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Thyroid metastasis as initial presentation of clear cell renal carcinoma

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ABSTRACT

INTRODUCTION: Metastatic tumors account for 1.4–2.5% of thyroid malignancies. About 25–30% of patients with clear cell renal carcinoma (CCRC) have distant metastasis at the time of diagnosis, being the thyroid gland a rare localization [5%].

PRESENTATION OF THE CASE: A 62-year woman who underwent a cervical ultrasonography and a PAAF biopsy reporting atypical follicular proliferation with a few intranuclear vacuoles “suggestive” of thyroid papillary cancer in the context of a multinodular goiter was reported. A total thyroidectomy was performed and the histology of a clear cell renal carcinoma (CCRC) was described in four nodules of the thyroid gland. A CT scan was performed and a renal giant right tumor was found. The patient underwent an eventful radical right nephrectomy and the diagnosis of CCRC was confirmed.

DISCUSSION: Thyroid metastasis (TM) from CCRC are usually apparent in a metachronic context during the follow-up of a treated primary (even many years after) but may sometimes be present at the same time than the primary renal tumor. Our case is exceptional because the TM was the first evidence of the CCRC, which was subsequently diagnosed and treated.

CONCLUSION: The possibility of finding of an incidental metastatic tumor in the thyroid gland from a previous unknown and non-diagnosed primary (as CCRC in our case was) is rare and account only for less than 1% of malignancies. Nonetheless, the thyroid gland is a frequent site of metastasis and the presence of “de novo” thyroid nodules in oncologic patients must be always considered and studied.

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1. Introduction

Clear cell renal carcinoma (CCRC) is a tumor with a highly metastatic capacity due to its rich vascularization and the presence of internal arterio-venous shunts. Up to 30% of all cases have extended disease at the time of diagnosis and recurrences have been reported over 20 years after resection of the primary tumor [1].

Thyroid metastasis (TM) from extrathyroid cancer accounts for 1.4–2.5% of malignant thyroid tumors, usually in relation with renal, bronchial and digestive tumors and melanoma [2,3]. We report the case of a patient with a diagnosis of CCRC which was made incidentally during the histological study of a specimen taken from a total thyroidectomy. We discuss the epidemiological, clinical and diagnostic implications, as well as the therapeutic options for TM in general and those associated with CCRC in particular.

2. Presentation of case

An otherwise healthy 62-year woman was studied for a goiter with no local symptoms of thyroid dysfunction. Physical exam and ultrasonography (US) showed a palpable multinodular goiter with a 22 mm dominant nodule poorly defined in the right thyroid lobe and no palpable lymph nodes. Fine needle aspiration biopsy (FNAB) was reported as atypical follicular proliferation with a few intranuclear vacuoles suggestive of thyroid papillary cancer (Bethesda 5). A total thyroidectomy with a prophylactic central compartment dissection was performed with a 3 days uneventful postoperative course. Histological study informed the presence in four adenomatoid nodules of groups of large cells arranged in nests and cords with optically clear cytoplasm and enlarged nuclei displaying coarse chromatin, findings clearly suggestive of renal origin, with focal infiltration of the thyroid capsule (Fig. 1). No primary (neither papillary nor follicular benign or malignant) thyroid neoplasm was found, resulting then the previous FNAB as a false positive for malignancy. Immunohistochemistry proved negative for specific thyroid transcription factor-1 (TTF-1) and thyroglobulin and positive for CD10. Abdominal computerized tomography (CT) and magnetic resonance imaging (MRI) detected the presence of a solid, hypervascular mass in the upper pole of the right

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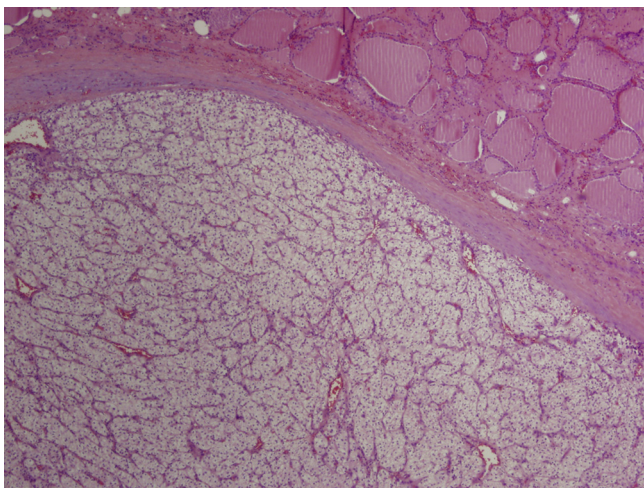


Fig. 1. Haematoxylin–eosin stain ($\times 4$) showing the interphase between the normal colloid follicular tissue and the nests of atypical cells (with abundant clear cytoplasm and central nucleus) separated by a bundle of sinusoidal vascular structures.

kidney measuring $12 \times 12 \times 10$ cm with a high content of cytoplasmic fat and the presence of microcalcifications and arterio-venous fistulas, growing into the perirenal space and displacing, though not infiltrating, the right hepatic lobe, the inferior vena cava and the ascending colon (Fig. 2A and B). Four weeks later, the patient underwent a radical right nephrectomy (including perirenal fat, right adrenal and lymph nodes of the renal hilum) with no postoperative complications. Histological study reported a conventional CCRC with Fuhrman nuclear grade 1 and extensive areas of necrosis and hemorrhage, infiltration of the Gerota capsule and extending into the renal vein, with no involvement of the resection border. The patient received no adjuvant chemotherapy, and remains free of disease after four years of follow-up (including a positron emission tomographic study one month ago).

3. Discussion

Clear cell renal carcinoma accounts for 3% of all malignant tumors in adults and it is the third most frequent urological tumor being more common in men and usually at the age of 65-year. About 25–30% of patients with CCRC have distant metastasis at the time of diagnosis. The most frequent sites of metastasis are the respiratory tract, skeleto-muscular system, lymph nodes, brain, liver and skin, with solitary metastasis found in 1–4% of cases. Saitoh studied a series of 1828 patients with CCRC and found that 5.2% of the previously asymptomatic patients had TM at autopsy [1,2].

The prevalence of TM in autopsy series of patients harboring non-thyroid malignancies is 1.2–24%, and they are usually small, silent and most frequently associated with renal carcinoma, breast, liver and lung cancer, and melanoma [3]. Although kidney is the second most vascularized organ in the body (after the suprarenal gland) and considering that metastatic spread to the thyroid gland is hematogenous, TM of CCRC are rare. This can be explained by: (1) filtering effect of lung passage; (2) the high intrathyroidal vascular flow, which hinders fixation of tumor emboli; and (3) the high concentration of oxygen and iodine in the thyroid tissue, which blocks proliferation of tumor cells [4]. Underlying thyroid disorder (adenoma, thyroiditis, multinodular goiter or primary tumor) may alter the vascular flow and have a role as a factor favoring the appearance of metastasis in the thyroid gland because of reducing content in oxygen and iodine. Heffes et al., in the largest series of TM from CCRC, found pre-existing thyroid disease in 42% of the 36 cases [5].

The symptoms of TM are very unspecific and there is not usually any repercussion on thyroid function. TM are usually detected after

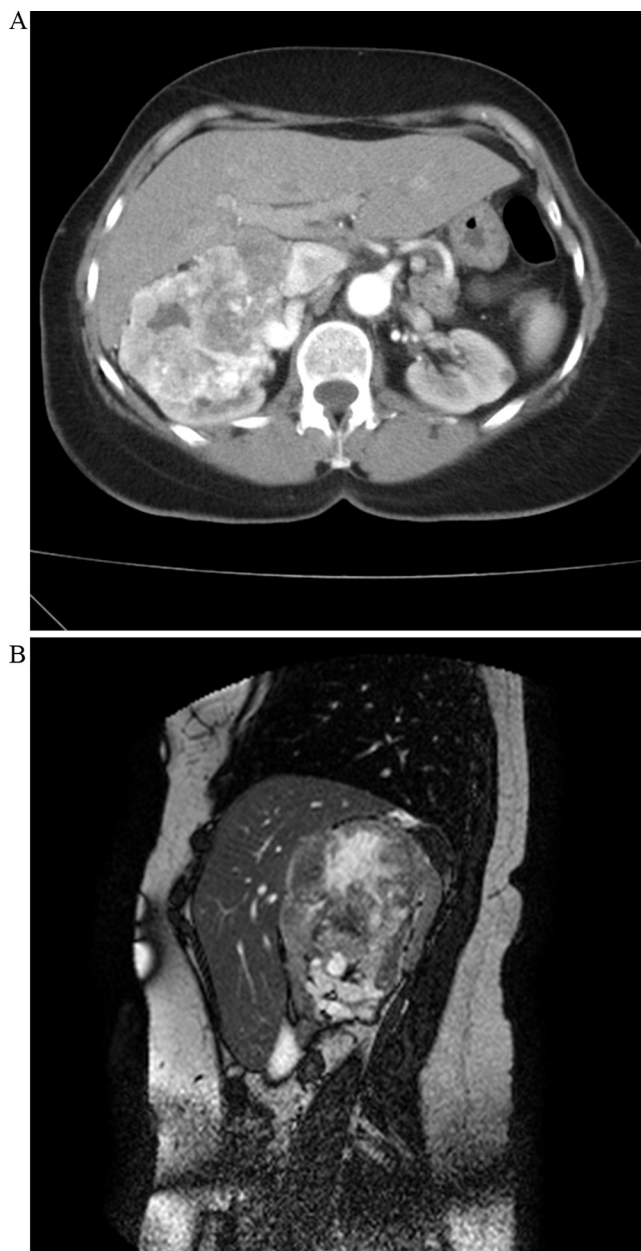


Fig. 2. (A) Transverse slice on abdominal CT. (B) Lateral sagittal slice on abdominal MRI (T1 weighted).

A heterogeneous and hypervascular mass on the right kidney, presenting arterio-venous shunts and calcifications, displacing but not infiltrating the liver, vena cava and hepatic flexure of the colon.

the diagnosis of the primary tumor, with a mean time to detection of 7–10 years (range, 1–322 months) and a peak incidence during the sixth decade of life. The presence of a long latency period is particularly typical of CCRC and it is a factor that hinders diagnosis even further [5].

Neither ultrasonography nor scintigraphy provide specific data, usually visualising the presence of a cold, hypoechoic nodule in a euthyroid patient. Fine needle aspiration biopsy is an important diagnostic tool that can provide a preoperative diagnosis, but sometimes the TM are not concrete nodules but a group of cells inside anatomically detected abnormalities in the thyroid gland. The presence of a predominantly interstitial pattern of infiltration is more compatible with the diagnosis of TM, as the pattern of primary thyroid tumors is follicular infiltration. The existence of large amounts of lipid material and glycogen (PAS positive), as well as the

absence of mucin, a negative stain for TTF-1 and thyroglobulin (both of them positive in primary thyroid cancer) and a positivity for CD10, all favor a diagnosis of CCRC and suggest metastasis. Medas et al. have recently presented a review of the complex and unusual context represented by patients with a renal cancer metastatic to a thyroid tumor (“tumor-to-tumor” metastases), remarking how difficult is to achieve the preoperative diagnosis of a secondary thyroid neoplasm [6].

Factors associated with a favorable prognosis of CCRC after resection of the TM include a long time interval between tumor resection and development of the metastasis (generally more than 10 years), complete excision of the metastatic focus, a single thyroid lesion with no disease extended elsewhere, extensive necrosis in the resected piece, slow tumor growth with no clinical symptoms (casual finding on examination or in follow-up imaging studies), and the histological characteristics of the primary tumor. Following nephrectomy, the mean 5-year survival can reach 80% in cases of single thyroid metastasis versus just 5% in cases of multiple metastases. A longer survival has been reported for TM due to CCRC (80% at 2 years) as opposed to TM due to other primary tumors (20% at 2 years) [5,7]. In a recent review of the literature related to this topic, Beutner et al. found only one case of synchronous primary CCRC and TM, being the majority of the cases metachronous late onset of the TM. [8].

Thus, the presence of thyroid nodules in a patient with a known history of malignant neoplasm in the kidney should orient us toward the possibility of metastatic disease. If the FNAB shows clear cells, a whole-body CT and PET are done to discard disease spread to other sites. CCRC is a tumor resistant to both chemotherapy and radiotherapy, remaining surgery the treatment of choice because survival is longer for patients undergoing thyroidectomy compared with those who do not. When TM are isolated, total thyroidectomy is indicated although some authors propose unilateral surgery (lobectomy and isthmectomy) in well-localized single lesions, attributing a possible cytostatic role of the thyroid hormones [9,10]. As far as we know, this is the first case report published of a CCRC diagnosed incidentally after a thyroidectomy performed by a suspect of papillary carcinoma.

4. Conclusion

Thyroid nodules with FNAB informed as suspicious for malignancy result occasionally in the diagnosis of a metastatic tumor from an unnoticed primary when thyroidectomy is performed. In these situations, CCRC is one of the most frequent metastatic tumors to the thyroid gland.

Conflicts of interest

The author and co-authors reveal that we don't have financial interests or connections, direct or indirect, or other situations that

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Author contribution

César Pablo Ramírez-Plaza is the main author of the paper. He had the idea of reporting the case and elaborated the discussion.

Marta Elena Domínguez-López is the doctor who diagnosed the disease and has elaborated the clinical case and collected the bibliography.

Francisco Blanco-Reina is the motivated urologist who wrote all the technical and discussed aspects about the relation of the renal tumors with the thyroid gland.

Patient's consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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