Parathyroid Carcinoma with Sarcomatoid Differentiation: A Case Report and Literature review

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Case Report

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Abstract

Background

Parathyroid carcinoma (PC) is a rare thyroid tumor. PC with sarcomatoid differentiation(PCSD) is even rarer and its exact etiology remains unclear. We here report a case of PCSD, and present the clinicopathological features and pathological diagnosis and review the literature.

Case presentation

A 71-year-old man presented with a mass of 4.5 cm × 3.5 cm in the right neck. The tumor was composed of nest-like transparent cells, and the septum had heterotypic rhabdoid cells with sarcomatoid differentiation. Immunophenotype was as follows: MyoD1, myogenin and desmin were positive; clear cells were positive for CGA, Syn and GATA-3; and Ki-67 proliferation index was 40%. Hematoxylin and eosin staining and immunohistochemistry were performed. The patient was diagnosed with PCSD, and died 6 months after surgery.

Conclusions

PCSD is a rare type of primary parathyroid tumor with high malignancy and poor prognosis. Definitive diagnosis should be based on histopathological morphology and immunophenotype, and surgical treatment should be performed as soon as possible.

Background

Parathyroid carcinoma(PC) is one of the rare cancers, accounting for less than 4% of cases of parathyroid diseases in the United States. DeQeurvain first described PC in 1904, which is characterized by high blood calcium and parathyroid hormone (PTH) levels. [1] However, PCSD is even rarer as a clinical solid tumor type. Nacamuli Randall first described this special type of parathyroid tumor in 2002. [2] Since then, only four such cases have been reported including 2 cases abroad and 2 cases in China. The exact etiology of PC with sarcomatoid differentiation remains unclear. Typical clinical manifestations may include hypercalcemia and high PTH level. It does not differ significantly from a general PC, but the tumor is more aggressive and has poor prognosis.

Case Presentation

Chief complaints

A 71–year-old male patient was admitted to hospital for hoarseness for > 1 month.

Imaging examination

Ultrasound showed that the right thyroid was enlarged, bilateral thyroid nodules were present, the right larger nodules were about 4.5 · 3.5 cm, belonging to TI-RADS 4a type, and the left nodules belonged to TI-RADS 3 type (Fig. 1). Enhanced computed tomography (CT) showed a space-occupying lesion in the right thyroid area, invading the trachea and mediastinum (Fig. 2).

Laboratory examination

Auxiliary examination showed that blood calcium was 2.34 (2.0–2.69) mmol/L, blood phosphorus 1.02 (0.87–1.45) mmol/L, PTH 89.1 (12.0–65.0) pg/ml, and tumor markers and other tests were all normal. Postoperative PTH was 40.9 (12.0–65.0) pg/ml, and serum calcium was 2.11 (2.0–2.69) mmol/L.

Pathological examination

Intraoperative frozen section pathology showed a malignant tumor with necrosis in the right thyroid area, which was confirmed by routine test and immunohistochemistry. Postoperative pathology suggested a malignant tumor in the right thyroid area, combined with immunohistochemical results, which was consistent with carcinosarcoma composed of rhabdomyosarcoma, and this case was of parathyroid origin (Fig. 3). Immunohistochemical results were as follows: cytokeratin (CK)5/6(−), P63(−), TG (−), PAX-8(−), CK7(−), CD30(−), Ki-67(40%+++), Bcl-2(−), cyclin D1 (+), HMB45(−), S-100(−), melan A (−), transcription termination factor-1 (−), CK (Pan)

(partial +), smooth muscle actin (−), desmin (partial +), myoblast determination protein (MyoD)1 (partial +), myogenin (partial +), epithelial membrane antigen (EMA) (partial +), CgA (partial +), Syn (partial +), TFE3 (−), GATA-3 (+), p53 (−) (Fig. 4).

Final diagnosis

PCSD.

treatment and outcome

This patient underwent palliative resection of the right neck mass. Intraoperative exploration revealed a large mass of about 6 cm in the right thyroid area, with unclear boundary, invading the esophagus and trachea, because the tumor invaded the surrounding organs severely and could not be completely separated, palliative resection was performed. This patient refused any further treatment after surgery, and died 6 months after surgery.

Discussion And Conclusions

PC is one of the rarest cancers. The 5-year survival rate of PC has been reported to be 78–85%, and the 10-year survival rate 49–77% [3–5]. It accounts for about 0.005% of all cancers [6]. The overall annual incidence rate is less than 1 case per million population.[7–8] The Surveillance, Epidemiology, and End Results (SEER) database showed that the incidence rate of parathyroid carcinoma was 3.6/10 million in 2000–2012. [8] The incidence rate of PC in Finland was 7.14/10 million from 2000 to 2013. [9] According to Xing XP, a Chinese scholar, among patients with primary hyperparathyroidism (PHPT) confirmed by surgery and pathology, PC accounted for 3.10–10.53%, [10] while PC accounted for < 1% of all PHPT patients in Europe and the United States, and 5% in Japan. [11, 12]

The exact pathogenesis of PC remains unclear. At present, most researchers believe that the occurrence of PC is new rather than transformed from adenoma, which is based on the inference that there are different gene changes between parathyroid adenoma and adenocarcinoma. The major genes reported are *cdc73/ HRPT2* [13–15], *gcm2* [16, 17] and *prune2* [18]. The detection rate of *cdc73/ HRPT2* gene mutation in sporadic PC is 46–70% [19, 20]. Nonaka *et al*. considered that *gcm2* is the main regulatory gene of parathyroid development, and the marker is only expressed in the parathyroid gland, including normal parathyroid tissue and all forms of benign and malignant parathyroid lesions [16]. Additionally, abnormal expression of noncoding RNA including miRNA and long noncoding (lnc) RNA may also be involved in the development of PC [21]. In the future, lncRNA PVT1, GLIS2-AS1 and anti-Gcm2 antibodies may become markers for the diagnosis of PC [22].

The diagnosis of PCSD is generally based on the combination of histology, biology and radiology. Multidisciplinary cooperation is the best model. The diagnostic standard is as strict as for thyroid follicular carcinoma. Capsule invasion and/or vascular invasion, perineural space infiltration, tumor perforation into surrounding tissues and/or metastasis should be present. The main criteria for diagnosis are as follows: (1) the cancer cells are arranged in trabecular shape with thick fibrous septum; (2) there is capsule or adjacent structure infiltration; (3) vascular invasion; (4) mitosis; (5) lymph node and/or other organ tissue metastasis; and (6) *GATA3*, *cam5.2*, *SYN* and *CGA*, which are important regulatory genes in parathyroid development, are positive. The loss of parafibromin and the high expression of PGP 9.5 and galectin-3 are helpful for the diagnosis of PC. At the same time, some tumor suppressor genes such as *Rb*, *APC*, *p27* and *BCL2* are often not expressed or weakly expressed. When Ki-67 index is > 5%, physicians should be alert to the possibility of malignant tumor [23].

In this case, the capsule was thickened and parathyroid carcinoma cells were arranged in a diffuse sheet and trabecular manner. The tumor cells with clear cytoplasm and those with deviated eosinophilic nuclei were in a mixed, diffuse lamellar arrangement and central necrosis was seen. In addition to the classic microscopic features of PC, there were rhabdomyoid tumor cells with eosinophilic cytoplasm, nuclear deviation and obvious nucleoli (Fig. 3). During the operation, invasion of peripheral organs, elevated PTH, multiple positive immunohistochemical markers and genes were found, with rhabdomyosarcoma-like differentiation. After comprehensive consideration, PCSD was diagnosed.

Most PC patients have hypercalcemia, and about 3% of them have no clinical symptoms [24]. The results of biochemical tests and the diameter of parathyroid lesions in PHPT patients can predict PC. In PHPT, the best cut-off point for predicting the diameter of parathyroid lesions in PC is 3.0 cm [25]. A retrospective analysis showed that preoperative ultrasound examination of parathyroid

lesions > 15 mm was valuable in the diagnosis of PC [26]. PCSD is rare and only five cases (including our case) have been reported in the literature (Table 1).

Table 1
Parathyroid carcinoma with sarcomatoid differentiation reported in the literature

Authors	Sex	Age (yr)	Maximum diameter mass (cm)	Blood calcium	Blood PTH	Positive Immunophenotype	Sarcomatoid differentiation	Prognosis
Taggart *et al*.	Female	57	4	Normal	Normal	CgA and vimentin were positive	Undifferentiated	Lung metastasis
Nacamuli *et al.*	Male	54	9	Elevated	Elevated	AE-1, PTH, CgA, Syn, and desmin were positive	Rhabdomyosarcoma and chondrosarcoma	Lung metastasis, adrenal metastasis and death 7 mo after surgery
Zhang Haitao *et al*.	Female	57	7	Elevated	Elevated	CK, Syn, PTH, Ki-67 was 50%	Undifferentiated	Unclear
Guan Zhongyan *et al.*	Female	62	3.5	Normal	Undetermined	CK8/18, CgA, CD56, galectin-3 and vimentin were positive	Unclear	Lung metastasis, and death 5 months after surgery
Present case	Male	71	4.5	Normal	Elevated	Desmin, MyoD1, Myogenin, EMA, CgA, Syn, CK, GATA-3 were positive,Ki-67 was 40%	Rhabdomyosarcoma	Esophageal and mediastinal invasion and death 6 mo after surgery

Among these five cases, there were more women than men, and the tumor diameter was > 3.5 cm, which was consistent with the report of Bae *et al*. The optimal cut-off point for predicting the diameter of parathyroid lesions was 3.0 cm. The serum calcium level of most patients with PC was significantly higher than 3.5 mmol/L. Serum PTH levels in patients with PC are usually 3–10 times higher than the upper limit of normal [25, 26]. Elevated serum calcium and PTH are more common in patients with PCSD. Therefore, when the serum calcium level is 3 mmol/L and the parathyroid lesion is > 3 cm (i.e., the so-called > 3 + > 3 rule) or ionic calcium > 1.77 mmol/L, physicians should be fully vigilant about the possibility of PC [27].

Radical resection is the only way to cure PCSD. The first operation is particularly important and should be performed as soon as possible. During the first operation for PC, parathyroid tumor with ipsilateral thyroid en bloc lobectomy including isthmus and ipsilateral central lymph node dissection should be performed [28–30]. If the tumor adheres to peripheral soft tissue, such as banded muscle and esophageal muscular layer, it should be removed as extensively as possible. If the recurrent laryngeal nerve is invaded, it should also be removed. Unfortunately, most of the PCSD have a high degree of malignancy. Most of them had distant metastasis in the early stage after surgery, and most of the patients died within 1 year after surgery.

Prophylactic lateral cervical lymph node dissection is generally not recommended because it does not prolong survival and may increase the incidence of complications. However, if lateral cervical lymph node metastasis is confirmed before surgery, therapeutic dissection is required. The biggest difficulty in the selection of surgical methods is the low accuracy of intraoperative frozen pathological diagnosis of PCSD. Unless there is obvious capsule, vascular invasion or regional lymph node metastasis, there are generally few direct reports of parathyroid cancer. When PCSD is diagnosed by parathyroid pathology after surgery, it is advisable to supplement surgery in time according to parathyroid cancer.

Chemotherapy drugs are generally ineffective against PCSD[31], and there are only a few successful reports[32]. PCSD is not sensitive to radiotherapy. Although there are reports of adjuvant radiotherapy to reduce local recurrence after the initial operation[33], due to the small number of cases and short follow-up time, adjuvant radiotherapy may only be used in PCSD patients with high risk of recurrence[34]. For local lesions, such as lung metastasis and vertebral metastasis, there are also individual cases of attempting radiofrequency ablation or absolute alcohol or combined percutaneous vertebroplasty to destroy metastases[35].

PCSD is a rare type of primary parathyroid tumor with high malignancy and poor prognosis. Definitive diagnosis should be based on histopathological morphology and immunophenotype, and surgical treatment should be performed as soon as possible.

Abbreviations

parathyroid carcinoma
PC
parathyroid carcinoma with sarcomatoid differentiation
PCSD
parathyroid hormone
PTH
computed tomography
CT
primary hyperparathyroidism
PHPT

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from all participants. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, China, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor in-Chief of this journal.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conceptualization: Liang Hu and Xiaojun Xie.

Supervision: Liang Hu and Xiaojun Xie.

Writing – original draft: Liang Hu.

Writing – review & editing: Xiaojun Xie.

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Informed consent statement: Informed consent was obtained from the patient.

Written informed consent: Patient has provided informed consent for publication of the case.

Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this report.

Ethical statement: Written informed consent was obtained from the patient. Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital, School of Medicine,Zhejiang University, China, in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

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Figures

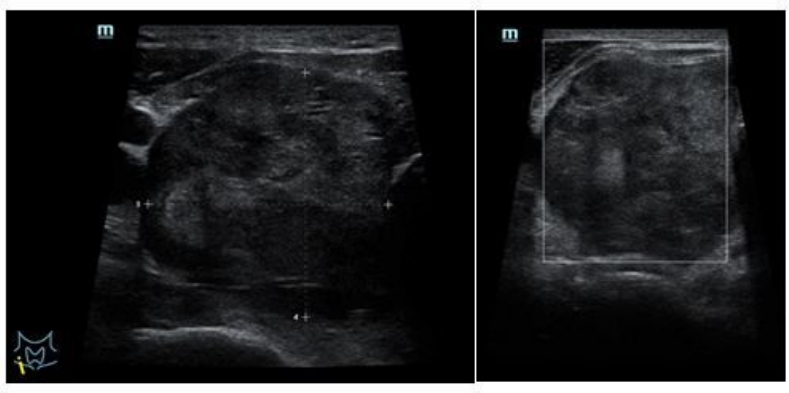

Figure 1

Ultrasonography showed a right thyroid mass.

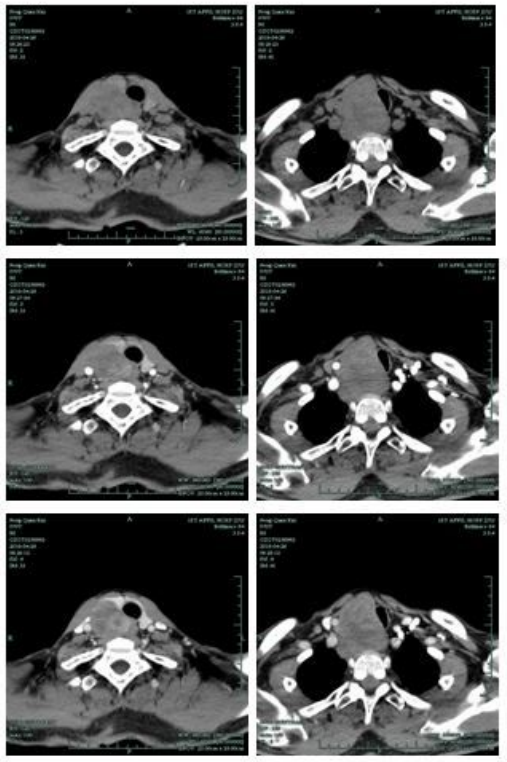

Figure 2

CT showed a large space-occupying lesion in the right thyroid region with invasion of the esophagus and mediastinum

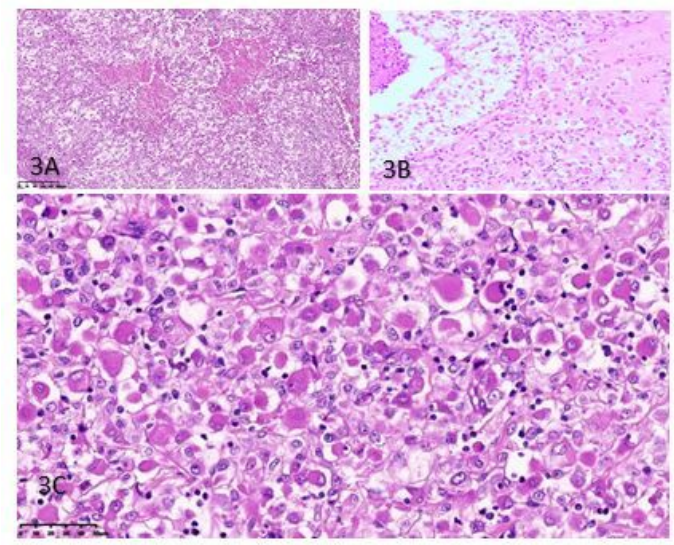

Figure 3

Tumor cells with clear cytoplasm and rhabdomyoid tumor cells with eosinophilic nuclei intermingled with diffuse patchy arrangement and necrosis in the center [hematoxylin and eosin (HE) 100□]. Junction between the typical parathyroid carcinoma cell region and the differentiated cell region of rhabdoid sarcoma (HE, 100□). Rhabdoid tumor cells, eosinophilic cytoplasm, nuclear deviation, and obvious nucleolus (HE, 400□).

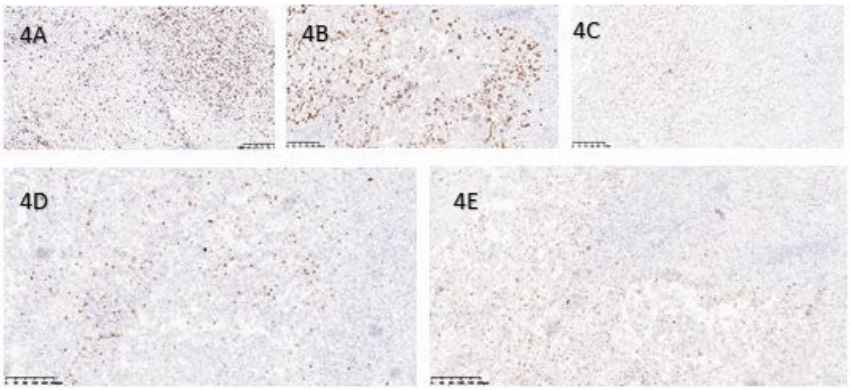

Figure 4

Ki 67 proliferation index was about 40%. esmin partially positive. GATA-3 positive. MyoD1 partially positive. myogenin partially positive.

Supplementary Files

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- CAREchecklist.pdf