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Case Report

A Case of Parathyroid Carcinoma in Renal Hyperparathyroidism

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Abstract

Introduction: Parathyroid carcinoma is a rare malignant endocrine tumor that is usually associated with primary hyperparathyroidism. The coexistence of parathyroid carcinoma and renal hyperparathyroidism is a rare phenomenon. Hence, we present a case of parathyroid carcinoma in a patient with tertiary hyperparathyroidism. ***Case Presentation:*** Our patient is a 31-year-old woman with a past medical history of end-stage renal failure (ESRF), on hemodialysis for the past 18 years. She was referred by her nephrologist to the endocrine surgery department for consideration of parathyroidectomy in view of long-standing tertiary hyperparathyroidism complicated by hypercalcemia. Bedside ultrasonography scan (US) of the thyroid revealed three parathyroid glands and a hypoechoic right lower pole thyroid nodule with central calcification. Fine-needle aspiration cytology was performed for the suspected thyroid nodule on the same day, which eventually yielded a follicular lesion of undetermined significance. A right hemithyroidectomy and total parathyroidectomy with deltoid implantation was performed. Intraoperative exploration revealed that the thyroid nodule noted at initial US was found to be the right superior parathyroid gland invading into the right thyroid itself. The right superior parathyroid gland was excised en bloc with the right hemithyroidectomy. Post-operatively, the patient was hypocalcemic but was discharged well on post-operative day 5. Histopathological diagnosis of the right hemithyroidectomy specimen containing the right superior parathyroid gland was consistent with that of

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parathyroid carcinoma. ***Conclusion:*** Parathyroid carcinoma is a rare entity that is difficult to diagnose. In patients with ESRF, the presence of concurrent tertiary hyperparathyroidism makes this even more challenging.

Introduction

Parathyroid carcinoma is a rare malignant endocrine tumor arising from the parathyroid glands, with an estimated prevalence of 0.005% of all malignancies. The first case of parathyroid carcinoma in literature was reported by De Quervain [1] in 1909. To date, there are about 1,100 cases of parathyroid carcinoma described in the literature, most of which are associated with primary hyperparathyroidism. The coexistence of parathyroid carcinoma and renal hyperparathyroidism is a rare phenomenon, with only 3% of parathyroid carcinoma cases associated with end-stage renal disease (ESRD) [2]. The first case of parathyroid carcinoma in renal hyperparathyroidism was reported by Berland et al. [3] in 1982, with only 55 reported cases in the literature. We present a case of parathyroid carcinoma in a patient with tertiary hyperparathyroidism.

Case Report

Our patient is a 31-year-old woman with a past medical history of end-stage renal failure, secondary to rapidly progressive glomerulonephritis from alpha-interferon-induced lupus-like activity and hepatitis B membranous nephropathy, for which she has been on hemodialysis for the past 18 years. In addition, she has a significant oncological history of bilateral renal cell carcinoma necessitating bilateral nephrectomy in 2014 complicated by multiple tumor recurrences.

She was referred by her nephrologist to the endocrine surgery department for consideration of parathyroidectomy in view of long-standing tertiary hyperparathyroidism complicated by hypercalcemia. Preoperatively, the patient's serum intact parathyroid hormone (PTH) was elevated at 262.2 pmol/L (normal: 1.6–7.2 pmol/L) and her serum calcium was 2.60 mmol/L (normal: 2.10–2.60 mmol/L). Bedside ultrasonography scan (US) of the thyroid revealed three parathyroid glands ranging from 1.5 to 2 cm in size, as well as a hypoechoic right lower pole thyroid nodule with central calcification measuring 1.91 by 1.79 cm (shown in Fig. 1). In view of the radiological findings, fine-needle aspiration cytology (FNAC) was performed for the suspected thyroid nodule on the same day, which eventually yielded a follicular lesion of undetermined significance (shown in Fig. 2). The patient was counseled on the radiological and pathological findings and was offered right hemithyroidectomy and total parathyroidectomy with deltoid implantation.

Intraoperative exploration revealed that the thyroid nodule noted at initial US was found to be the right superior parathyroid gland invading into the right thyroid itself. The right superior parathyroid gland was excised en bloc with the right hemithyroidectomy, and there was no macroscopic invasion of surrounding structures and muscles. The remaining 3 parathyroid glands were identified and excised and were clinically hyperplastic (shown in Fig. 3). Detailed examination of the thyroid beds did not reveal any additional palpable parathyroid glands or clinical lymphadenopathy. Post-operatively, the patient was hypocalcemic with a serum calcium of 1.98 mmol/L and was started on intravenous 5% calcium

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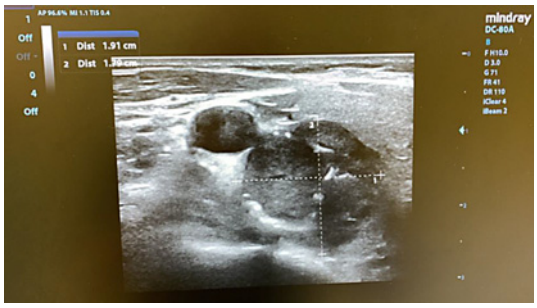

Fig. 1. US findings. A 1.91 cm by 1.79 cm hypoechoic thyroid nodule with central calcification was found in the right lower pole.

gluconate infusion and high calcium bath dialysis while inpatient. Our patient was discharged well on post-operative day 5 and seen in the clinic 3 weeks post-operatively.

Histopathological diagnosis of the right hemithyroidectomy specimen containing the right superior parathyroid gland was consistent with that of parathyroid carcinoma (shown in Fig. 4). The tumor cells appeared cytologically bland with inconspicuous mitotic activity. However, the carcinoma exhibited capsular and vascular invasion into the thyroid gland, with focal involvement of the circumferential margin. Notably, the isthmic margin was free of tumor. The other right inferior, left inferior, and left superior parathyroid glands were benign hypercellular parathyroid tissue, histologically consistent with parathyroid hyperplasia.

Discussion

This case illustrates the complexity of diagnosing parathyroid carcinoma in the context of tertiary hyperparathyroidism. The preoperative or intraoperative diagnosis of parathyroid carcinoma poses significant challenges. Preoperative diagnosis of parathyroid carcinoma can be challenging due to its nonspecific clinical manifestations and extensive similarities in clinical and biochemical features with benign parathyroid tumors. The finding of metastasis is the only certain criterion of malignancy. Hence, in the absence of thyroid infiltration, locoregional or distant metastases, it can be even more challenging for clinicians to make the diagnosis. In our case, the patient did not have any distant metastasis. There is no gold standard test to diagnose parathyroid carcinoma preoperatively. Currently, preoperative US of parathyroid lesions have some utility in differentiating parathyroid carcinoma from benign parathyroid lesions. Ultrasound features suggestive of malignancy include a larger parathyroid gland size, irregular shape, presence of calcification, invasion of surrounding tissue, and presence of suspicious lymph nodes. According to the guidelines of the American Association of Endocrine Surgeons, preoperative parathyroid FNAC is not recommended if parathyroid carcinoma is suspected [4]. This is due to the risk of tumor seeding the biopsy tract, as well as the possibility of hematoma or abscess formation, which might interfere with subsequent surgeries. In our case, the parathyroid carcinoma was initially thought to be a thyroid nodule on the US scan; as such, an FNAC was performed as part of a thyroid nodule workup.

The cellular resemblance between parathyroid cancer and follicular thyroid lesions further complicates the assessment of FNAC results. Overlapping characteristics include epithelial cells arranged in a microfollicular pattern and the presence of colloid-like material in the background. As shown in Figure 2, the FNAC features remarkably overlapped between a follicular lesion of thyroid origin and a parathyroid lesion. In our patient, the initial FNAC of the thyroid nodule revealed an follicular lesion of undetermined significance; however, the final histopathological diagnosis was consistent with that of parathyroid cancer. The

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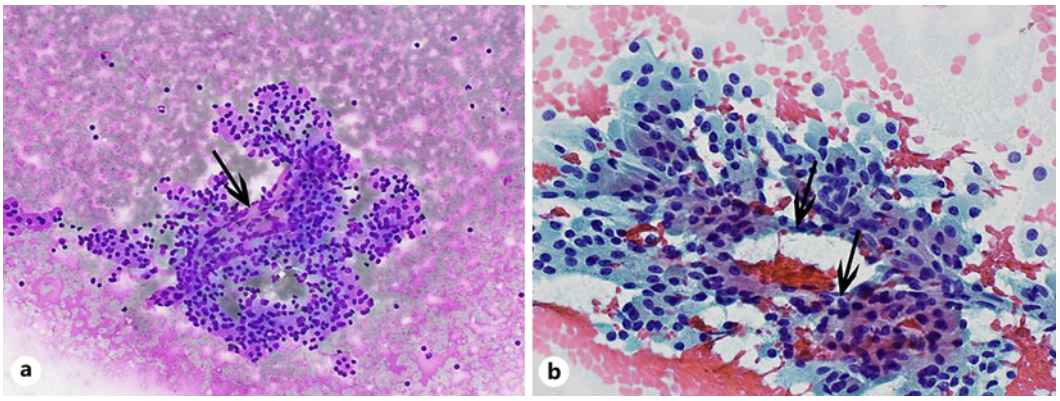

Fig. 2. Fine-needle aspiration cytology (FNAC) findings. **a** Sheet of monotonous lesional epithelial cells with crowding, nuclear overlap and occasional traversing capillary (arrow). There is no obvious colloid in the background (Hemacolor stain). **b** Lesional cells exhibit oncocyte-like morphology with mildly enlarged hyperchromatic nuclei and abundant granular cytoplasm. Occasional endothelial cells of traversing capillaries (arrows) are present (Papanicolaou stain).

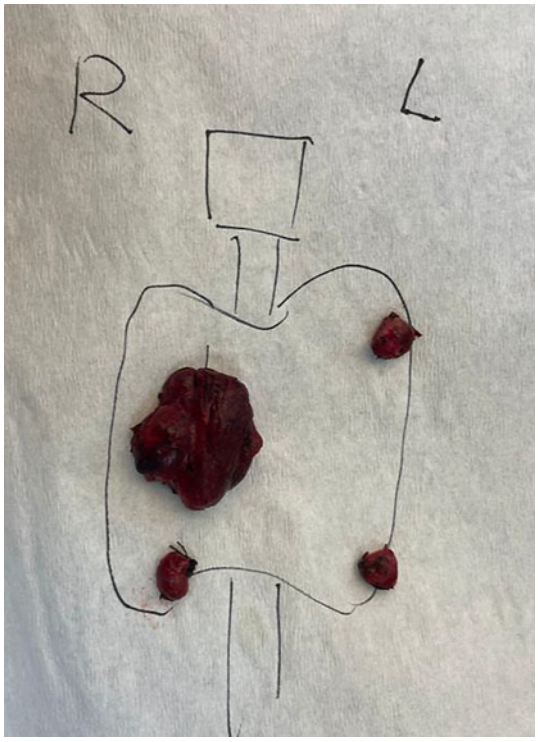

Fig. 3. Intraoperative image showing the excised right thyroid nodule containing the right superior parathyroid gland and the three other parathyroid glands.

histological definition of parathyroid carcinoma, according to Erikson et al.'s [5] overview of the WHO classification of parathyroid tumors in 2022, includes one of the following criteria: (a) invasion of blood vessels, (b) lymphatic invasion, (c) neural invasion, (d) invasion of local anatomical structures, or (e) metastasis that is histologically or cytologically identified. In our patient, histological examination revealed an infiltrative growth pattern with capsular and vascular invasion. Vascular invasion was confirmed with immunohistochemical detection of ERG (erythroblast transformation-specific-related gene) protein. These findings were highly suggestive of parathyroid malignancy.

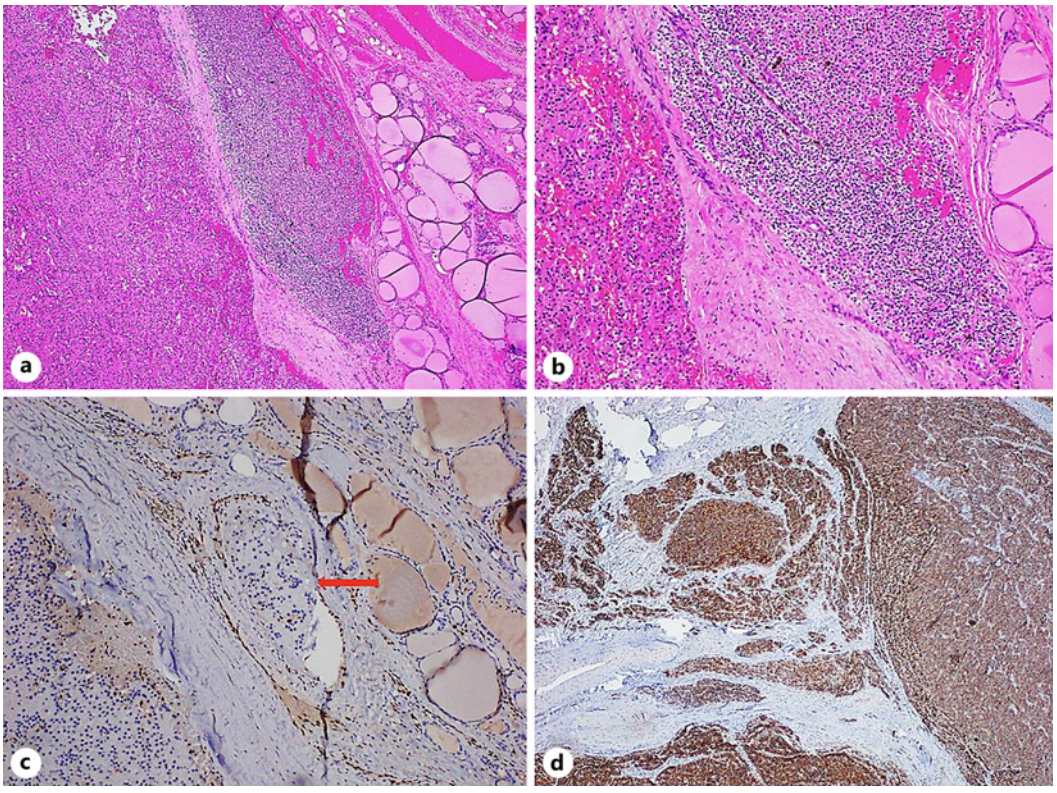

Fig. 4. Histopathological findings show parathyroid carcinoma exhibiting capsular and vascular invasion into the thyroid gland, with focal involvement of the circumferential margin. **a** Tumor demonstrates capsular invasion into adjacent thyroid gland parenchyma. H&E stain, ×40 magnification. **b** Tumor demonstrates capsular invasion into adjacent thyroid gland parenchyma. H&E stain, ×100 magnification. **c** Tumor demonstrates vascular invasion as highlighted by the red arrow. ERG immunohistochemical stain, ×100 magnification. **d** Parathyroid nature of the tumor is confirmed by diffuse strong expression with PTH immunohistochemical study. PTH immunohistochemical stain, ×40 magnification.

Immunohistochemistry may play a role in the diagnosis of parathyroid cancer. Majority of the genetic alterations known to affect parathyroid cancer occur in the *CDC73* germline gene, which encodes a protein called parafibromin, a nuclear protein that regulates cell growth and survival. It is estimated that parafibromin is responsible for up to 70% of sporadic parathyroid cancers [6]. Kim et al. [7] found that a negative or weakly positive parafibromin expression demonstrated a 94.4% specificity for the diagnosis of parathyroid cancer. Thus, parafibromin immunohistochemistry may be useful for identifying parathyroid carcinomas, especially those that do not have all the classic histological features.

Some studies have suggested that severe hypercalcemia (>14 mg/dL), very high serum PTH levels (five to ten times the upper limit of normal), the presence of a parathyroid crisis, simultaneous renal and skeletal manifestations, and palpable neck masses should raise suspicion for parathyroid cancer [8]. It should be highlighted, however, that serum calcium and PTH levels are not useful indicators of parathyroid carcinoma in patients with long-standing ESRD as the kidney develops autonomous parathyroid function and hypercalcemia. PTH levels in hemodialysis patients are often significantly elevated, ranging from two to nine times over the upper normal limit [9]. As a result, elevated PTH levels are commonly associated with ESRD and may be ineffective when used to diagnose parathyroid cancer. Our patient's preoperative workup revealed an elevated PTH level of 262.2 pmol/L (normal:

1.6–7.2 pmol/L) and an adjusted total serum calcium level of 2.60 mmol/L (normal: 2.10–2.60 mmol/L mmol/L) despite her being on oral cinacalcet 75 milligrams once daily.

Tertiary hyperparathyroidism occurs most commonly due to longstanding secondary hyperparathyroidism caused by chronic kidney disease. It is defined as chronic autonomous hypersecretion of PTH by the parathyroid glands, resulting in persistent hypercalcemia and elevated PTH serum levels that can remain even after resolution of the underlying renal disease such as with kidney transplantation. In patients with tertiary hyperparathyroidism, histopathological assessment of the parathyroid glands often reveals a hyperplastic process alone. The exact mechanisms behind the development of parathyroid cancer in the context of renal hyperparathyroidism remain unclear. However, it has been postulated that the sustained hyperphosphatemia and high levels of PTH leading to parathyroid hyperplasia may possibly contribute to neoplastic transformation. It is believed that mutations in the *CDC73* gene encoding parafibromin on chromosome 1q31.2 is the main gene responsible for parathyroid cancer. This mutation is found in less than 1% of benign parathyroid adenomas and is hence a strong indicator of parathyroid cancer. Parafibromin belongs to the hPAF transcriptional complex and facilitates transcription activity via histone modification and chromatin remodeling [10]. Parafibromin has tumor suppressive properties and regulates cell growth and division in parathyroid glands. Thus, mutations in CDC73 may result in a loss of parafibromin function, contributing to malignant change of the parathyroid glands.

A total of 90% of parathyroid cancers are hormonally functional tumors, which present with signs and symptoms of hypercalcemia due to high serum PTH levels [11]. Initially, the clinical presentation of parathyroid carcinoma closely resembles that of benign parathyroid hyperfunction, with non-specific signs and symptoms of hyperparathyroidism. It is only in advanced stages that patients manifest signs and symptoms indicative of local tumor growth and infiltration into adjacent tissues. Patients with parathyroid carcinoma in tertiary hyperparathyroidism usually present with symptoms of hyperparathyroidism, such as myalgia and arthralgia, weight loss, nephrolithiasis, as well as bone disease. The clinical features of hemodialysis patients who develop parathyroid cancer vary greatly and remain poorly understood. Imaging modalities such as ultrasonography, 99mTc-sestamibi scintigraphy, and magnetic resonance imaging may aid in identifying suspicious lesions, but histopathological examination of tumor tissue following surgical resection remains crucial for definitive diagnosis.

En bloc resection of the tumor with negative margins provides the best survival outcomes. Removal of the ipsilateral thyroid lobe or uninvolved ipsilateral parathyroid gland may be necessary to achieve this goal, but this has not been shown to improve survival in parathyroid carcinoma patients [12]. In certain circumstances, additional treatment options such as radiation therapy or chemotherapy may be considered. Specifically, several single or combination regimens, including dacarbazine alone or in combination with 5-fluorouracil and cyclophosphamide, have shown modest success in case reports [13]. Radiation therapy may be considered to relieve symptoms and enhance quality of life in individuals with inoperable symptomatic parathyroid cancer who have undergone all traditional therapies. However, the current evidence on adjuvant and neoadjuvant therapies is sparse, hence limiting their utility in treating parathyroid cancer. Parathyroid carcinoma is known to be a radio-resistant tumor; therefore, the use of radiotherapy is contentious. Similarly, chemotherapy is utilized even less than radiotherapy as no clinical trials have been published to evaluate its efficacy, with most treatment regimens coming from anecdotal experience and isolated case reports. In our patient, adjuvant therapy was not offered, and she was instead planned for regular surveillance.

Most parathyroid carcinomas are sporadic and occur with no known cause. However, there are established links between parathyroid carcinoma and specific genetic syndromes,

namely, multiple endocrine neoplasia syndromes types I and IIa, non-syndromic familial isolated primary hyperparathyroidism, as well as hyperparathyroidism-jaw tumor syndrome [14]. The patient in this case had no family history of hyperparathyroidism. However, she was referred to a geneticist in view of her previous primary malignancies.

In conclusion, parathyroid carcinoma is a rare entity that is difficult to diagnose. In patients with ESRD, the presence of concurrent tertiary hyperparathyroidism makes this even more challenging. Patients with ESRD and hypercalcemia with exceptionally high PTH may have their suspicion for parathyroid cancer disguised since the parathyroid carcinoma laboratory findings are frequently attributed to ESRD. Furthermore, the patient's young age should not rule out the likelihood of parathyroid cancer. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000536444); [15].

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Interpretation of histological images: B.W. and N.J.H.T. Draft and review of manuscript: V.M.Z., E.K.F.L., D.P., J.W.K.L., and R.P. Final approval of version to be published: R.P.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 De Quervain VF. Parastruma maligna aberrata. Deut Zschr Chir. 1909;100:334–52.
2 Favia G, Lumachi F, Polistina F, D'Amico DF. Parathyroid carcinoma: sixteen new cases and suggestions for correct management. World J Surg. 1998;22(12):1225–30.
3 Berland Y, Olmer M, Lebreuil G, Grisoli J. Parathyroid carcinoma, adenoma and hyperplasia in a case of chronic renal insufficiency on dialysis. Clin Nephrol. 1982;18(3):154–8.

4 Patel KN, Yip L, Lubitz CC, Grubbs EG, Miller BS, Shen W, et al. The American Association of Endocrine Surgeons Guidelines for the Definitive Surgical Management of Thyroid Disease in Adults. Ann Surg. 2020;271(3):e21–93.
5 Erickson LA, Mete O, Juhlin CC, Perren A, Gill AJ. Overview of the 2022 WHO classification of parathyroid tumors. Endocr Pathol. 2022;33(1):64–89.
6 Cetani F, Pardi E, Marcocci C. Parathyroid carcinoma. Front Horm Res. 2019;51:63–76.
7 Kim HK, Oh YL, Kim SH, Lee DY, Kang HC, Lee JI, et al. Parafibromin immunohistochemical staining to differentiate parathyroid carcinoma from parathyroid adenoma. Head Neck. 2012;34(2):201–6.
8 Machado NN, Wilhelm SM. Parathyroid cancer: a review. Cancers. 2019;11(11):1676.
9 (KDIGO) CKD-MBD Work Group. Chapter 1: introduction and definition of CKD–MBD and the development of the guideline statements. Kidney Int. 2009;76.
10 Chaudhary K, Deb S, Moniaux N, Ponnusamy MP, Batra SK. Human RNA polymerase II-associated factor complex: dysregulation in cancer. Oncogene. 2007;26(54):7499–507.
11 Shane E. Clinical review 122: parathyroid carcinoma. J Clin Endocrinol Metab. 2001;86(2):485–93.
12 Harari A, Waring A, Fernandez-Ranvier G, Hwang J, Suh I, Mitmaker E, et al. Parathyroid carcinoma: a 43-year outcome and survival analysis. J Clin Endocrinol Metab. 2011;96(12):3679–86.
13 Owen RP, Silver CE, Pellitteri PK, Shaha AR, Devaney KO, Werner JA, et al. Parathyroid carcinoma: a review. Head Neck. 2011;33(3):429–36.
14 Cardoso L, Stevenson M, Thakker RV. Molecular genetics of syndromic and non-syndromic forms of parathyroid carcinoma. Hum Mutat. 2017;38(12):1621–48.
15 Gagnier JJ, Kienle G, Altman DG, Moher D, Sox H, Riley D; the CARE Group. The CARE guidelines: consensus-based clinical case reporting guideline development.