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Imaging findings of malignant bilateral carotid body tumors: A case report and review of the literature

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Abstract. Carotid body tumors (CBTs) are a rare type of extra-adrenal paraganglioma, which originate from the carotid body. A 29-year-old woman was admitted to the Department of Head and Neck Surgery, Beijing Tongren Hospital (Capital Medical University, Beijing, China) with hoarseness of the throat, which had progressively worsened over seven months. The patient had a family history of CBTs. Computed tomography and ultrasound imaging revealed multiple well-enhanced masses located at the bilateral carotid bifurcation and in the left parapharyngeal space. Surgery and pathological examination confirmed that the patient had developed regional lymph node metastasis. Significantly enhanced multiple pulmonary and hepatic lesions indicated that the patient had also developed distal metastasis. A genetic analysis performed on the family members of the patient revealed that the family carried a mutated succinate dehydrogenase D gene. In the present study, a systemic review of the literature indicated that extra vigilance is required in familial forms of CBT, in order to increase the standard of treatment for CBT patients.

Introduction

Carotid body tumor (CBT) is an extra-adrenal paraganglioma that may also be termed chemodectoma. CBTs originate from the neural crest tissue in the carotid bifurcation. Usually, CBT is a solitary occurrence. The majority of cases are considered to be benign, with only 10-20% demonstrating malignant inclinations (1). Therefore, malignancy is uncommon, and distant metastasis is rare. CBTs are generally presented as unilateral neoplasms that are located in the carotid bifurcation, without distant metastasis. CBTs account for ~0.03% of all neoplasm types (2).

Familial forms of CBT account for 6.0-12.5% of all CBT cases (3). Familial forms are rarely reported in the literature, and there have been few reports of cases worldwide since the 1930s (4-12). Due to the presence of a specific gene mutation in familial forms of CBT, multifocal lesions and distant metastases are more likely to occur in familial forms compared with non-familial cases. The present study reports the case of a patient with bilateral CBT in association with systemic metastasis. The radiological findings of a malignant CBT and associated metastases are discussed in detail.

Case report

On November 1, 2013, a 29-year-old woman was admitted to the Department of Head and Neck Surgery, Beijing Tongren Hospital (Capital Medical University, Beijing, China) with hoarseness of the throat and bilateral neck pain, which had progressively worsened over seven months. Three months prior to admittance, the patient developed dysphagia. An ultrasound examination in Ningxia People's Hospital (Yinchuan, China) approximately two months prior to admittance revealed neoplasms in the bilateral neck. The masses were ~4.5x2.5 cm and ~2.0x1.0 cm in size (right and left side, respectively). The diagnosis was considered to be bilateral CBTs. Then the patient went to Beijing Tongren Hospital and was also diagnosed as CBTs. The diagnosis was considered to be reasonable, as the patient disclosed that 9 family members had also possessed lumps in the neck region. Surgery was previously performed on the patient's elder brother, who had also been confirmed with a diagnosis of CBT.

The vital signs of the patient were normal upon admission. The only physical findings of importance were restricted to the neck. On the right side, a mass ~4.5x2.5 cm in size was palpated over the carotid bifurcation. The mass had a clear margin, was firm and non-tender and was not easily moved.

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A mass ~2.5x1.5 cm in size was identified in the II region of the right neck. The second mass was not as firm as the first, but moved slightly. On the left side, a somewhat smaller mass ~2.0x1.0 cm in size was also palpated at the carotid bifurcation. The mass was firm, non-tender and was not easily moved. No enlarged lymph nodes were identified in the supraclavicular region.

Firstly, a computed tomography (CT) scan of the neck with contrast enhancement and CT angiography was performed (Fig. 1A and 1B). The CT imaging revealed a solid, well-defined mass ~4.6x2.3x2.8 cm in size that was located at the right carotid bifurcation, and surrounded the external carotid artery (ECA) and the internal carotid artery (ICA). The mass was well-enhanced following the contrast enhancement administration. The adjacent internal jugular vein (IJV) was compressed significantly. An enhanced mass of 2.5x1.4x1.2 cm in size identified in the posterior region of the lesion indicated an enlarged lymph node. The CT scan also revealed a similar neoplasm at the left carotid bifurcation that infiltrated into the left parapharyngeal space and extended to the base of the skull. The ECA was displaced anteromedially, the ICA was displaced posterolaterally and the adjacent IJV was compressed. No enhanced lymph nodes of >1.0 cm in the short diameter were identified in the region.

A grayscale ultrasound revealed an inhomogeneous hypoechoic, well-defined neoplasm in the right neck that spread across the carotid bifurcation, and the ECA and ICA were encased by the mass (Fig. 1C). A significantly enlarged lymph node that was oval in shape and did not exhibit a normal echogenic hilum was identified in the posterior region of the neoplasm (Fig. 1D), which indicated regional lymph node metastasis. A relatively small mass was also detected in the left carotid bifurcation; however, the upper margin was not detected clearly due to the deep location of areas of the lesion. No additional enlarged lymph nodes were detected in the bilateral neck and supraclavicular region.

Following the aforementioned examinations, the diagnosis of malignant CBT was suspected. Therefore a systemic review of the patient was essential. Additional non-enhanced CT examinations revealed multiple nodules scattered in the bilateral lung field (Fig. 2A). An enhanced CT scan revealed numerous nodules of various sizes within the liver and heterogeneous significant enhancement at the arterial phase (Fig. 2B). The central region of the lesion in the left hepatic lobe remained unenhanced in the scanning time and the low density within the nodules indicated a central necrosis of the malignancy.

Three lymph nodes from the II region of the right neck were resected for pathological examination in order to guide the selection of chemotherapy. Upon microscopic examination, the tumor cells exhibited the typical Zellballen growth pattern, including nuclear pleomorphisms and mitoses. The cell nests were separated by large epithelial cells of the blood sinusoid. Immunohistochemically, the diagnosis of the neurologically originating neoplasm was confirmed by the expression of chromogranin, synaptophysin and neuron specific enolase (NSE) (Figs. 3A-3D).

Combined with the radiological findings, the pathological examination established a diagnosis of bilateral CBT with regional lymph node, pulmonary and hepatic metastases.

Due to the family history of head and neck tumors, early onset and malignant bilateral nature of the disease, a genetic analysis was performed to identify mutations in the succinate dehydrogenase (SDH) B, C and D genes. Among the patient's 31 family members, 12 were identified as expressing the SDHD mutant gene, accounting for 38.7% (12/31) of the family.

Written informed consent was obtained from the patient for the publication of this article and any accompanying images.

Discussion

Carotid body tumors (CBTs) are rare neoplasms and a type of extra-adrenal paraganglioma. CBTs are often diagnosed using the location, clinical symptoms and imaging findings of the tumor (13). The majority of CBTs are benign; however, certain lesions may demonstrate malignant inclinations and behavior. In addition, there has been considerable debate associated with the definition of malignancy in CBTs. Lack *et al* used histological findings, consisting of central necrosis of clusters, invasion of vascular spaces and mitoses, to define a malignant CBT (14). However, other studies considered that pathological examinations do not allow the differentiation between benign and malignant tumors. Only the presence of regional lymph nodes or distant metastasis may indicate malignancy (3,13,15-17). Therefore, malignant CBTs are usually diagnosed using the development of local recurrence, regional lymph node metastasis or the presence of distant metastasis.

Previously, studies have stressed the importance of an accurate list of anamnestic information in order to detect the presence of familial chemodectoma. The present study demonstrates that it is useful to consider the analysis of SDH genes. The analysis may detect gene mutations, which may be important for starting a familial genetic counseling process that may allow the early diagnosis of relatives. In the present study, only two of the patient's family members underwent surgery or biopsy; however, all relatives underwent a gene analysis and mutation of the SDHD gene was detected. In familial cases, hereditary CBT genes code for subunits B, C or D of succinate dehydrogenase, a mitochondrial enzyme (11). Certain genetic mutations are transmittable to offspring in the familial form of CBT (4,5), and patients with the SDHD gene mutation are more likely to develop head and neck paragangliomas and multifocal tumors, such as bilateral CBTs (18). Among the 31 family members of the present patient, 13 expressed the SDHD gene mutation; however, 9 had developed bilateral CBTs, accounting for 29.0% (9/31) of all family members. The incidence in the present study was slightly increased compared with the study conducted by Rush (25.9%; 7/27) (19). Of the three types of genetic mutation, SDHC gene carriers are seldom associated with malignancy and this mutation usually occurs as an isolated mutation (11). However, patients with the SDHD or SDHB genetic mutation are more likely to develop CBTs at a relatively early age (18,20,21). All 9 family members with CBT identified masses in the neck during their thirties and forties. The 3 members without masses were young in age, at ~3, 4 and 7 years old. Predicting the development of CBTs in the 3 children may be challenging. However, the incidence

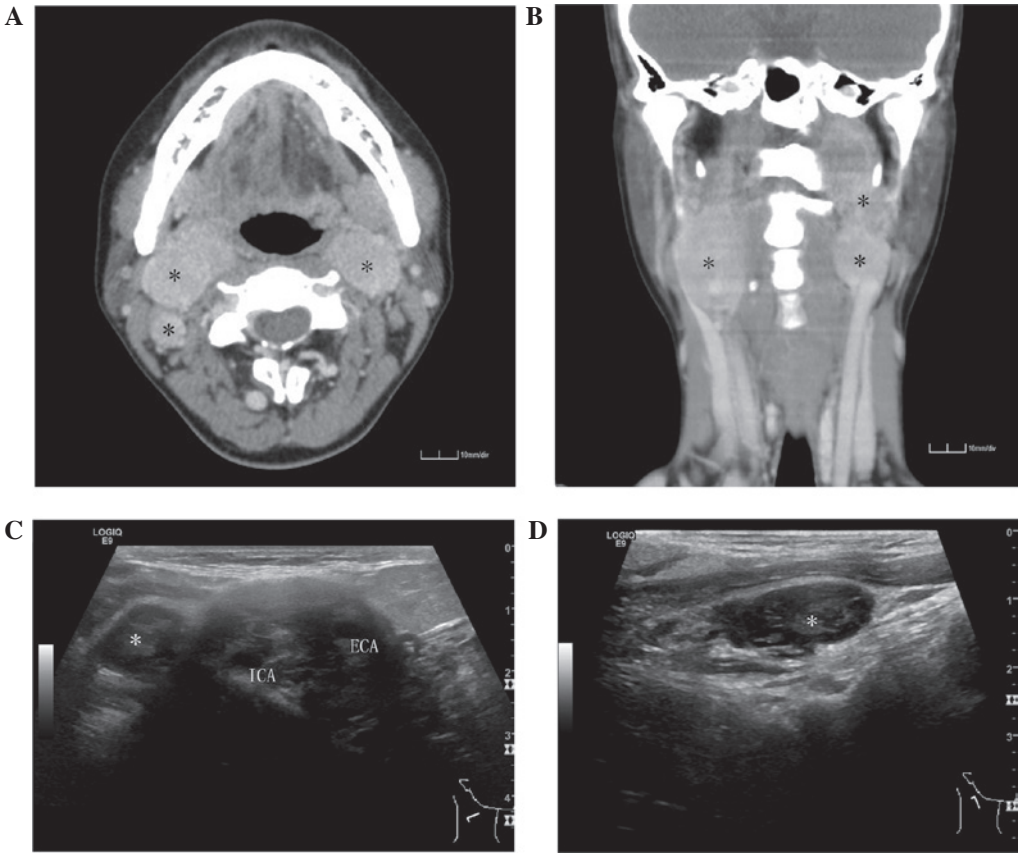

Figure 1. (A) Enhanced-CT and (B) CTA scans revealed the bilateral masses with enhancement (asterisks). (C) Transverse B-mode ultrasounds revealed an inhomogeneous hypoechoic, well-defined mass in the right neck. (D) An enlarged lymph node was also identified in the right side of the neck (asterisk). CTA, computed tomography angiography.

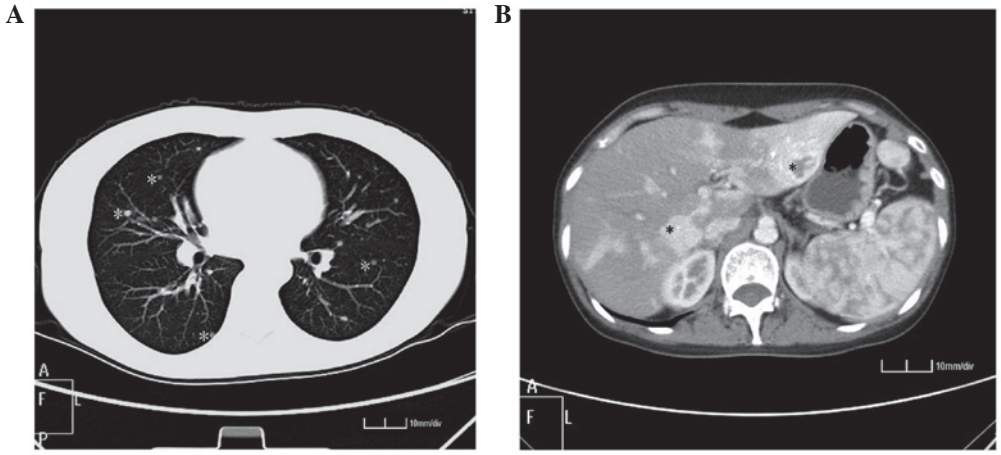

Figure 2. (A) Non-enhanced CT examinations revealed multiple nodules scattered in the two lung fields (asterisks). (B) Enhanced CT scan demonstrated numerous nodules in various sizes within the liver, including heterogeneous significant enhancement at the arterial phase (asterisks). CT, computed tomography.

of CBTs is increased in the familial form compared with sporadic cases, which elucidates the requirement for extra vigilance in order to enable the early detection of disease (21). A previous study reported that the incidence of malignancy is decreased in mutated SDHD gene carriers compared with mutated SDHB gene carriers, affecting 0/34 and 11/32 family members, respectively (18). The only family member to demonstrate malignant CBT in the SDHD-positive family members reported in the present study is a rare case.

Radiological findings are important in diagnosing CBT. Usually, CT and computed tomographic angiography (CTA) scans, magnetic resonance (MR) and magnetic resonance angiography (MRA) imaging, conventional ultrasounds, color Doppler ultrasounds and carotid conventional angiography (CA) are used (22). The CT images best revealed the shape, size, margin, blood supply and adjacent infiltrations of the tumor in the present case. On CT images, a carotid tumor is identified as a well-defined soft tissue mass with

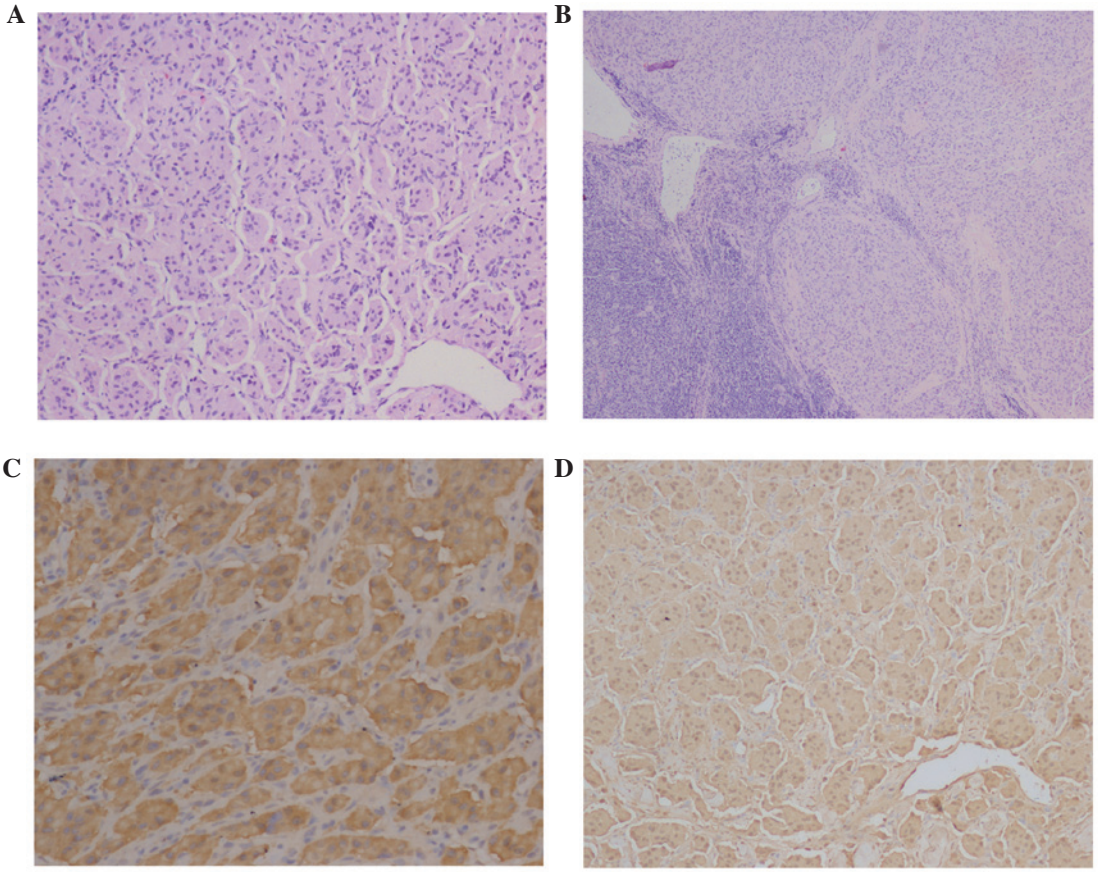

Figure 3. Histopathological characterization of tumor invasion to the regional lymph node; original magnifications, (A) x20 and (B) x4. Tumor cells demonstrated the characteristic Zellballen pattern of paragangliomas. Immunohistochemically, the tumor cells demonstrated strong cytoplasmic reactivity to (C) synaptophysin (original magnification, x40) and (D) neuron-specific enolase (original magnification, x40).

a homogeneous enhancement that is located within the carotid sheath. Larger tumors are frequently inhomogeneous due to necrotic and hemorrhagic regions (23). The ECA is usually displaced anteromedially and the ICA is typically displaced posterolaterally, which strongly indicates a diagnosis of CBT (24). These features were characteristically identified in the images of the present study. Fritzsche *et al* regarded signs such as increased tumor weight, confluent necrosis and the presence of vascular or extensive local invasion as indications of malignant CBTs (25). However, these signs were not always present in malignant cases. In the present study, confluent necrosis and vascular invasion was not identified. The majority of the tumor regions were clear; however, the size of the tumor and local invasion may be indications of malignancy. Potential indicators to better diagnose a malignant CBT according to the present study may include: i) The surrounding of the ECA and ICA by the tumor and ii) the upwards infiltration of the lesion reaching up to the base of the skull, which indicates a neurological tumor with an infiltrative growth pattern along the nerve; and iii) the presence of enlarged and significantly enhanced regional lymph nodes and multiple pulmonary and hepatic lesions, which support metastasis. Additionally, Serra *et al* evaluated metalloproteinase (MMP) levels in the plasma, using the enzyme-linked immunosorbent assay (ELISA) test, and in tissue samples, using western blot analysis (26). The previous study reported that patients with malignant CBTs showed significantly increased levels ($P<0.01$) of MMP-1, MMP-2 and MMP-3 compared with patients with benign CBTs. This finding may provide another key point of differentiation between benign and malignant CBTs.

An ultrasound is a rapid, convenient and non-invasive measure that may be used to detect the margin, vascularity and invasion of a mass, and any regional lymph node metastasis. Ultrasounds are more useful for screening familial cases and follow-up procedures. In total, 31 members of the patient's family were scanned using an ultrasound in the present study, 9 of which were identified as having unilateral or bilateral CBT. The possible diagnosis of CBT may be anticipated when a solid mass is detected at the carotid bifurcation. A Doppler analysis of the mass is useful to evaluate intratumor blood flow and is valuable in differentiating chemodectomas from other solid, non-hypervascular masses (27). Doppler analysis may reveal the association between the tumors and carotid artery clearly. Doppler imaging is also sufficient for the primary diagnosis of CBT as it may reveal abundant blood flow, which is characterized as an intense blush of the tumor (28). Contrast ultrasonography may also aid the evaluation of the blood supply to the tumor (29). Therefore, the ultrasound is a suitable technique for the identification of a CBT. However, ultrasounds are also unable to determine whether the CBT is benign or malignant. The possibility of a malignant CBT may only be considered if significant vascular infiltration, regional lymph node invasion or distant

metastasis are present. Ultrasounds are also limited due to an inability to identify deeply located lesions (27). In the present study, the ultrasound failed to identify the margin of the left lesion that infiltrated into the left parapharyngeal space, which may have led to the neglect of the broad extent of the mass, if no additional CT or MR scans had been used.

Microscopic features may not predict the biological behavior of CBTs. According a previous study, malignant CBTs may present with a typical Zellballen growth pattern, necrosis and vascular invasion (30). A highly proliferative and broadly infiltrative growth pattern, necrosis and vascular or perineural invasion were also reported in other cases of malignant CBT (25). The present study reported the pathological features of the lymph node metastasis of the CBT rather than the features of the tumor due to the high risk associated with fine-needle aspiration biopsy or surgery (31). Obtaining histological confirmation of distant metastases may also be challenging; however, in the present study, the Zellballen growth pattern of the lymph node metastasis was quite similar to that of CBT. Additionally, the immunohistochemical examination aided the diagnosis of a neuroendocrine-originating tumor, which was indicated by a strong cytoplasmic reactivity to synaptophysin and NSE. Future studies should note that the aforementioned diagnostic features may also be detected in benign CBTs. Nuclear pleomorphisms and mitoses may provide additional evidence of a malignant mass.

In conclusion, familial cases of bilateral CBTs are rare. Families with members that possess the SDHD gene mutation may demonstrate a significantly increased incidence of multifocal lesions. Radiological images are complementary techniques that may be used to evaluate the extent of lesions. Pathological features and immunohistochemical examinations may be used as diagnostic tools for the identification of NSEs. Malignant CBTs may present the following features: i) The ECA and ICA are surrounded by the tumor; ii) the upwards infiltration of the lesion reaches the skull base, which may indicate a neurological tumor, with an infiltrative growth pattern along the nerve; and iii) metastasis supported by enlarged and significantly enhanced regional lymph nodes and multiple pulmonary and hepatic lesions. An ultrasound may reveal the association between the tumors and carotid artery clearly. However, with the exception of the ELISA and western blot analysis of the MMP level, CT imaging and pathological examinations do not aid the differentiation between benign and malignant tumors if infiltration or local/distant metastases are not exhibited. Extra vigilance is required in order to enable the early detection of CBTs in the familial setting.

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