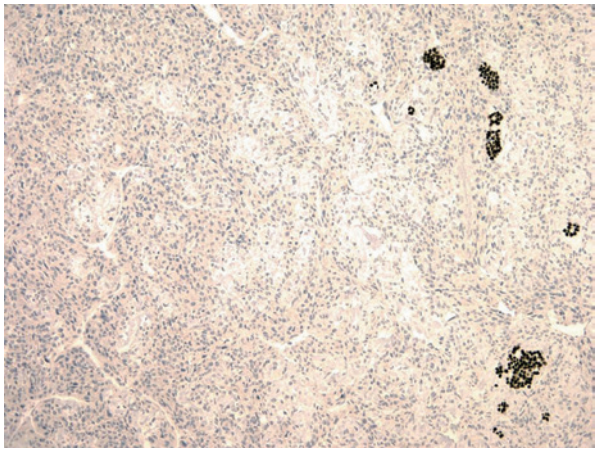


Figure 7. Immunostaining of thyroid osteosarcoma positive for vimentin and negative for CK (epidermal marker).

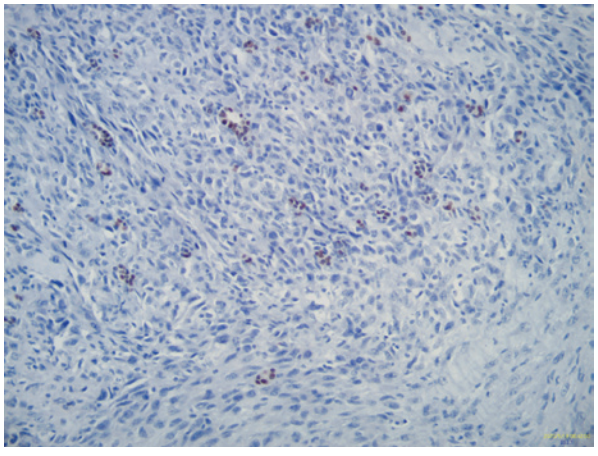


Figure 8. (400x) Immunostaining of thyroid osteosarcoma negative for PAX8.

Due to primary thyroid osteosarcoma with lung metastasis and dyspnea deterioration, the patient received intraluminal tracheal stenting via bronchoscopy. Palliative chemotherapy of epirubicin and cyclophosphamide were prescribed. However, secondary chemotherapy was discontinued because of impaired renal function. Follow-up chest CT revealed rapid progression of the residual tumor in the left superior mediastinum and hypopharynx causing right displacement of the airway. Parenteral corticosteroids, oxygen, and bronchodilator inhalation were given for symptomatic relief. However, as the rapidly growing residual tumor increasingly compressed and obstructed the airway, the patient developed apnea and bradycardia. He eventually died of respiratory failure after total thyroidectomy in two and a half months.

Discussion

In 2014 WHO sarcoma classification, sarcoma was divided into different categories such as chondrogenic, osteogenic, fibrogenic, fibrohistiocytic Ewing sarcoma, osteoclastic giant cell-rich notochordal, vascular, myogenic, lipogenic, and epithelial, tumors of undefined neoplastic nature, and undifferentiated high-grade pleomorphic sarcoma. Osteosarcoma was included in the category of osteogenic sarcoma [1]. According to the 2016 Taiwan cancer registry annual report, osteosarcoma was found over nose (one male patient, two female patients), ear, and bone area (29 male patients, 26 female patients). Osteosarcomas are common primary malignant tumors of the bone in adults, and often found in children or adolescents[2]. Extraosseous primary osteosarcoma occupies less than five percent[3] and has been reported in breast, lung, urinary bladder, prostate, and heart[4]. There were only a dozen of thyroid osteosarcoma published in the previous literature.

Primary osteosarcoma of the thyroid was first described by Foerster in 1860[1,5]. The classification of differentiated thyroid malignancy includes follicular, papillary, and medullary[6]. Primary thyroid sarcoma was reported to range between 0.01 to 1.5%[7]. Here we reported the complete management course of an extremely rare primary thyroid sarcoma with neck metastases and trachea invasion, which was easily misdiagnosed as poorly differentiated or anaplastic thyroid cancer[8,11].

Clinical presentation included long-term goiter, rapidly enlarging neck mass, recurrent hoarseness, dysphagia, cough, or shortness of breath. The mean age of diagnosis is over forty years, peaking at about 60-79 years old. The female-to-male ratio is 1.5-1:1[8]. We reviewed seventeen journal articles and noted that the most common symptom is rapid growing mass within one to three months with an average age of about 54 years old (36-82 years)[3,4, 8-21]. The tumor is often large, firm, solid, and non-tender. The size of tumor ranges from 2 to more than 10 cm, so it can easily induce airway obstruction or swallowing difficulty, or even causes superior vena cava syndrome[11]. Tumor is located commonly at the right side, but sometimes bilaterally that compresses trachea or mediastinum.

Thyroid function is usually within normal range, but some cases develop symptoms of palpitation and thyrotoxicosis. With our patient, he had predominant increased TSH receptor antibody 43% (reference range <14%), so autoimmune thyroid disease resulted in hyperthyroidism. After methimazole treatment, diarrhea improved and weight returned about 2 kilograms. However, it might be related thyroid osteosarcoma that body weight regained not so much. Hyperthyroidism due to thyroid cancer was discussed in the several journals. Neoplastic cells infiltration destroys normal thyroid cells, which results thyroid hormone is released from thyroid follicular cells. One of the possible reasons has been postulated that increased production of antibodies to the TSH receptor, which upregulates cell activation and growth[22]. Somatic mutation in TSH recep-

tor genes of the cancer cells actives cyclic adenosine monophosphate (cAMP) cascade which induces hormonogenesis[23]. But these theories need further study to verify.

Thyroid ultrasonography characteristics include heterogenous, hypoechoic, mass with irregular margin, accompanied by extensive hyperechoic calcification and abundant blood flows. The atypical dense coarse calcification can be found in neck X ray[10,17]. Fine needle aspiration cytology reported rare atypical cells or no evidence of malignancy cells[9,10, and 19]. Possible cause might be that calcification impends the penetration of fine needle, resulting in delayed diagnosis or misleading the physician to overlook the severity of the tumor. Core needle biopsy was administered in two cases of these journals, which found malignant neoplasm with osteoid areas or sclerotic fibrous tissue[10,19]. However, anaplastic thyroid carcinoma may show osteoid and chondroid cells pattern (carcinosarcoma). CT of osteosarcoma shows heterogenous, multiple thyroid nodules, and irregular margin, with special characteristics of calcification patch and ossified mass. Tumor is typically separated from the major neck vessels and the trachea is significantly narrowed and displaced[8,10,15].

According to previous systematic review, the pathology of primary thyroid sarcoma was most frequently diagnosed in angiosarcoma, malignant hemangioendothelioma, malignant fibrous histiocytoma, and leiomyosarcoma. The differential diagnosis included anaplastic thyroid carcinoma, medullary thyroid carcinoma, spindle epithelial tumor with thymus-like differentiation (SETTLE), synovial sarcoma, and metastasis of osteosarcoma. Cytology frequently shows a high degree of cell polymorphism[8,24]. Immunohistochemical examination carries important significance for differential diagnosis. Vimentin staining is positive, while cytokeratin, TTF-1(thyroid transcription factor-1), calcitonin, chromogranin, synaptophysin, and S-100 staining are mostly negative[8,9]. The clinical presentation, ultrasonography, histologic pattern, and immunohistochemical staging differentiation of thyroid malignancy were listed in table 1.

Conventional osteosarcoma is subclassified based on histologic features (e.g., osteoblastic, chondroblastic), but they are not related to the treatment and prognosis[1]. Metastasis is commonly found in lungs and bones and patients died within 12 months of diagnosis because of tumor recurrence, metastasis, or local extension after aggressive therapy[5]. Surgical intervention is the first choice owing to the rapid tumor progression observed within its clinical course. The standard chemotherapy for treating conventional osteosarcoma includes methotrexate, doxorubicin, and cisplatin. In metastatic and recurrence disease, chemotherapy of etoposide plus ifosfamide, with or without carboplatin might be considered. In isolated pulmonary metastases patient, long term survival possibly attaches to 50 percents but most metastatic osteosarcoma have a poor prognosis[25]. Because of old age, we chose de-escalation chemotherapy from doxorubicin to epirubicin and from ifosfamide to cyclophosphamide. They decreased the toxicity and side effect of chemotherapy to our patient. After neoadjuvant chemotherapy, the degree of tumor necrosis is an important prognostic factor[26]. With our patient, we even performed intraluminal tracheal stenting. However, the rapidly growing tumor narrowed the trachea and induced respiratory failure. Local radiotherapy or tracheostomy might be considered for its management.

Conclusion

We shared a case of well-differentiated primary thyroid osteosarcoma with characteristics of rapid progression and coarse calcification that requires urgent surgical intervention. It mimics anaplastic thyroid carcinoma associated with poor prognosis.

Table 1. Comparison of thyroid malignancy

	Thyroid osteosarcoma	DTC	ATC
Clinical presentation	rapid growing tumor, dysphagia, dyspnea	most no symptoms, enlarging nodules	rapid enlarging painless tumor, hoarseness
Blood test	euthyroid status or hyperthyroidism	most euthyroid or hyperthyroidism	euthyroid or hypothyroidism
Ultrasound	hypo or iso-echoic, coarse calcification, trachea and esophageal compression	hypoechoic, irregular margin, microcalcification	hypoechoic, invasion to adjacent tissue
Histologic pattern	spindle or polyhedral pattern, frequent mitoses, neoplastic cartilage and bone	PTC: papillary structure, grooving, Psammoma bodies FTC: poorly formed follicles, invasion of capsule and vessels MTC: round, polyhedral, spindle cells patterns, amyloid stroma	spindle cell, pleomorphic giant cell, squamoid cell pattern, mitosis
Immunohistochemical markers			
PAX8	-	+	+/-
TTF-1	-	+	-/+
Thyroglobulin	-	+	-
Synaptophysin	-	- (MTC +)	-
Chromogranin	-	- (MTC +)	-
Calcitonin	-	- (MTC +)	-
CEA	-	- (MTC +)	-
p53	-/+	- (invasive +)	+
Vimentin	+	-	+/-
S100	-	+	-
CD99	+	-	-
CE31	-	-	-
Management	thyroidectomy, chemotherapy, radiotherapy	thyroidectomy, radioiodine ablation, target therapy	thyroidectomy, chemotherapy, radiotherapy, target therapy

Abbreviation: DTC, differentiated thyroid carcinoma; ATC: anaplastic thyroid carcinoma; PTC: papillary thyroid carcinoma, FTC: follicular thyroid carcinoma, MTC: medullary thyroid carcinoma; PAX-8, paired-box gene 8; TTF-1, thyroid transcription factor-1; CEA, carcinoembryonic antigen; p53, tumor protein p53; S100, S-100 proteins; CD99, leukocyte common antigen 99; CD31, leukocyte common antigen 31.

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甲狀腺功能亢進與原發性甲狀腺惡性骨肉瘤合併肺臟轉移

陳智帆[1] 劉洋帆[2] 黃佩雯[3]

新竹馬偕紀念醫院 [1]內分泌科 [2]胸腔外科 [3]病理科

摘 要

惡性骨肉瘤(osteosarcoma)罕見原發於甲狀腺的部位，目前在期刊發表只有十多個案例。病人起初以腹瀉與體重減輕為表現，接受抗甲狀腺藥物(antithyroid agents)治療甲狀腺功能亢進。甲狀腺腫瘤經穿刺細胞學檢查(fine needle aspiration cytology)，並無發現惡性細胞(negative for malignancy cells)。後來呼吸困難與咳嗽痰中帶血，發現甲狀腺腫瘤中有鈣化斑塊，壓迫氣管造成呼吸衰竭，甲亢治療穩定後進行手術，病理報告是原發性甲狀腺惡性骨肉瘤，術後接受化療與放射線治療。原發性甲狀腺惡性骨肉瘤(primary thyroid osteosarcoma)，是分化良好的甲狀腺腫瘤，容易與治療預後不佳的甲狀腺不分化癌(anaplastic thyroid carcinoma)混淆，有大片鈣化斑塊是特徵之一。甲狀腺惡性骨肉瘤成長速度極快，且腫瘤位於致命的呼吸道位置，需外科緊急介入手術，是影響預後的關鍵因素。