Letter to the Editor

Occurrence of parathyroid carcinoma following parathyroid adenoma resection

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Introduction

Parathyroid carcinoma (PC) is an extremely rare malignant neoplasm that accounts for approximately 0.005% of all cancers (1). Distinguishing it from benign parathyroid adenoma (PA) can be difficult because of the absence of distinctive growth and histological characteristics and idiosyncratic serum calcium ion and parathyroid hormone (PTH) concentrations. In contrast to PA, local invasion and distant metastasis are frequent in PC even after radical excision, which is the standard treatment. We report a rare case of PC diagnosed in a patient who had previously undergone parathyroidectomy for PA that demonstrates the endocrinologic and oncologic challenges in treating PC.

Case presentation

A 23-year-old woman presented with a 1-month history of back pain, hoarseness, and thyromegaly. Serum calcium concentration was 3.71 mmol/L (reference range, 2.03–2.54 mmol/L) and phosphate concentration was 0.87 mmol/L (reference range, 0.96–1.62 mmol/L). PTH concentration was 2,209.0 pg/mL (reference range, 15.0–68.3 pg/mL). Her medical history was remarkable for a kidney stone 7 years earlier that was treated with lithotripsy. There was no known history of parathyroid disease or endocrine neoplasia in her family. ^{99m}Tc-methoxyisobutylisonitrile (MIBI) single-photon emission computed tomography (SPECT)/computed tomography (CT) indicated increased activity in the right upper parathyroid (*Figure 1*) and a cystic left thyroid lesion causing tracheal compression. The patient underwent total thyroidectomy and right upper parathyroidectomy. Pathologic examination of the surgical specimen confirmed right upper PA and a large thyroid cyst. Serum calcium and PTH concentrations on the day after surgery decreased to 1.94 mmol/L and 13.3 pg/mL, respectively.

Twelve months later, calcium and PTH concentrations had increased to 3.19 mmol/L and 507.4 pg/mL, respectively. ^{99m}Tc-MIBI imaging was performed to identify a possible ectopic PA, which was negative (*Figure 2A*,*2B*). To verify the SPECT/CT results and exclude other neuroendocrine neoplasms, ^{68}Ga-DOTATATE positron emission tomography (PET)/CT and ^{18}F-fluorodeoxyglucose (FDG) PET/CT were performed and were negative (not shown). Alendronate sodium and furosemide were prescribed to control hypercalcemia. Five months later, PTH concentration was 1,746 pg/mL and serum calcium were 3.56 mmol/L. Repeat MIBI imaging showed two foci of mildly increased activity in the left neck (*Figure 2C*) and left upper mediastinum (*Figure 2D*). Re-exploration surgery was not performed until PTH

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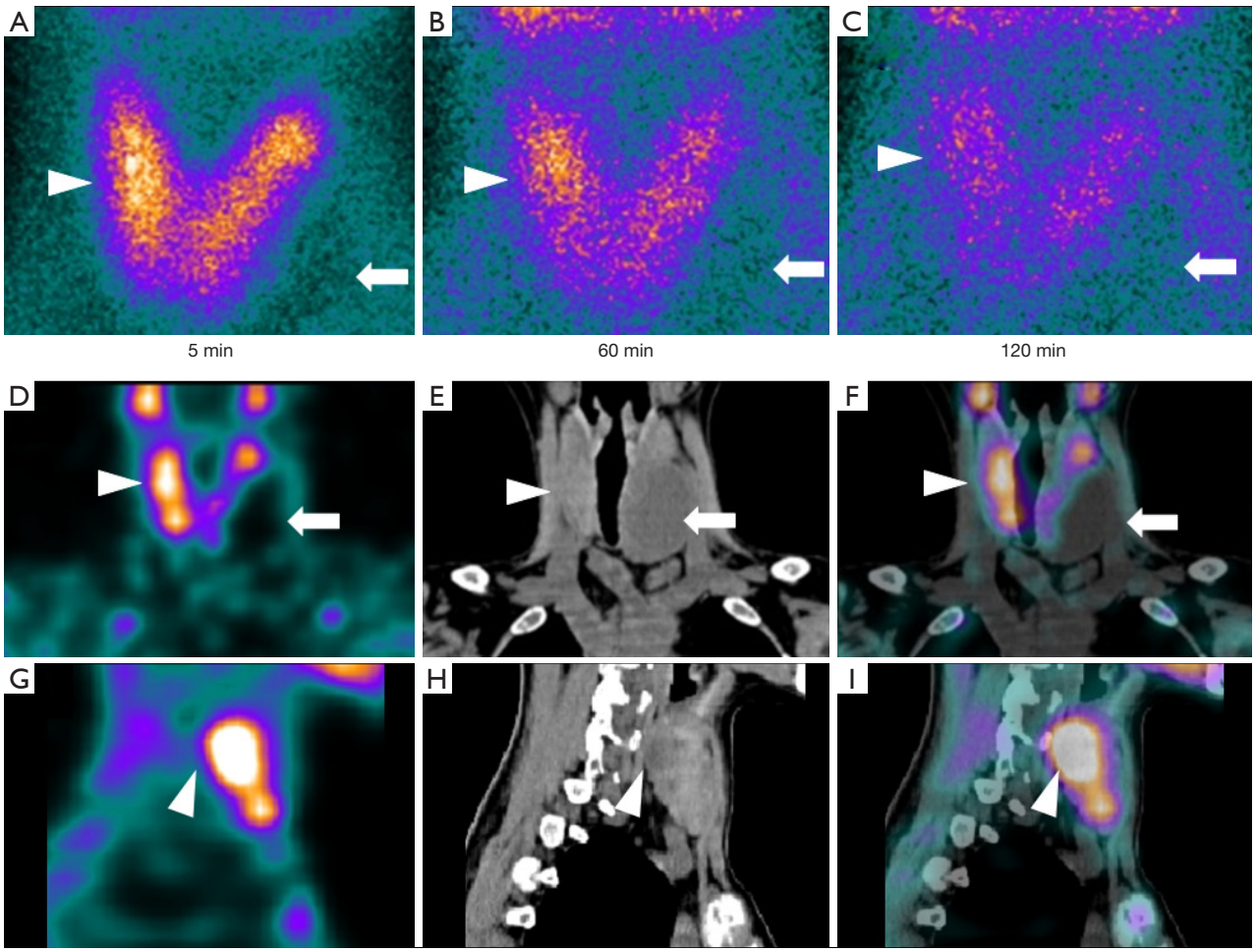

Figure 1 Initial ^{99m}Tc-MIBI parathyroid SPECT/CT. Static scintigraphy (A-C), coronal and axial SPECT/CT images 60 minutes after tracer injection (D-I) revealed a focus of mildly increased activity in the right upper lobe (arrowheads) and a low-density nodule in the left lobe (arrows). ^{99m}Tc-MIBI, ^{99m}Tc-methoxyisobutylisonitrile; SPECT/CT, single-photon emission computed tomography/computed tomography.

concentration increased to >3,000 pg/mL two months later owing to personal reasons. Histopathologic findings indicated that both lesions were PC.

Although PTH concentration decreased to 348.6 pg/mL on the second day after surgery, it then increased during follow-up. Repeat MIBI imaging 6 months later showed elevated activity at the surgical sites, which suggested recurrent PC (*Figure 2E,2F*). The patient refused another operation. Despite medical treatment, PTH and calcium concentrations remained elevated (*Figure 2G*, 1,739.5–2,320.51 pg/mL and 3.06–4.31 mmol/L, respectively) and the patient died 8 months later. Pathologic examinations of parathyroid adenoma and parathyroid carcinoma of this patient was shown in *Figure 2H* and *Figure 2I*.

This study was approved by the Institutional Research Ethics Committee of Union Hospital, Huazhong University of Science and Technology. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Primary hyperparathyroidism (PHPT) is characterized by

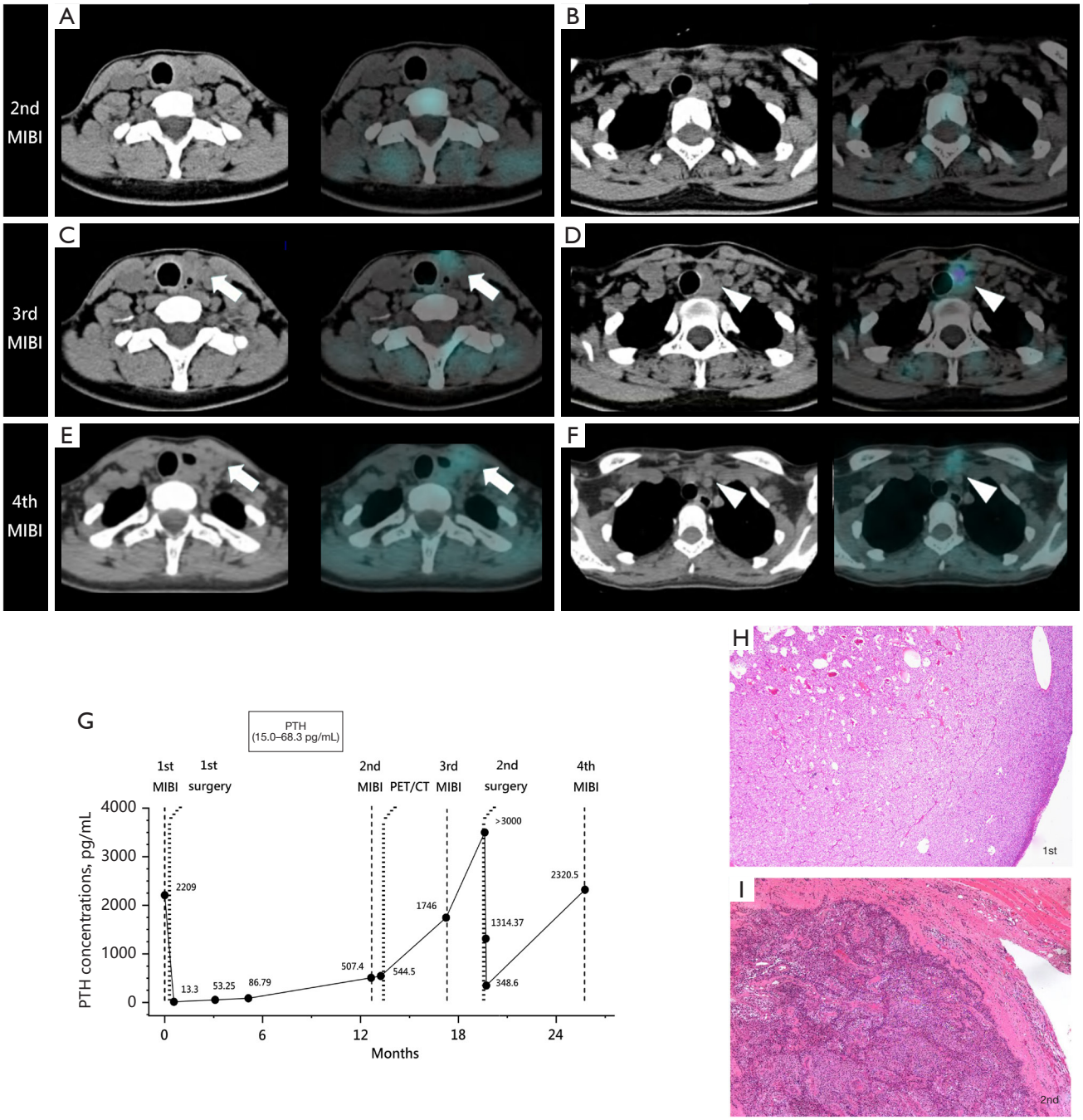

Figure 2 An overview of the development of patient's disease. (A,B) ^{99m}Tc-MIBI SPECT/CT 12 months after parathyroidectomy to evaluate elevated calcium and parathyroid hormone concentrations was negative. (C,D) MIBI imaging 5 months later showed two foci of mildly increased activity in the left neck (arrows) and left upper mediastinum (arrowheads). (E,F) Repeat MIBI imaging 6 months after carcinoma resection demonstrated elevated activity at the surgical sites, suggesting recurrent parathyroid carcinoma (arrows and arrowheads). (G) A timeline chart shows imaging studies and parathyroid hormone concentrations over time. (H) Pathologic examination (H&E staining) under 40× magnification of a specimen from the first surgery confirmed parathyroid adenoma. (I) Both lesions were parathyroid carcinoma on histopathologic examination (H&E staining) under 100× magnification. MIBI, methoxyisobutylisonitrile; PTH, parathyroid hormone; PET/CT, positron emission tomography/computed tomography; ^{99m}Tc-MIBI SPECT/CT, ^{99m}Tc-methoxyisobutylisonitrile single-photon emission computed tomography/computed tomography; H&E staining, hematoxylin and eosin staining.

excessive PTH secretion. Fewer than 1% of PHPT cases are caused by PC (2). In contrast to PA, PC is associated with poor prognosis: up to 50% of cases recur and 10-year overall survival ranges between 60% and 70%. Most patients die from uncontrolled severe hypercalcemia (3). Distinguishing benign parathyroid neoplasms from malignant ones is difficult when relying on histopathology or biochemical indices. Although PC should be considered in patients with markedly evaluated PTH concentration and severe hypercalcemia (4), these criteria are non-specific. Moreover, no specific histological characteristics allow distinction between PA and PC. Our patient presented with typical symptoms of PHPT and the initial histopathology was consistent with PA. However, PTH concentration remained high and PC was confirmed after the second surgery. Although the PC could have been present initially, it also may have developed after the first surgery. Co-existing PC and PA has been previously reported (5,6); however, PC following PA resection has not.

Surgical resection is the most effective treatment for PC (3). In patients with inoperable PC, calcimimetics are the most effective way to control hypercalcemia (7). These agents increase the sensitivity of the calcium sensing receptor (CASR) to ionized calcium and reduce PTH secretion. Cinacalcet is a second-generation calcimimetic used in patients with inoperable PC that is effective in treating hypercalcemia in approximately two-thirds of patients (8). The effectiveness of other therapies, such as radiotherapy and chemotherapy, has not been verified and requires further study (3).

Because reoperation is hardly to perform without positive imaging findings (9), our patient's elevated PTH concentration after the first surgery was treated medically. ^{99m}Tc-MIBI scintigraphy is currently recommended as first-line imaging (10). Ultrasonography may also be helpful. Features such as large size (>3 cm), irregular borders, tissue invasion, heterogeneous appearance, decreased echogenicity, and tumor depth/width ratio ≥1:1 suggest PC (11). Combining ^{99m}Tc-MIBI and cervical ultrasonography is associated with 81% to 95% sensitivity in detecting hyperfunctioning parathyroid lesions (12). ^{99m}Tc-MIBI SPECT/CT is considered the most effective method to detect PA and PC (13). However, intensity of MIBI uptake in parathyroid lesions cannot differentiate benign from malignant (14). Although ^{99m}Tc-MIBI SPECT/CT allows more precise localization, sestamibi scanning can produce false-positive results in the setting of thyroiditis, thyroid cancer, Hurthle cell adenoma, follicular adenoma, and lymph node metastasis (15). Moreover, sensitivity of sestamibi scanning is limited in patients with multiglandular disease (16).

PET/CT can improve detection of the smallest pathological glands, which cannot be visualized by SPECT/CT (17). Sensitivity of FDG PET/CT for detection of PC is high in all disease phases (18); however, it did not detect any lesions after the first surgery in our patient. Neither did ^{68}Ga-DOTATATE PET/CT, which was used to rule out neuroendocrine tumors (19). DOTATATE uptake may have been lacking in our patient because PC mainly expresses somatostatin receptor 5 (20), while DOTATATE has higher affinity for somatostatin receptor 2. ^{11}C-methionine (MET) PET/CT has been previously used as second-line imaging after negative or inconclusive conventional imaging and could have been considered. Preoperative ^{11}C-MET PET/CT can localize hyperfunctioning parathyroid glands in 74% of patients with negative ^{99m}Tc-MIBI scintigraphy (21). One isolated patient who harbored a ^{99m}Tc-MIBI and ^{18}F-FDG-negative, while ^{11}C-MET-positive recurrent PC has been described (22). Moreover, ^{18}F-fluorocholine (FCH) PET/CT, which has better sensitivity than SPECT/CT for locating lesions responsible for PHPT (23), might be an alternative method to diagnose PC. This modality is better than ^{11}C-MET PET/CT for detection of pathologic parathyroid tissue in patients with biochemical evidence of PHPT and negative or inconclusive ^{99m}Tc-MIBI imaging (24). However, a further prospective study is warranted (25).

CT and magnetic resonance imaging (MRI) are useful to determine the local extent of PC, local invasion, and distant spread. CT features suggestive of malignancy include high short-to-long axis ratio, irregular shape, peritumoral infiltration and calcification, and minimal contrast enhancement (26). On MRI, parathyroid hyperplasia or adenoma lesions are usually small in size, homogenous, and well-defined. Signal intensity is low on T1-weighted sequences and high on T2-weighted sequences; contrast enhancement is high. In contrast, PC is large, ill-defined, and very heterogeneous on MRI, including diffusion-weighted imaging sequences (27). Four-dimensional CT can also be utilized for PC (28). It may be considered when radionuclide imaging is negative or in patients with distorted neck anatomy (17).

The outcome in our patient might have been different if re-exploration surgery had been performed earlier; however, we were unable to convince the patient it was indicated after two lesions were noted on the third MIBI scan. As a new

term to the 2022 WHO classification, atypical parathyroid tumor should be in consideration when PA was diagnosed. It has similar histologic features often seen in PC, but they do not show unequivocal invasion which is required for the diagnosis of PC (29). The limitation of our case is the lack of immumohistochemical staining of operative specimens which could make the pathological diagnosis more definitely. Moreover, it should be mentioned that PC is classified as low grade, or minimally invasive PC (MIPC), and high grade, or widely invasive PC (WIPC), based on degree of microscopic infiltration (30). Considering our patient's typical symptoms and moderately elevated PTH concentration, it is possible that MIPC might have co-existed with PA in the initial presentation. However, it was not identified in the specimen from the first operation. Compared with typical PA and PC lesions, MIPC lesions are larger and better defined on MIBI imaging (31). However, PA, MIPC, and WIPC cannot be reliably differentiated based on imaging alone. Some studies proposed that the histological criteria for differentiating MIPC from PC are capsular and vascular invasion and the degree of infiltration (limited vs widespread) (30,32). Because WIPC requires extensive surgery and is associated with a more aggressive clinical course and higher mortality than MIPC (33), as well as the lack of targeted tracers or makers that can distinguish MIPC and WIPC, further studies regarding early differentiation of the two are warranted.

In conclusion, we report a case of PC arising after PA resection. Since the prognosis of PC is poor, early diagnosis and treatment would benefit patients. In addition to experience and solid researches, additional diagnostic methods are also urgently needed for early detection.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-994/coif). FS reports that the research was supported by Open Program of Nuclear Medicine and Molecular Imaging Key Laboratory of Hubei Province (No. 2021fzyx026). XL reports that this research was supported by National Natural Science Foundation of China (No. 82030052). XX reports that this research was supported by National Natural Science Foundation of China (No. 81801737). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Institutional Research Ethics Committee of Union Hospital, Huazhong University of Science and Technology. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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