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Case Report

Chromophobe renal cell carcinoma-like thyroid carcinoma: possible misdiagnosis as metastatic renal cell carcinoma

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Abstract: To date, multiple thyroid cancer variants have been reported. Herein, we report a rare case of chromophobe renal cell carcinoma-like thyroid carcinoma (CRETHCA) in a 60-year-old woman, for which the morphologic findings resembled those of chromophobe renal cell carcinoma (ChRCC). ChRCC of the kidney is characterized by large polygonal tumor cells with distinct cell borders, perinuclear clearing, multiple binucleate cells, and strongly positive immunostaining for paired box gene 8 (PAX8) and carbonic anhydrase IX (CA IX). In our case, the thyroid gland tumor was incidentally detected by routine medical screening without sufficient medical information; it showed similar histology and immunohistochemical features to ChRCC and was initially misdiagnosed as metastatic ChRCC. Additional tests, including kidney computed tomography and positron emission tomography, revealed no abnormalities in the patient's kidney; therefore, we diagnosed the tumor as CRETHCA. Focal weak staining for thyroid transcription factor 1 (TTF-1) was the only supporting evidence that it was a primary thyroid neoplasm. To the best of our knowledge, this is the second report of CRETHCA in literature. This novel variant is very difficult to distinguish from metastatic ChRCC and can be a diagnostic challenge for pathologists. Further studies of similar cases should be done to define this new entity.

Keywords: Chromophobe renal cell carcinoma, misdiagnosis, poorly differentiated carcinoma, thyroid carcinoma

Introduction

There are many histologic types of thyroid cancer, including papillary carcinoma (PTC), follicular carcinoma, Hurthle cell carcinoma, poorly differentiated carcinoma, and anaplastic carcinoma. These cancers are relatively common, and their histopathologic and clinical characteristics have been well established. Diagnosis of these tumors is usually not challenging with the aid of ancillary tests, including immunohistochemical staining and molecular tests such as *BRAF* and *RAS* mutation analyses [1].

However, some rare types of thyroid cancer have very similar histologic features to cancers of other organs. Thyroid mucinous carcinoma is extremely rare and is characterized by abundant extracellular mucin pools, which are very similar to mucinous (colloid) carcinomas of other organs, such as the colorectum or lungs [2]. Spindle epithelial tumors with thymus-like differentiation (SETTLE) also have similar histologic features to biphasic synovial sarcoma, which has both glandular epithelioid and spindle cell components [3]. Mucoepidermoid carcinoma and squamous cell carcinoma can also occur in other organs. The differential diagnosis of these rare tumors is difficult for pathologists. In most cases, additional immunohistochemical staining is essential to rule out metastatic lesions from other organs.

Herein, we report a case of primary thyroid cancer with histologic and immunohistochemical features similar to those of metastatic chromophobe renal cell carcinoma (ChRCC). This tumor was first introduced as a novel entity by Hirokawa et al. in 2017 [4]. They discovered three cases of tumors out of 12,064 surgically resected primary thyroid cancer cases from their archives and suggested that this novel disease be named chromophobe renal cell car-

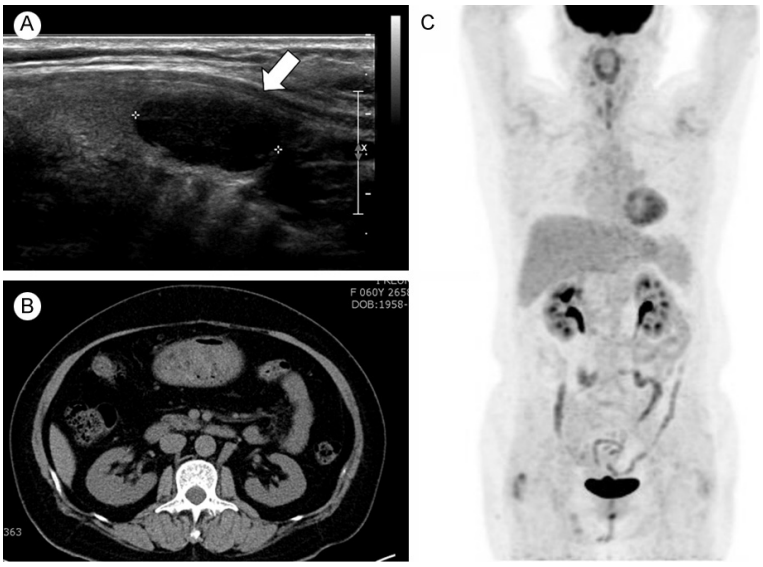

Figure 1. Imaging studies. A. A 1.5-cm low echoic oval mass (arrow) was identified in the left thyroid by ultrasonography. B. There was no suspicious primary lesion in either kidney based on CT scan. C. Torso PET scan also revealed no other primary sites.

cinoma like thyroid carcinoma (CRETHCA). This is the second report of CRETHCA in literature.

Case description

Presentation

A 60-year-old woman presented for a routine medical screening examination at an outside clinic. Her family history was unremarkable, and no abnormalities were observed on physical examination or laboratory evaluation. Ultrasonography revealed a 1.5-cm hypoechoic ovoid mass in the left thyroid and multiple nodules on both sides (**Figure 1A**). Laboratory test results were unremarkable: intact-parathyroid hormone [PTH], 47.44 pg/mL [11~62]; triiodothyronine (total), 1.91 nmol/L [1.2~2.8]; free-thyroxine, 15.13 pmol/L [10~25]; thyroid-stimulating hormone, 2.62 μ/L [0.3~4]; thyroglobulin, 50.48 ng/mL [2~70]; and anti-Tg Ab, negative. Fine needle aspiration was performed at a local clinic. We reviewed the aspiration cytology slides submitted to our hospital. We diagnosed the tumor as class VI based on the Bethesda classification. The patient underwent total thyroidectomy and central lymph node dissection. After surgery, computed tomography (CT) of the kidney (**Figure 1B**) and positron emission tomography (PET) scan (**Figure 1C**) were performed.

Cytologic examinations

Conventional aspiration cytology showed some sheets and clusters of cancer cells with marked blood obscuring (**Figure 2A**). The tumor cells had a polygonal or round shape with more abundant cytoplasm compared to other well-differentiated thyroid carcinoma cells. The nuclei were oval shaped with irregular membranes resembling koilocytes and with occasional grooves (**Figure 2B**). Diagnosis was less than optimal with severe blood-obscuring artifacts. We diagnosed the tumor as a malignancy with the possibility of papillary carcinoma.

Histologic examination

After aspiration cytology, the patient underwent total thyroidectomy. Gross examination of the resected specimen revealed two distinct masses in the left lobe. The first mass was a 1.5-cm, well demarcated, grayish colored mass with a thin fibrous capsule. The mass showed a homogeneous cut surface with no necrosis or hemorrhage (**Figure 3A**). The second mass was a firm, white small mass, and was diagnosed as micropapillary carcinoma. Histologic examination of the first mass, which was examined by fine needle aspiration cytology, showed an encapsulated mass with a thin fibrous capsule. The tumor cells showed a nested or solid growth pattern and were surrounded by a thin vascular stroma with definite trans-capsular invasive foci (**Figure 3B**). The tumor cells were large, polygonal-shaped, and had a wrinkled nuclear contour and perinuclear halo, mimicking koilocytes. The cells had abundant clear to eosinophilic cytoplasm, and binuclear tumor cells were frequently observed (**Figure 3C**). No necrosis or mitotic activity was observed.

Ancillary tests

We performed immunohistochemical staining for the differential diagnosis. Tumor cells stained diffuse and strongly positive for CA IX (**Figure 4A**), PAX8 (**Figure 4B**), and cytokeratin 7 (CK7). Vimentin was also expressed in the

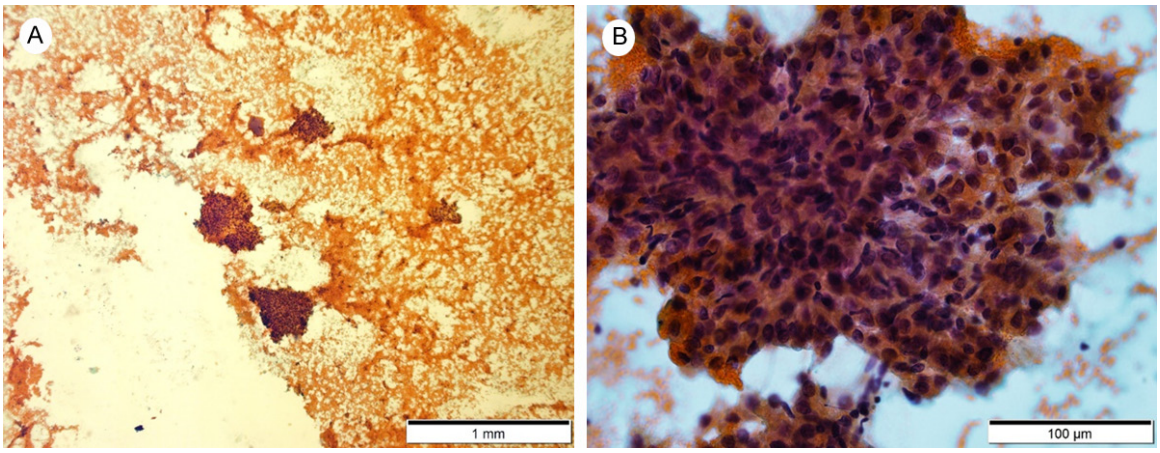

Figure 2. Fine needle aspiration cytology of CRETHCA. A. Aspiration cytology showed some sheets and clusters of cancer cells with marked blood obscuring (PAP stain, ×40). B. The nuclei of tumor cells were oval shaped with irregular membrane resembling koilocytes and had occasional grooves (PAP stain, ×400).

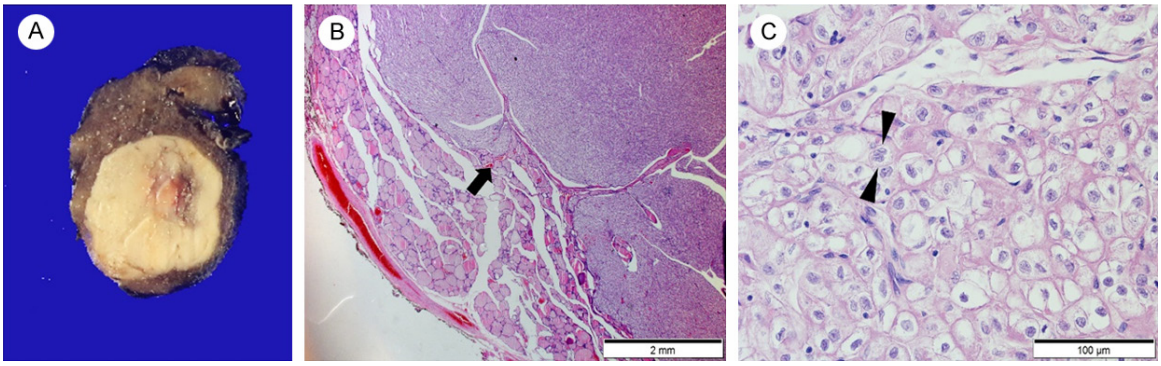

Figure 3. Histologic examination of CRETHCA. A. Grossly, the tumor was surrounded by thin fibrous capsule and the cut surface of tumor was homogeneous. B. Histologic examination revealed a relatively encapsulated mass with a nested growth pattern surrounded by thin vascular stroma with definite invasive foci (arrow) (H&E, ×20). C. The large polygonal tumor cells showed wrinkled nuclear contour and perinuclear halo, mimicking koilocytosis. The cells exhibited abundant clear to eosinophilic cytoplasm. Binuclear tumor cells (arrowhead) could be frequently observed (H&E, ×400).

tumor cells with weak intensity. The cells were focally positive for TTF-1 (**Figure 4C**) and thyroglobulin (**Figure 4D**). However, calcitonin, PTH, synaptophysin, and cluster of differentiation 10 (CD10) were completely negative. Immunohistochemical staining for p53 showed wild-type pattern with weak nuclear staining of less than 10% of the tumor cells. The smaller mass beside the main tumor exhibited typical features of PTC. Histology of the main tumor revealed the typical morphologies of chromophobe renal cell carcinoma (ChRCC), with strong immunoreactivity for CA IX and PAX8, which are very sensitive diagnostic markers of RCC. Based on these findings, the patient was initially diagnosed with metastatic RCC. She underwent additional CT of the kidney (**Figure 1B**) and torso PET scan (**Figure 1C**) to identify the primary tumor of the kidney. However, there were no suspicious primary lesions in either kidney. We could not find any other possible primary organs.

Additional molecular tests for BRAF V600E (BRAF Pyro kit, Qiagen, Germany) and NRAS mutation (NRAS Pyro kit, Qiagen, Germany) were performed using the pyrosequencing technique, and the BRAF V600E mutation was not detected in RCC, such as tumors and PTC. The NRAS test revealed a missense mutation in codon 61 (Q61R) in PTC. No alterations in NRAS in codons 12, 13, and 61 were identified in RCC-like tumors.

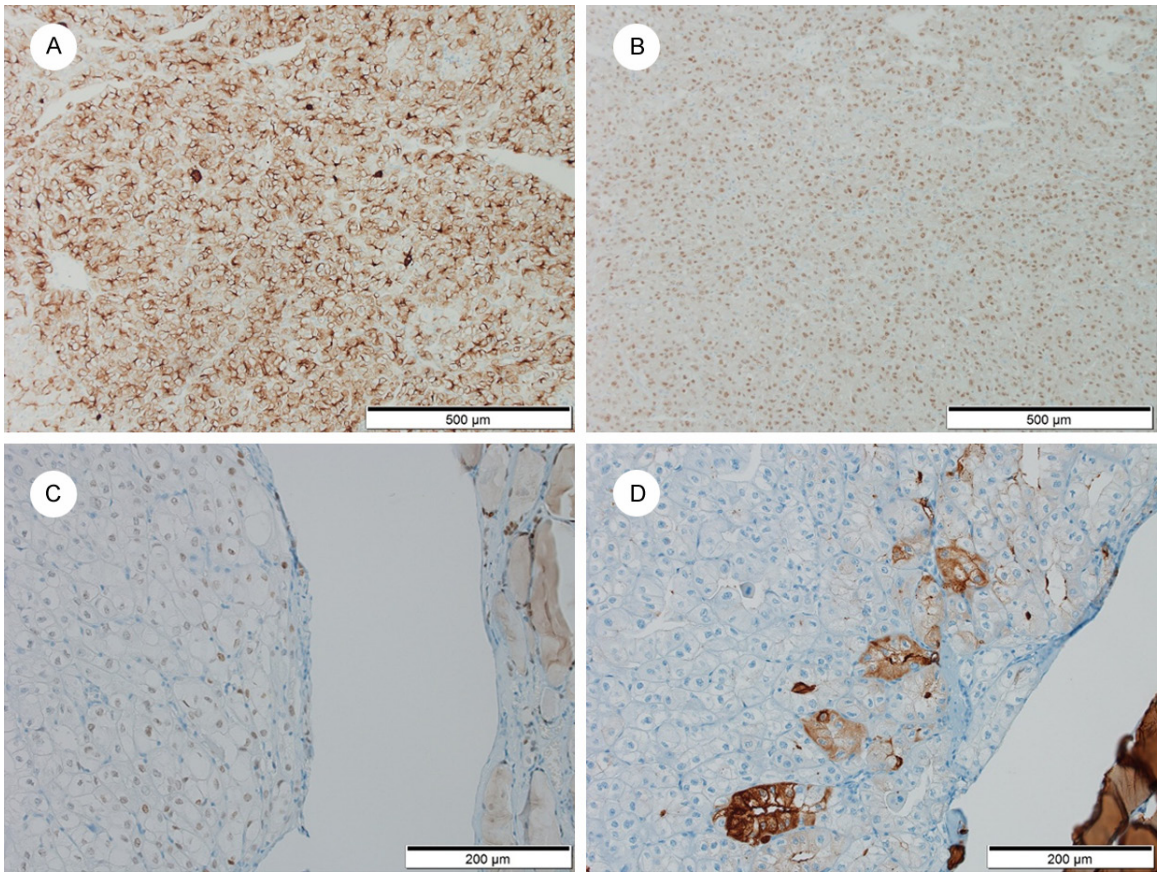

Figure 4. A. The tumor cells stained positive for strong CA IX (×100). B. PAX8 is also strongly expressed in tumor cells (×100). C. However, the cells presented focal positivity for TTF-1 (×200). D. Thyroglobulin was expressed focally at the periphery of the tumor (×200).

Diagnosis and follow-up

We reviewed the literature and found one report that discussed a novel type of thyroid tumor mimicking ChRCC with distinct clinicopathological characteristics by Hirokawa et al. [4]. They named it CRETHCA. Although it was a novel disease, the morphologic and clinical findings of our case were consistent with CRETHCA. Thus, the patient was diagnosed with CRETHCA. For 36 months follow-up, imaging studies showed no evidence of local recurrence or distant metastasis.

Discussion

Chromophome renal cancer (ChRCC) is a subtype of RCC with a more favorable prognosis. ChRCC accounts for less than 5% of all RCCs [5]. It arises from the intercalated cells of the collecting ducts [6]. ChRCC is characterized by a distinct histology wherein the tumor cells are arranged in a solid and sheet-like pattern with delicate vascular septa. They are usually large, and polygonal in shape with distinct cell borders, and pale or reticulated (chromophobe) cytoplasm [5]. However, the size of the eosinophilic variant of tumor cells is less, with oxyphilic cytoplasm. Tumors are usually composed of these two types of cells in variable proportions. This tumor has distinct cytologic features, including perinuclear haloes, frequent binucleation, and markedly irregular nuclear contours [7, 8]. Therefore, they look like koilocytes, which are characteristic squamous cells infected by human papilloma virus.

CRETHCA was newly introduced by Hirokawa et al. in 2017 [4]. Until now, only three cases have been reported, all in their study. They found these three cases out of 12,064 resected thyroid cancer cases. Therefore, CREHTCA may be extremely rare. They suggested that it is a novel histologic type of thyroid cancer with dis-

tinct clinicopathologic features. All three cases had very similar histology to that of ChRCC. The tumor cells were large, polygonal shaped, with a trabecular patterned arrangement. They had abundant pale, granular, and eosinophilic cytoplasm with koilocyte-like irregular nuclei [4]. Therefore, they were named CRETHCA.

Interestingly, in the previous study, all patients were young adults aged between 15 and 21 years. In Hirokawa's study, two patients had a TSC-associated history, including epilepsy and several benign tumors in other organs. These two cases shared not only histologic features, but also clinical features, with TSC-associated ChRCC. TSC is an autosomal dominant genetic disorder that results in the mutation of either *TSC1* (chromosome 9q34), encoding the protein hamartin, or of *TSC2* (chromosome 16p13), encoding the protein tuberin [9]. These proteins act as tumor suppressors in the *mTOR* pathway. Therefore, a common manifestation of TSC is the occurrence of various tumors in many organs [10]. Renal involvement is very common, and approximately 80% of patients with TSC exhibit renal manifestations. Angiomyolipoma or renal cyst is a common type of renal manifestation. RCC is rare, and only 2%-4% of TSC patients have been reported to have RCC [9]. Various types of RCC, including clear cell RCC, papillary RCC, ChRCC, and RCC, have been reported in TSC patients. Despite its low incidence, ChRCC is a common type of RCC in TSC patients, which usually occurs in younger age groups, similar to the CRETHCA cases [11]. Based on this, they suspected that the etiopathogenesis of CRETHCA could be linked to genetic abnormalities in TSC [4]. However, our patient and another case from Hirokawa's study were not associated with TSC. Thyroid involvement in TSC is rarely reported. A few cases of papillary carcinoma and medullary thyroid carcinoma in TSC patients have been reported [4, 12, 13]. Thus, the relationship between thyroid tumors and TSC has been controversial. More cases and comprehensive genetic analysis are needed to determine the relationship between TSC and CRETHCA.

The most important differential diagnosis of CRETHCA is metastatic RCC of the thyroid gland. In our study, the initial diagnosis was metastatic ChRCC. Secondary thyroid tumors are very uncommon, accounting for only 2% of thyroid cancers [5, 6]. In daily practice, pathologists rarely encounter secondary tumors, which are found in 0.13% of thyroidectomies and 2.3-7.5% in fine needle aspiration biopsies [5]. Based on clinical studies, the kidney has been reported to be the most common source of metastatic disease of the thyroid, and clear cell renal cell carcinoma is the most common primary tumor [7]. ChRCC is a rare tumor with a favorable prognosis and lower rate of distant metastasis. Thyroid metastasis in ChRCC has rarely been reported.

In most cases, distinguishing metastatic RCC from primary thyroid neoplasms is not problematic. However, RCC can initially present as a single thyroid mass. Sometimes, it can mimic microfollicular or alveolar patterns, which are frequently observed in thyroid neoplasms [1]. Occasionally, metastatic clear cell RCC resembles primary thyroid neoplasm with clear cell features. The oncocytic cytoplasm of ChRCC can also mimic Hurthle cell neoplasm of the thyroid. Therefore, obtaining a differential diagnosis can be difficult. Integrating the medical history and clinical and ancillary test findings of patients usually helps in accurate diagnosis of the situation. In particular, immunohistochemistry (IHC) for thyroid markers, such as TTF-1, TG, and PAX8, is useful in distinguishing metastatic tumors from thyroid neoplasms. All four cases from our and Hirokawa's studies showed positive staining for TTF-1, TG, and PAX8 [4]. This supports the identity of tumors as a primary thyroid neoplasm.

However, pathologists should carefully interpret IHC for PAX8. *PAX8* is a paired-box gene important in embryogenesis of the thyroid, Müllerian, and renal/upper urinary tracts, and expression of PAX8 has been previously described in carcinomas from each of these sites [14]. Therefore, PAX8 is a highly sensitive diagnostic marker for thyroid epithelial tumors. It is expressed in most types of thyroid neoplasms, including papillary carcinoma, follicular neoplasm, and poorly differentiated carcinoma. PAX8 is expressed in approximately 90% of thyroid neoplasms. The sensitivity and specificity were similar to those of TTF-1 and TG [15]. However, it can also be expressed in most renal cell carcinomas and is not a helpful marker for distinguishing metastatic renal cell carcinoma from thyroid neoplasms. Four CRETHCA cases showed diffuse strong positiv-

ity for PAX8. In this situation, additional IHC markers for thyroid cancer, such as TTF-1 and TG, as well as markers for RCC, such as CD10, vimentin, CA IX, and CD117 may be helpful. Three CRETHCAs from Hirokawa's study showed negative expression of CD10, CA IX, and CD117. However, our case was negative for CD10, but positive for CA IX and vimentin. Therefore, a combination of these markers is essential. Additional BRAF and RAS mutation tests, which are commonly observed in thyroid neoplasms, may be helpful. All four cases had wild-type *BRAF* and *RAS*.

Imaging studies are also important. In our case, the tumor expressed thyroid markers (TG, TTF-1, and PAX8) and renal cell carcinoma markers (RCC marker, vimentin, and PAX8). In this situation, imaging studies to search for primary renal mass are essential. Therefore, we performed kidney CT and PET scans. After confirmation of the absence of a renal mass, we finally diagnosed the tumor as CRETHCA. There have been several reports of metastatic RCC without primary renal lesions [16], although this condition is extremely rare, and it remains unclear how this could happen. One theory is that the renal mass is too small for detection. According to this theory, the primary renal mass may be found later. Thus, regular follow-up of imaging studies of the kidney is needed to completely exclude the possibility of metastatic RCC. Another theory is the spontaneous regression of the primary tumor. Therefore, thorough history-taking and reviewing of previous medical records are also essential.

In conclusion, we report the fourth case of CRETHCA, a novel subtype of thyroid malignancy. We describe its distinct pathologic characteristics, which share histologic and immunohistochemical features with typical ChRCC. Given that very few reports of CRETHCA are available in the literature, its evaluation and diagnosis could be challenging. It can be easily misdiagnosed as metastatic RCC without precise history taking and imaging studies. To avoid this, the medical history, clinical features, and histologic findings of the patients should be carefully considered. Immunohistochemical staining of TTF-1 and TG may be helpful. To the best of our knowledge, this is the first report of CRETHCA in an elderly patient. Future studies should investigate the differences between young and elderly patients with CRETHCA. More cases are needed to precisely define this new entity.

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Disclosure of conflict of interest

None.

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