Primary follicular thyroid carcinoma metastasis to the kidney and widespread dissemination: A case report

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Abstract. Distant metastases are more common in follicular thyroid carcinoma (FC) than in papillary thyroid carcinoma. However, FC metastasis to the kidney with eggshell calcification, as observed in the present case, is rare. The current report presents a case of a 67-year-old woman exhibiting a solitary tumor in the mid pole of the left kidney. Radical nephrectomy was performed, as the tumor was diagnosed as a primary renal carcinoma using contrast-enhanced computed tomography. Once the tumor was confirmed to be FC, total thyroidectomy was performed. Following administration of an oral therapeutic dose of 100 mCi ^{131}I, functional imaging demonstrated the presence of multifocal metastases in the chest and abdomen. Euthyrox® was prescribed orally to aid normal thyroid function. Follow-up 6 months later using radionuclide imaging demonstrated the disappearance of the multifocal metastases in the chest and abdomen. The distant metastasis of FC may represent the initial symptom of the primary lesion, which was neglected. Ultrasound is an effective method to examine nodules located on the thyroid.

Introduction

Follicular thyroid carcinoma (FC) is the second most common malignancy of the thyroid, and accounts for ~10% of all thyroid malignancies (1). FC predominantly affects elderly females (2). Follicular adenomas are more common than follicular carcinomas (3,4). In contrast to adenomas, carcinomas exhibit microscopic vascular or capsular invasion (5). Follicular carcinoma patients with extensive vascular invasion exhibit a poorer prognosis, and distant metastases are occasionally present (5-8). Hematogenous metastasis is most commonly observed, via the systemic circulation or the paravertebral plexus. Lymphatic spread, which is less common, is also possible. Distant metastases are more common in FC than in papillary thyroid carcinoma (PC) (9). Furthermore, distant metastasis occurs in >20% of FC cases and lung and bone metastases are common (10-12). However, FC metastasis to the kidney is rare (1). Ultrasound is useful for the evaluation of thyroid nodules due to its high resolution, lack of radiation exposure, portability and ease of use (13,14). A number of retrospective studies have investigated the features of follicular carcinomas exhibited on ultrasound. Calcifications are common features of thyroid malignancies. Previously, eggshell calcifications were considered an indicator of benign tumors (15). However, cases of PC associated with this type of calcification have been reported (16,17). To the best of our knowledge, only a small number of cases of follicular carcinoma with an eggshell calcification have been reported in the literature (18). The present study reports a case of FC with metastasis to the kidney in a patient exhibiting widespread dissemination of the disease.

Case report

In July 2010, a 67-year-old woman was referred to the Department of Urinary Surgery, West China Hospital of Sichuan University (Chengdu, China) upon being diagnosed with a solitary tumor in the left kidney at Chengdu No. 1 People's Hospital (Chengdu, China). The present study was performed in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Sichuan University. Written informed consent was obtained from the patient. Physical examination and laboratory tests were normal. Ultrasound (US; iU22; C5-2 MHz convex transduced and L12-5 MHz linear probe; Philips Healthcare, Bothell, WA, USA) examination revealed a solitary heterogeneous hyperechoic mass with an interior irregular anechoic area located in the mid pole of the left kidney (Fig. 1A). The shape of the tumor was regular and the margin was circumscribed. The size of the tumor was 2.8x2.3x2.5 cm, and there were no internal color Doppler signals. The patient was additionally examined by contrast-enhanced computed tomography (CECT; Philips Brilliance; Philips Medical Systems, Cleveland, OH, USA), and the preoperative diagnosis was suspected to be primary

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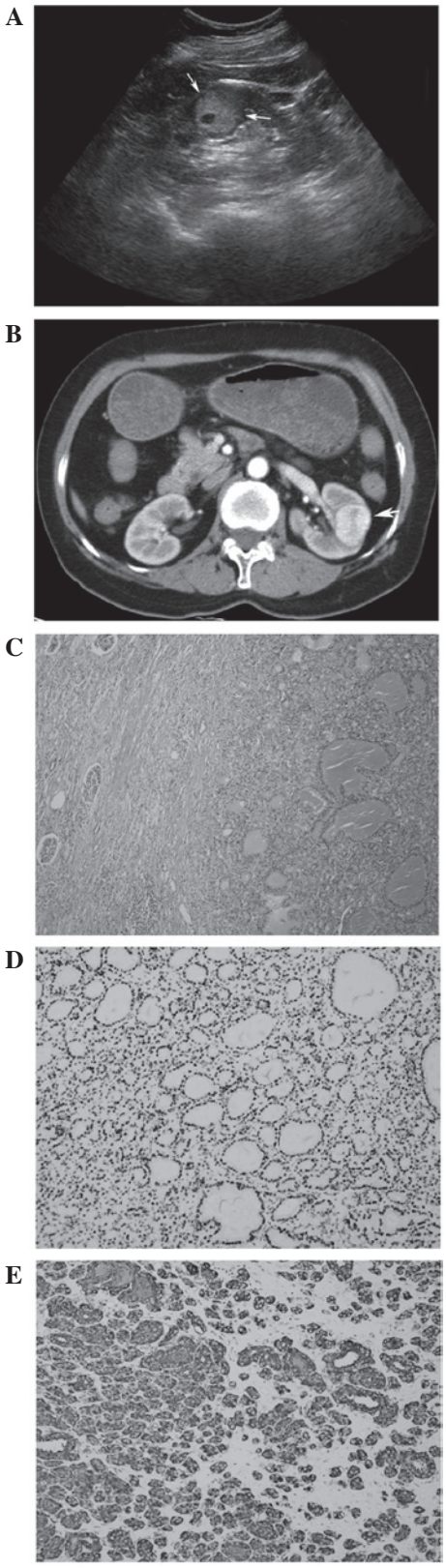

Figure 1. (A) Ultrasound imaging identified a solitary heterogeneous hyperechoic mass in the left kidney (white arrows). (B) A solitary high-density mass was detected in the left kidney by contrast-enhanced computed tomography (indicated by the white arrow). (C) The tumor cells in the kidney, the majority of which were arranged into small follicles, were consistent with the original site. A small quantity of gelatin was noticed in the follicles, interior of the kidney, glomeruli of the remnant tumor and renal tubule (hematoxylin and eosin staining; magnification, x200). The tumor cells in the kidney were visualized by immunohistochemistry staining for (D) thyroid transcription factor-1 and (E) hTG, which revealed positive staining of the nuclei and the cytoplasm, respectively (magnification, x200).

malignancy of the left kidney (Fig. 1B). Therefore, the patient underwent a left radical nephrectomy. Hematoxylin and eosin stained sections of the dissected surface of the resected mass were evaluated using a BX51 Olympus microscope (Olympus Corporation, Tokoyo, Japan), which revealed a distinct puce color and focal hemorrhagic necrotic contents. The postoperative pathological diagnosis was metastatic FC (Fig. 1C-E). Six months later, the patient was readmitted to the West China Hospital of Sichuan University for thyroid surgery.

The patient's initial clinical manifestation of the disease was a sensation of cold or occasional heat, with no dyspnea or dysphagia. On palpation, a moderately tender mass with an irregular and rough surface was identified in the right lobe of the thyroid, which was observed to move during deglutition. No regional lymphadenopathy was noted. US examination with a high-frequency linear probe transducer (12.5 MHz) revealed a hypoechoic lesion with eggshell calcification and incomplete halo in the upper pole of the right lobe of the thyroid gland. Simultaneously, a hyperechoic lesion with heterogeneous enhancement was noted in the mid pole of the thyroid, which presented macrocalcifications and an incomplete halo. The size of the lesion located in the upper pole of the thyroid was 2.5x2.3x2.5 cm, and the size of the lesion in the mid pole was 2.9x2.5x3.4 cm. The shape of the upper lesion was regular and its margin was circumscribed, while the shape of the lower lesion was irregular and its margin was ill-defined. The eggshell calcification was continuous, with marked echo attenuation at the back of the upper lesion (Fig. 2A). Doppler study revealed the presence of a punctiform and an irregular-distribution blood flow signal in the upper and lower lesion, respectively (Fig. 2B). Doppler-like blood flow was noted inside the lesion, with a high resistance index of Doppler waveform. CECT of the neck revealed an upper lesion exhibiting low density in the right lobe of the thyroid, with a high density of calcification in the margins, and an additional lower lesion with low density, macrocalcifications, circumscribed margin and incomplete halo (Fig. 2C and D). Thyroid profile demonstrated levels of thyroid stimulating hormone (TSH), 0.74 mU/l (normal, 0.27-4.20 mU/l); free triiodothyronine, 6.40 pmol/l (normal, 3.60-7.50 pmol/l); free thyroxine, 16.08 pmol/l (normal, 12.00-22.00 pmol/l); human thyroglobulin (hTG), 52.48 μg/l (normal, 1.40-78.00 μg/l); anti-TG antibody (TgAb), 15.89 IU/ml (normal, <115.00 IU/ml); and anti-thyroid peroxidase (TPO) Ab, 12.84 IU/ml (normal, <34.00 IU/ml). The patient's levels of serum bone alkaline phosphatase were markedly increased (38.78 μg/l; normal, 11.40-24.60 μg/l). The patient underwent total thyroidectomy and subsequent excision of the cervical lymph node of the central zone of the thyroid.

During surgery, the thyroid was observed to be markedly hyperemic, with abundant vasa vasorum. The dissected surface of the two lesions in the right lobe of the thyroid exhibited distinct white contents, without haemorrhagia or necrosis. Two lymph nodes of ~0.5 cm in diameter located behind the trachea were also excised. The postoperative pathological results of the two lesions confirmed the diagnosis of FC, while the resected lymph nodes did not display infiltration (Fig. 2E and F). Postoperative laboratory tests revealed serum levels of TSH, 3.19 pmol/l; calcium, 1.90 mmol/l (normal, 2.10-2.70 mmol/l); magnesium, 0.77 mmol/l (normal, 0.67-1.04 mmol/l); inorganic phosphorus, 0.74 mmol/l (normal, 0.81-1.45 mmol/l); and

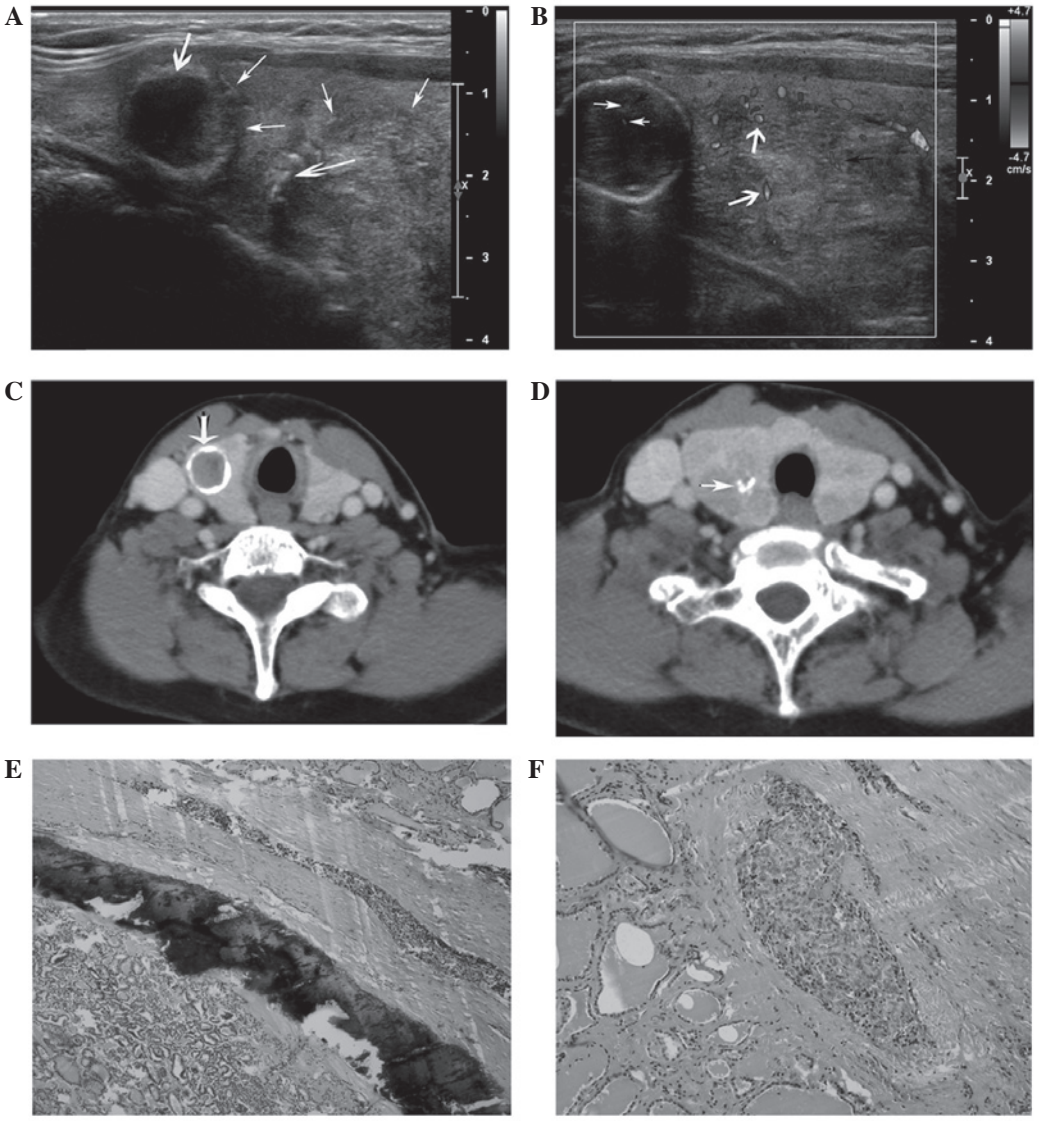

Figure 2. (A) A hypoechoic lesion exhibiting eggshell calcification, and a heterogeneous hyperechoic lesion exhibiting macrocalcifications were detected in the right thyroid lobe via ultrasound imaging (indicated by the black arrows). The halo of the two nodules was incomplete and their thickness was unequal (indicated by the white arrows). (B) A punctiform blood flow signal was observed in the upper lesion (indicated by the white arrows), and a blood flow signal of irregular distribution was observed in the lower lesion (indicated by the black arrow) in color Doppler flow imaging. Contrast-enhanced computed tomography identified (C) a low-density mass exhibiting eggshell calcification in the upper pole of the right thyroid lobe and (D) a low-density mass located in the mid pole of the right thyroid lobe (indicated by black arrows). (E) The primary focal tumor cells displayed a cubic shape and were arranged into small follicles, in contrast to the structure of the peripheral tumor, which presented a thicker fiber-coat and focal flake-like Aizen calcifications. Isolated tumor cells infiltrating through the encapsulation were also observed (hematoxylin and eosin staining; magnification, x100). (F) The infiltrating primary tumor cells were observed to be fiber-coated, arranged in solid small follicles and connected with blood vessels (hematoxylin and eosin staining; magnification, x400).

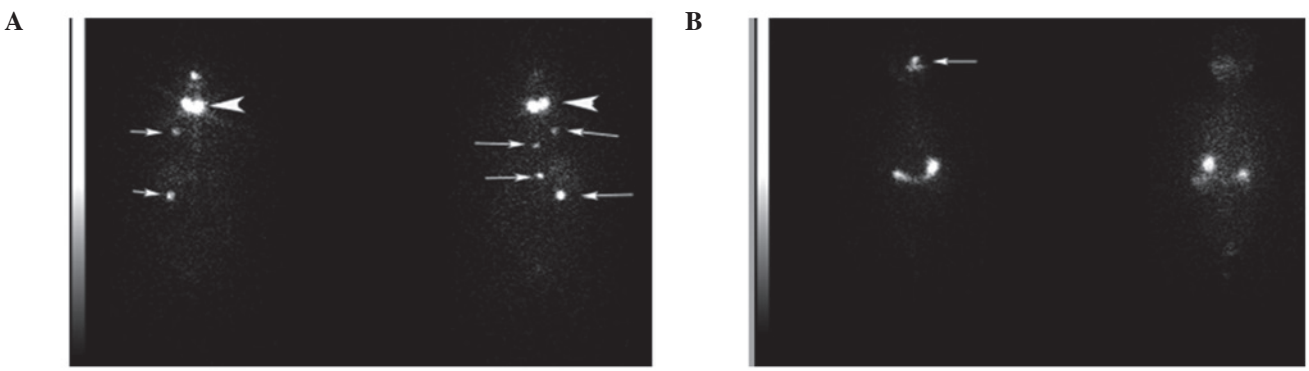

Figure 3. (A) Radioactive ^{131}I imaging identified remnants of thyroid parenchyma in the cervix and multifocal metastases in the chest and abdomen (indicated by the white arrowheads and arrows, respectively). (B) Functional imaging performed six months later, demonstrated the disappearance of the multifocal metastases in the chest and abdomen. However, remnants of thyroid parenchyma were still observed in the cervix (indicated by the white arrow).

calcitonin, 1.40 pg/ml (normal, 0.07-12.97 pg/ml). The patient experienced a favorable postoperative recovery, and was readmitted to the West China Hospital of Sichuan University for radionuclide therapy two months later. Radioactive ^{131}I (Chengdu Gaotong Isotope Co., Ltd., Chengdu, China) uptake by the thyroid was determined to be 3.7% in 24 h using a Precedence SPECT/CT Imaging System (Philips Healthcare). A small number of parenchyma cells corresponding to remnants of the thyroid were identified in the thyroid region. Following administration of an oral therapeutic dose of 100 mCi ^{131}I, functional imaging of the parenchyma remnants in the thyroid and cervical region revealed the presence of multifocal metastases in the chest and abdomen (Fig. 3A). Further treatment with thyroid suppression therapy using oral Euthyrox® (100 μg; Merck KGaA, Darmstadt, Germany) was administered daily. The patient underwent functional imaging therapy with oral ^{131}I six months later, which demonstrated the disappearance of the multifocal metastases (Fig. 3B). The thyroid profile results demonstrated revealed levels of TSH, 79.06 mU/l; TgAb, 19.90 IU/ml; TPOAb, 19.47 IU/ml; and hTG, 0.74 μg/l.

The patient was last observed during follow-up in July 2013, and the patient was alive and well. Following this the patient was lost to follow-up.

Discussion

FC is usually more aggressive and metastasizes more frequently than PC (10). Metastasis of FC to the bones and lungs are common, while metastasis to other tissues and organs, including the kidney, skin and skull base, is rare (19-22). FC differs from PC in its main route of metastasis, since FC primarily metastasizes via the blood, whereas PC primarily metastasizes via the lymphatic system (23), which explains why the incidence of cervical lymphadenopathy in FC is lower than in PC (24). In the present case, the cervical lymph nodes were not infiltrated, as confirmed by postoperative pathological examination.

High-frequency US is an important method for examining thyroid nodules (25). FC is frequently misdiagnosed as follicular thyroid adenoma (FTA), due to the similar characteristics displayed by FTA and FC in US imaging (9). Particularly, the presence of cervical lymphadenopathy is an indirect sign of carcinoma in US diagnosis (23). Metastasis is often the initial symptom of FC, since patients usually remain asymptomatic in regards to thyroid function (1). This leads to metastases frequently being misdiagnosed as primary tumors until the postoperative pathological examination confirms the primary lesion to be FC (19), as occurred in the present case.

The presence of two FC lesions located in the same lobe of the thyroid, with multiple foci and low occurrence rate, has been previously reported in the literature (26), in contrast to the frequent multicentricity observed in PC (27). In the present case, one lesion displayed continuous peripheral eggshell calcification, while the other lesion exhibited macrocalcifications. It is well known that calcification may occur in benign and malignant thyroid lesions (28). To date, three distinct representations of intrathyroidal calcification have been described: Eggshell, dystrophic and fine stippled psammomatous calcification (29). Psammomatous calcification is typically suggestive of PC (30,31), while eggshell calcification, including Hürthle cell carcinoma, is rare and usually considered benign (32). However, Yaturu and Rainer (33) have reported that eggshell calcification does not exclude the presence of cancer. Furthermore, previous studies have confirmed the occurrence of eggshell calcification in FC (34-36). Therefore, the presence of eggshell calcification is not a specific method to distinguish between benignancy and malignancy (15). Seo *et al* (37) reported that margin calcification is more common in FC than in FTA. In the present case, the lesion exhibiting eggshell calcification also displayed punctiform blood flow signals, in agreement with previous findings by Lee and Rho (35). In previous studies, a lesion with characteristics of FC, including solid echogenicity, ill-defined margins, incomplete halo and macrocalcifications, was identified by US (32,35,38,39). In addition, the mass displayed a hyperechoic appearance, which is common in FC (27,37). Previous studies have confirmed that the internal signal displayed by FC lesions in color Doppler flow imaging is a risk factor for the diagnosis of FC by US (37,40-42). Additionally, the patient's gender and age have also been associated with an increased risk of being diagnosed with FC (37,43,44).

Fine-needle aspiration (FNA) biopsy has provided a cost-effective and minimally invasive method of determining the presence of malignancy in thyroid nodules, or the risk of developing it (45). Unlike PC, which may be accurately diagnosed by US using FNA biopsy, a diagnosis of FC typically requires an assessment of vascular or capsular invasion, which must be confirmed by histological evaluation (46). Consequently, a diagnosis of FC may only be suspected from FNA biopsies (46). Due to the clinical features of FC, it is important to improve the accuracy of the diagnosis of FC by US, which is currently the main method used to detect thyroid nodules (46). Thus, improved detection methods may reduce misdiagnosis rates of primary FC of thyroid nodules or metastasis to other tissues and organs.

In conclusion, FC often presents at a higher tumor stage, with distant metastases in 25-30% of cases, which is most commonly observed in the lung and bone. However, other metastatic sites have also been reported. Given the rarity of FC metastasis to the kidney, the present case was diagnostically challenging, since the identification of distant metastases may represent initial symptoms of the disease. A renal solitary malignancy should be considered with metastasis pre-surgery and a general check is required, which was observed in the present patient; there was widespread dissemination of FC metastasis pre-surgery. Radioiodine and chronic thyroid-stimulating hormone suppression are effective treatments for widespread metastases, and US is the most important imaging tool for diagnosing thyroid disease. US imaging characteristics of FC may appear atypical during thyroid examination. Therefore, various risk factors should be considered when diagnosing thyroid nodules, including the patient's gender and age.

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