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CASE REPORT

Mixed Medullary-Papillary Thyroid Carcinoma with Mixed Lymph Node Metastases: a Case Report and Review of the Literature

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Abstract: Papillary thyroid and medullary thyroid cancers are two distinct types of thyroid neoplasms. Co-occurrence of these cancers is rare, especially in mixed tumours with lymph node metastases. A 66-year-old man presented with a thyroid tumour. Thyroid ultrasonography revealed three separate nodules in the thyroid, suspected to be associated with lymph node metastasis. Although preoperative thyroid function was normal, calcitonin and carcinoembryonic antigen levels were elevated. The patient underwent a total cervical thyroidectomy with bilateral radical dissection. Histological and immunohistochemical analyses identified mixed medullary and papillary thyroid carcinoma (MMPTC) in the nodules in the left lobe of the thyroid and the isthmus. Mixed metastatic spread was observed in several lymph nodes from the neck dissection specimen. Accurate diagnosis of the rare co-occurrences of papillary and medullary thyroid carcinomas is crucial. TSH suppression can be effective for treating papillary thyroid carcinoma, whereas radical surgery is the preferred treatment for medullary thyroid carcinoma. Identifying lymph node metastasis before surgery is a key surgical strategy.

Keywords: thyroid, carcinoma, medullary, papillary, lymph

Introduction

The thyroid gland, consisting of two connected lobes, is one of the largest endocrine glands in the human body, weighing 20–30g in adults. Thyroid lesions are often found on the gland, with a prevalence of 4%–7%. Most of them are asymptomatic, and thyroid hormone secretion is normal. Thyroid carcinomas fall into four clinical categories: papillary, follicular, medullary, and undifferentiated thyroid carcinoma. Papillary thyroid carcinoma (PTC) and medullary thyroid carcinomas (PTC and MTC, respectively) are two types of cancer. PTC is the most prevalent pathological type of thyroid cancer and arises from the thyroid follicular epithelial cells. MTC is the most malignant type of thyroid cancer and originates from the parafollicular cells of the thyroid.[1] These two types of tumours have different clinical manifestations. It is rare for PTC and MTC, also known as mixed medullary papillary carcinoma, to co-exist in a single patient. MTC cannot be diagnosed by genetic testing alone. However, things are different for PTC, and the diagnostic value of the detection of BRAF V600E mutation for PTC has been widely recognized. Therefore, the correct diagnosis of mixed cancers is essential, as it can affect the surgical method and prognosis. Herein, a rare case of medullary and papillary thyroid carcinoma (MMPTC) is reported.

Case Report

A Chinese man of 66 years of age with a clinical history of 7 years of cerebral infarction had his thyroid gland examined while hospitalized in the Department of Internal Neurology. He had no prior treatment or a history of thyroid or endocrine disease in his family. Thyroid palpation revealed that the left lobe thyroid nodules were not more than 2.5 cm in diameter and had no tenderness. An ultrasound scan showed an iso-echo mass in the lower left lobe pole measuring

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2.5 cm and a hypoechoic nodule in the right lobe measuring 0.7 cm. Swollen lymph nodes were found in zones II, III, IV, V of the left neck, and zone IV of the right neck, so the possibility of secondary changes was considered.

The serum levels of free thyroxine, free triiodothyronine, thyrotropin, anti-thyroglobulin antibodies, anti-thyroperoxidase antibody, thyrotropin receptor antibody, and thyroglobulin were within the normal ranges. Preoperative serum calcitonin and carcinoembryonic antigen levels were elevated. Serum calcium, phosphorus, and parathyroid hormone levels were normal.

The patient received a four-part fine needle aspiration (FNA) at our hospital. Atypical cellular lesions of unclear significance were found on fine-needle aspiration of a right lobe lump. Nodule cytology results from the left and right lobes were identical; however, the nodule of the left lobe's genetic test showed that the HRAS gene had a mutation but no BRAF gene mutation. The lymph nodes in the VI right side of the neck showed blood composition with many epithelial cell nests, consistent with papillary carcinoma, Tg > 500.000 ng/mL. Fine-needle aspirate of the lymph nodes in the left II region of the neck revealed blood composition with many lymphocytes, Tg 0.85 ng/mL.

After excluding all surgical contraindications, a total thyroidectomy with radical lymph node dissection was performed. A greyish-white nodule was observed. Three nodules were identified in the left thyroid lobe and isthmus. The maximum diameter of the larger nodule was 4.5 cm, and two grey-white nodules were seen with the maximum diameter of 0.6 cm and 0.7 cm, respectively. A total of 83 lymph nodes, ranging from 1.8 cm to 2 cm in maximum diameter, were isolated by bilateral cervical lymph node dissection. Of 83 dissected lymph nodes, 23 showed metastases. Of the 23 metastatic nodes, 21 had medullary carcinoma metastases, and two had mixed medullary and papillary thyroid carcinoma metastases. At the time of pathological examination, a PTC with a maximum diameter of 0.6 cm is found in the right lobe of the thyroid. The left lobe of the thyroid gland is a mixed medullary-papillary carcinoma, while most of the components are medullary carcinomas, and approximately 10% are papillary carcinomas. The cellular morphological features of PTC and MTC can be seen separately under haematoxylin and eosin HE staining at 200 × magnification (Figures 1 and 2). TTF1, CT, and CEA were positive, while PAX8 and TG were partially positive when immunohistochemistry was amplified 200 × under a microscope (Figures 3–7).

After the surgical procedure, the serum calcitonin and CEA levels remained elevated, whereas parathyroid hormone (PTH) levels were below the normal range. After 14 days of hospitalisation, the patient was discharged and was administered levothyroxine, alfacalcidol, and calcium carbonate tablets to regulate hormone levels after surgery. The patient was reexamined in our hospital one month after surgery, and the TSH was 12.71 uIU/mL, exceeding the average value; calcium had reached the normal level, while PTH was still slightly lower than the average value. The patient's condition has been relatively stable until now (Three months later). He had made an appointment for ^{131}I therapy but had not yet received ^{131}I therapy.

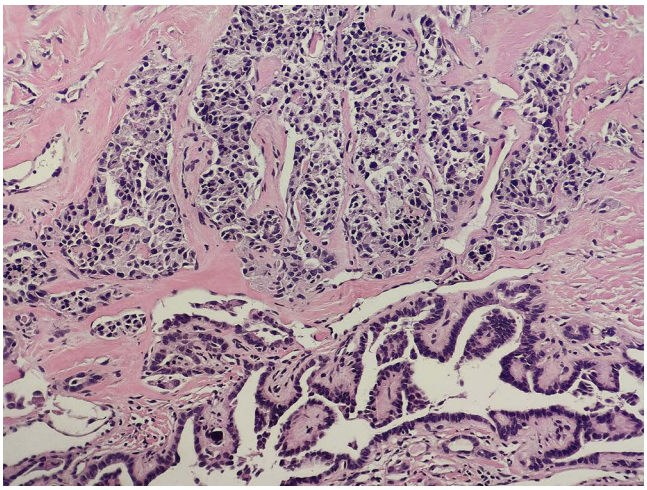

Figure 1 The upper part is MTC and the lower part is PTC.

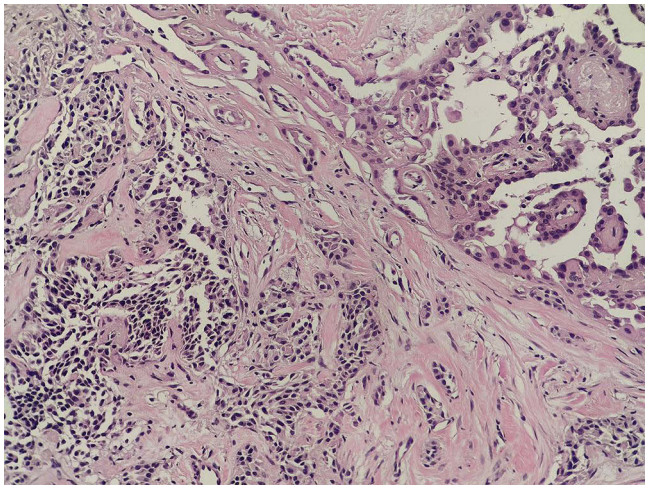

Figure 2 The upper right is PTC, and the lower left is MTC.

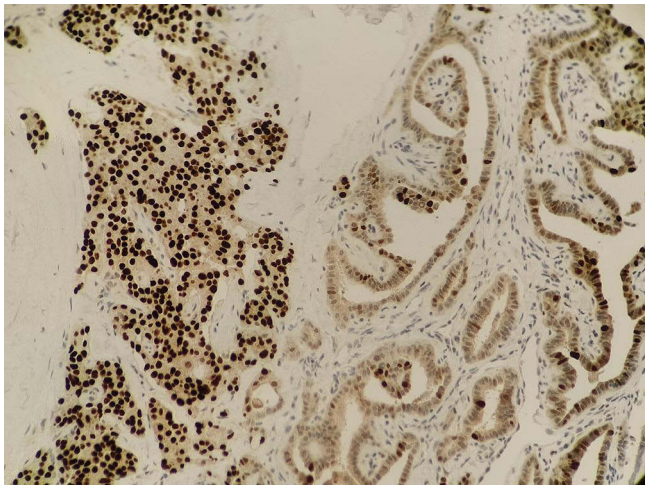

Figure 3 TTF1 immunohistochemistry showed MTC on the left and PTC on the right.

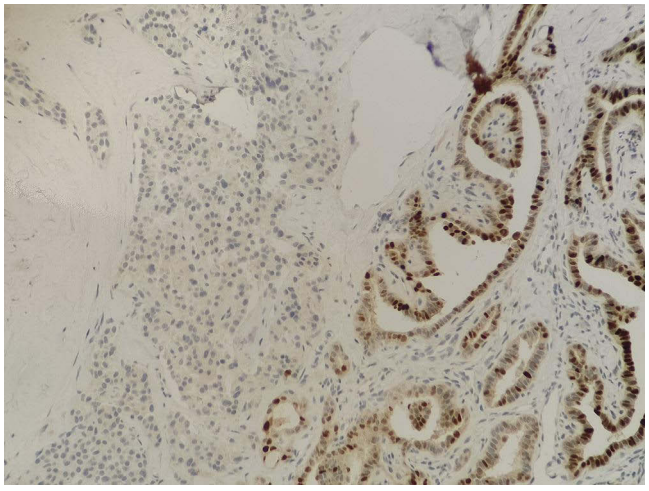

Figure 4 PAX8 immunohistochemistry was positive for PTC.

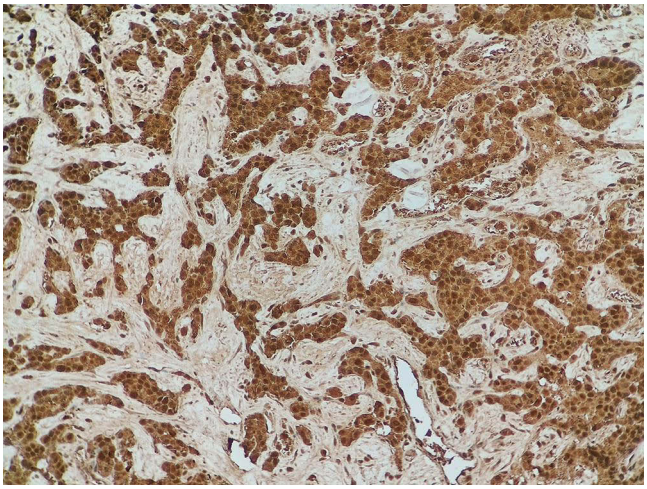

Figure 5 CT immunohistochemistry was positive for MTC.

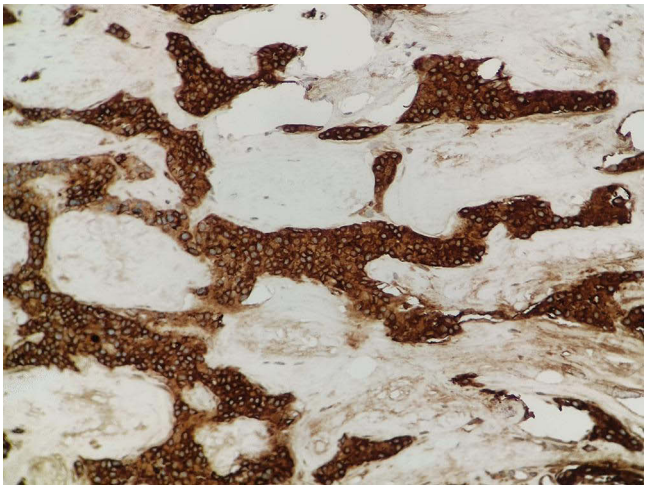

Figure 6 CEA immunohistochemistry was positive in MTC.

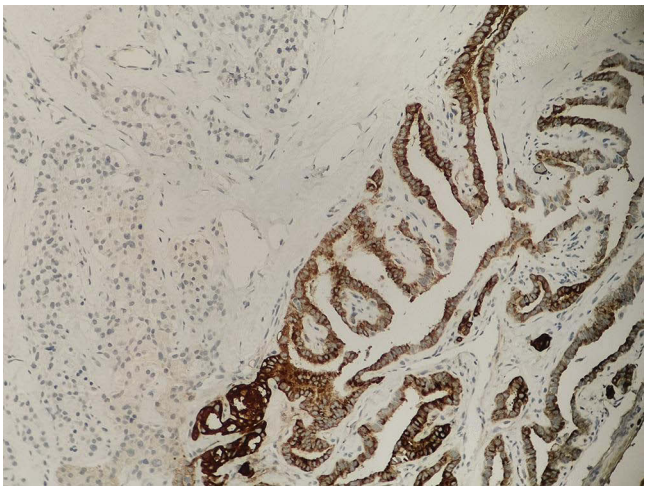

Figure 7 TG immunohistochemistry was negative in MTC and positive in PTC.

Discussion

PTC is a differentiated thyroid carcinoma derived from the thyroid follicular epithelial cells. The three leading causes of PTC are genetic factors, radiation exposure, and hormonal changes. Genetic factors are mainly related to oncogene and tumour suppressor gene mutations, especially P53 gene mutation. The mutant p53 gene is highly methylated, and the oncogene c-myc is hypomethylated and highly expressed, an essential reason for oncogene transformation. At the same time, apoptosis-related regulatory genes, such as p53, RAS, bcl-2, and c-myc, are mutated or abnormally expressed, resulting in an imbalance between cell proliferation and apoptosis, which causes thyroid gland cancer. Another risk factor for thyroid cancer is exposure to radiation,[2] with the incidence of thyroid tumours linearly correlated with acute X-ray and γ radiation exposure. The longer the exposure time, the younger the age, the higher the incidence; nuclear radiation caused RET gene rearrangement (accounting for 60% of all cases), activating proto-oncogenes leading to thyroid papillary carcinoma.[3,4] This theory has been proven previously. TSH, oestrogen, and growth hormones promote thyroid cancer growth.

Medullary thyroid carcinoma (MTC) is a neuroendocrine tumour of neural crest origin responsible for 3–5% of all thyroid cancers.[5] The degree of malignancy is relatively high in thyroid cancer, and its prognosis is relatively poor. Proto-oncogene RET mutations are most patients' leading pathogenic cause of medullary carcinoma. Missense mutations, rearrangements, and the loss of RET in germ cell proto-oncogenes are associated with the inherited type, whereas somatic proto-oncogene mutations are associated with the sporadic type. RET contains 21 exons that encode tyrosine kinase receptor proteins.[6] After gene mutation, protein conformation changes induce cell hyperplasia and carcinogenesis.

The coexistence of these two types of cancer is a rare phenomenon that can be attributed to two conditions: mixed cancer and collision cancer. Our case falls into the former category because lesions with MTC and PTC features were found at the same site. However, the aetiology of these mixed cancers remains unknown. These two findings were remarkable in our case. First, mixed medullary-papillary carcinomas have metastases. The metastases were three with maximum diameters of 4.5 cm, 0.6 cm, and 0.7 cm, respectively. Mixed MTC and PTC metastases were detected in two of the 83 cervical lymph nodes. Lymph node spread in mixed medullary-papillary cancer can exhibit the characteristics of MTC or PTC; however, both characteristics are rare. In the same way, the occurrence of metastasis is an extremely rare phenomenon in the case of mixed medullary-papillary carcinoma. However, all our patients had them, which will inevitably bring significant challenges to their prognosis.

Ultrasound and CT can be used to determine benign and malignant tumours, location, and lymph node status, but they cannot determine the nature of the tumour. Therefore, the diagnosis of medullary and papillary thyroid carcinoma in the clinic still depends on fine-needle puncture and serum calcitonin levels. However, diagnosing medullary and papillary thyroid carcinoma by puncture is not correct, and there has been no confirmation that genes are reliable, so the diagnosis can only be made by serum calcitonin and cytological diagnosis results. The Bethesda classification system for reporting thyroid cytopathology is the standard for interpreting FNA. They were categorised into six groups: nondiagnostic or unsatisfactory specimen (I), benign lesion (II), atypia of undetermined significance (AUS), follicular lesion of undetermined significance (FLUS) (III), follicular neoplasm or suspicious follicular neoplasm (IV), suspicious malignancy (V), and malignant (VI). Thyroid nodules that fall within Bethesda categories III–IV have an overall malignancy risk of 15%–40%. Research shows that patients with FNA as AUS have a higher probability of postoperative malignancy than those with traditional cognition, and patients with FNA categorised as Bethesda II also occasionally have a possibility of postoperative malignancy. In this case, preoperative FNA was performed, both lobes were found to be AUS, and the postoperative pathology was malignant, which also suggests that surgeons should be alert to patients with FNA as AUS before surgery.[7,8]

The current treatment strategy for mixed medullary papillary carcinoma is similar worldwide. Typically, preoperative thyroid ultrasonography and enhanced computed tomography (CT) are performed to pinpoint the location of the nodule and lymph node metastasis, and cytology is used to diagnose the nature of the mass. A preoperative examination was performed to determine the mode of operation and extent of lymphadenectomy. In our patient, the thyroid gland was removed, and the neck lymph nodes were dissected bilaterally. However, lymphadenectomy has no established surgical indications. At present, the anatomical range of the central region dissection (level VI) is clearly defined: the upper

boundary reaches the thyroid cartilage, the lower boundary reaches the level of the thymus or stem of the brachiocephalus, and the lateral boundary is the medial margin of the arterial sheath on both sides. This region includes the anterior tracheal, tracheoesophageal sulci, and anterior laryngeal (Delphian) lymph nodes and should be regarded as a whole during surgery for systematic and routine dissection. Additionally, suspected lymph nodes were removed based on preoperative CT and ultrasound. Therefore, prophylactic neck lymphadenectomy is not recommended. Ultrasonography of the patient showed enlarged lymph nodes at levels II, III, IV, and VI of the left side of the neck and level IV of the right neck. Considering the possibility of secondary changes, Enhanced CT showed abnormally enhanced lymph nodes at levels II, III, IV, and VI on the left and right sides of the neck. The patient underwent radical lymph node dissection. According to the postoperative pathology, no lymph node metastasis was found in the left level II, left intermuscular, and right level III lymph nodes. However, owing to the particularity of mixed medullary-papillary carcinoma, we performed an enlarged lymph node dissection to avoid the risk of recurrence.

The postoperative pathology, in this case, showed a PTC in the right lobe. As a differentiated thyroid cancer, controversy still exists regarding surgical methods, including total thyroidectomy (TT) and subtotal thyroidectomy (STT). The three most common complications of thyroid surgery are bleeding, recurrent laryngeal nerve (RLN) palsy, and post-operative hypocalcaemia. Mulita et al showed no significant difference in the incidence of haematoma, wound infection, hypoparathyrothyroidism, or temporary RLN palsy between the TT and STT groups. TT is safe for treating differentiated thyroid cancer and does not increase early complications.[9]

The most commonly used haemostatic instruments for thyroid surgery include the LigaSure vessel (LS) and harmonic scalpel (HS). Mulita et al showed that both devices had the same safety profile in thyroidectomies, especially for complications requiring re-operative bleeding. Simultaneously, for patients with thyroid cancer, HS can more effectively stop bleeding and save operation time.[10] In this case, HS was used for haemostasis during surgery. Even after TT and extensive cervical lymph node dissection, postoperative haemorrhage or haematoma did not occur.

In addition to conventional TSH inhibition therapy for the postoperative treatment of patients with mixed medullary and papillary thyroid carcinoma, ^{131}I therapy is administered to patients with severe metastases accompanied by nerve and vascular invasion. Studies have shown that treatment with ^{131}I can reduce recurrence and improve the overall prognosis in patients with tumours larger than 4 cm in diameter or with neck or middle lobe lymph node metastases at intermediate risk and older than 45 years. Studies have also shown no significant effect on recurrence or overall survival in low-invasive intermediate-risk patients aged less than 45 years with minimal extrathyroid infiltration but no lymph node metastasis and small cancer focus. Whether ^{131}I should be performed requires the assessment of the patient's age, tumour size, number, and diameter of lymph node metastases and extranodal invasion, as well as the histopathological type and vascular invasion. Some patients may experience gastrointestinal reactions, radioactive thyroiditis, salivary gland inflammation, taste changes, transient myelosuppression, or other adverse reactions after the treatment. The incidence was positively correlated with the cumulative therapeutic dose. Glucocorticoids and other drugs can be administered to improve symptoms before and after treatment according to the patient's condition. Approximately 25% of women with ^{131}I show transient menopause, reduced menstrual volume, or irregular menstruation after treatment, which can last for 4~10 months. A large dose of multiple treatments can lead to menopause one year or earlier, but ^{131} does not cause infertility, faecal birth, or foetal malformations in women.[11] Whether ^{131} therapy increases the occurrence of secondary primary malignancies (SPM), such as acute and chronic myeloid leukaemia, colorectal tumours, and salivary gland tumours, is controversial.[2]

Conclusion

In this case, emphasis was placed on mixed medullary-papillary carcinoma with mixed medullary-papillary lymphatic metastasis, which was rare in our patient. Determining tumour properties using calcitonin levels and cytological diagnosis has also been emphasised. Lymphatic metastasis was determined by ultrasonography and MRI, together with the importance of determining the nature of the mass and lymph nodes by postoperative pathology.

Informed Consent

The patient gave informed consent and agreed to participate in the study.

Consent for Publication

Informed consent was obtained from the patient for the publication of this case report, and the ethics committee of the Affiliated Hospital of Integrative Chinese and Western Medicine of Nanjing University of Chinese Medicine approved this consent process and the publication of case details (IRB file number: 2023-LWKYZ-023).

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Disclosure

All authors have no conflict of interest related to this study.

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