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

DI-MING CAI1, HUI-YAO WANG2, YONG JIANG3, SHYAM SUNDAR PARAJULY1, YE TIAN1, BU-YUN MA1, YONG-ZHONG LI1, BIN SONG4 and YAN LUO1

Departments of 1Ultrasound, 2Resident Doctor Training, 3Pathology and 4Radiology, West China Hospital, Sichuan University, Chengdu, Sichuan 610041, P.R. China

Received January 1, 2015; Accepted October 30, 2015

DOI: 10.3892/ol.2016.4417

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 131I, 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 hypoechoic 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
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, Tokyo, 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 hypoechogenic lesion with eggshell calcification and incomplete halo in the upper pole of the right lobe of the thyroid gland. Simultaneously, a hyperechogenic 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 131I (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 131I, 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 131I 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 PC 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 multilocularity 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 psammomatosus 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 benignity 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.

References

1. Sampson E, Brierley JD, Le LW, Rotstein L and Tsang RW: Clinical management and outcome of papillary and follicular (differentiated) thyroid cancer presenting with distant metastasis at diagnosis. Cancer 110: 1451-1456, 2007.
2. Xu H, Zeng W and Tang Y: Metastatic thyroid follicular carcinoma presenting as a primary renal tumor. Intern Med 51: 2193-2196, 2012.
3. Carpi A, Nicolini A, Gross MD, Fig LM, Shapiro B, Fanti S, Rampini L, Polico C and Rubello D: Controversies in diagnostic approaches to the indeterminate follicular thyroid nodule. Endocr Pathol 19: 443-452, 2008.

4. Goldstein RE, Nettieville JL, Burkey B and Johnson JE: Implications of follicular neoplasms, atypia, and lesions suspicious for malignancy diagnosed by fine-needle aspiration of thyroid nodules. Ann Surg 235: 656-662, 2002.

5. Sobrinho-Simões M, Eloy C, Magalhães C, Lobo C and Amaral T: Follicular thyroid carcinoma. Mod Pathol 24 (Suppl 2): S10-S18, 2011.

6. Benbassat CA, Mechlis-Frish S and Hirsch D: Clinicopathological characteristics and long-term outcome in patients with distant metastases from differentiated thyroid carcinoma. Eur J Med 30: 1088-1090, 2014.

7. Angeles-Angales A, Chable-Montero F, Martinez-Benitez B and Albores-Saavedra J: Unusual metastases of papillary thyroid carcinoma: Report of 2 cases. Ann Diagn Pathol 13:189-196, 2009.

8. Tanriverdi O, Avci A, Yagun I and Polat M: A case report of breast and liver metastases of thyroid follicular carcinoma. J Can Res Ther 11: 652, 2015.

9. Grebe SK and Hay ID: Follicular thyroid cancer. Endocr Rev Metab Clin North Am 24: 761-801, 1995.

10. D’Avanzo A, Treseler P, Uhart J, Wong M, Streja L, Greepman SS, Siperstein AE, Duh QY and Clark OH: Follicular thyroid carcinoma: Histology and prognosis. Cancer 100: 1123-1129, 2004.

11. Iwai H, Ohno Y, Ito H, Kiyokawa T and Aoki N: Renal rupture associated with a poorly differentiated follicular thyroid carcinoma metastasizing to the thigh muscle, lung and kidney. Intern Med 44: 848-852, 2005.

12. Cocchetti G, Puxeddu P, Del Zingaro MD, D’Amico F, Cottini E, Barillaro F and Mearini E: Laparoscopic partial nephrectomy of thyroid cancer metastasis: Case report and review of the literature. Onco Targets Ther 6: 355-360, 2013.

13. Remonti LR, Kramer CK, Leitão CB, Pinto LC and Gross JL: Thyroid ultrasound features and risk of carcinoma: A systematic review and meta-analysis of observational studies. Thyroid 25: 538-550, 2015.

14. Coquia SF, Chu LC and Hamper UM. The role of sonography in thyroid cancer. Radiol Clin North Am 52: 1283-1294, 2014.

15. Taki S, Terahata S, Yamashita K, Kinuya K, Nobata K, Kakuda K, Kodama Y and Yamamoto I: Thyroid calcifications: Sonographic patterns and incidence of cancer. Clin Imaging 28: 368-371, 2004.

16. Kim BM, Kim MJ, Kim EK, Kwak YJ, Hong SW, Son EJ and Kim KH: Sonographic differentiation of thyroid nodules with eggshell calcifications. J Ultrasound Med 27: 1425-1430, 2008.

17. Yoon DY, Lee JW, Chang SK, Choi CS, Yun EJ, Lee SK and Rho BH: Follicular thyroid carcinoma with an eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

18. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Sonographic-pathologic correlation. J Clin Ultrasound 42: 172-175, 2014.

19. Yaturu S and Rainer L: Thyroid nodule with eggshell calcification and oncocytic thyroid cancer. Med Sci Monit 16: CS25-CS28, 2010.

20. Cheng SP, Lee JJ, Lin J and Liu CL: Eggshell calcification in follicular thyroid carcinoma. Eur Radiol 15: 1773-1774, 2005.

21. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification presenting as an intensely hypermetabolic lesion on 18F-FDG PET/CT. J Clin Ultrasound 38: 107-110, 2010.

22. Lee SK and Rho BH: Eggshell calcification and oncocytic thyroid cancer: A multivariate analysis. Rofo 186: 489-495, 2014.

23. Rosario PW: Thyroid nodules with atypia or follicular lesions of undetermined significance (Bethesda Category III): importance of ultrasonography and cytological subcategory. Thyroid 24: 1115-1120, 2014.

24. Zhang JZ and Hu B: Sonographic features of thyroid follicular carcinoma in comparison with thyroid follicular adenoma. J Ultrasound Med 33: 221-227, 2014.

25. McHenry CR and Phitayakorn R: Follicular adenoma and carcinoma of the thyroid gland. Oncologist 16: 589-593, 2011.

26. Iared W, Shigemura T, Amin MB, Vassalou JW, Hendrichsen TL, Hay ID and Mandrekar JN: Thyroid follicular carcinoma: Sonographic features of 50 cases. AJR Am J Roentgenol 194: 44-54, 2010.

27. Jiang J, Shang X, Wang H, Xu YB, Gao Y and Zhou Q: Diagnostic value of contrast-enhanced ultrasound in thyroid nodules with microscopic thyroid carcinoma. Kaohsiung J Med Sci 31: 75-77, 2015.

28. Khoo ML, Asa SL, Witterick JI and Freeman JL: Thyroid calcification and its association with thyroid carcinoma. Head Neck 24: 655-652, 2002.

29. Sun Y, Fang S, Dong H, Zhao C, Yang Z, Li P and Wang J: Correlation between osteopontin messenger RNA expression and microcalcification shown on sonography in papillary thyroid carcinoma. J Ultrasound Med 30: 765-771, 2011.

30. Kwaik JY, Kim EK, Son EJ, Kim MJ, Oh KK, Kim JY and Kim KL: Papillary thyroid carcinoma manifested solely as microcalcifications on sonography. AJR Am J Roentgenol 199: 227-233, 2007.

31. Lee SK: Hürthle cell thyroid adenoma with an eggshell calcification: Sonographic-pathologic correlation. J Clin Ultrasound 42: 172-175, 2014.

32. Yaturu S and Rainer L: Thyroid nodule with eggshell calcification and oncocytic thyroid cancer. Med Sci Monit 16: CS25-CS28, 2010.

33. Cheng SP, Lee JJ, Lin J and Liu CL: Eggshell calcification in follicular thyroid carcinoma. Eur Radiol 15: 1773-1774, 2005.

34. Lee SK and Rho BH: Follicular thyroid carcinoma with an eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

35. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification presenting as an intensely hypermetabolic lesion on 18F-FDG PET/CT. J Clin Ultrasound 38: 107-110, 2010.

36. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

37. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification presenting as an intensely hypermetabolic lesion on 18F-FDG PET/CT. J Clin Ultrasound 38: 107-110, 2010.

38. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

39. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

40. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

41. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

42. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

43. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

44. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

45. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.

46. Lee SK and Rho BH: Follicular thyroid adenoma with eggshell calcification: Report of 3 cases. J Ultrasound Med 28: 801-806, 2009.