THYROID METASTASIS FROM CLEAR CELL CARCINOMA OF THE KIDNEY 16 YEARS AFTER NEPHRECTOMY

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Abstract

The thyroid gland is one of the most vascularized organs in the body. However, metastatic disease to the thyroid gland is rare. When it does occur kidney is the most common primary tumor site, followed by melanoma, lung, breast, esophagus, uterus and colon carcinoma.

We describe the case of an isolated thyroid metastasis from clear cell renal carcinoma occurring 16 years after nephrectomy. An 82 years-old woman presented for the recent growth of a right thyroid nodule, diagnosed 3 years before, when a fine needle aspiration biopsy found a benign cytology suggesting a well-differentiated follicular thyroid adenoma. Her medical history included type 2 diabetes mellitus, atrial fibrillation and a right nephrectomy for a clear cell renal carcinoma done 16 years before. The patient has lost weight but she was otherwise asymptomatic. The right lobe goiter was painless, firm, and mobile with deglutition, without signs of local compression or latero-cervical lymphadenopathy. Thyroid ultrasonography revealed an enlarged (9.9 cm) macronodular right lobe, with multiple cystic areas, with normal left lobe and a thrombus in the right internal jugular vein. Thyroid function tests were normal.

The patient was suspected of thyroid carcinoma and underwent a near total thyroidectomy.

Histopathological examination revealed a metastasis of clear cell renal carcinoma in the right thyroid gland lobe (8.5/5/5 cm). Further imaging showed no primary tumor or other metastases.

Metastatic renal carcinoma to the thyroid should be considered in any patient presenting with a thyroid mass and a medical history of operated renal cell carcinoma, since it can occur up to 25 years after nephrectomy.

Key words: metastasis, thyroid secondary neoplasm, clear cell renal carcinoma.

INTRODUCTION

Thyroid nodules are quite common, occurring in up to 50% of the population, as indicated by

ultrasonography; only about 5% of these nodules are thyroid cancer (1). A metastatic neoplasm of the thyroid gland identified during life is an uncommon cause of thyroid enlargement; usually, metastases are found at autopsy as part of widespread disease (2). The thyroid gland is one of the most vascularized organs in the body and one would expect it to be a frequent site of metastatic disease (2). Although metastatic disease to the thyroid gland is rare, when it does occur kidney is the most common primary tumor site (3). Other primary sites include melanoma, lung, breast, esophagus, uterus and colon carcinoma (1). If metastatic renal cancer is limited to the thyroid gland only, prompt and appropriate surgical intervention can be curative (4). Metastatic renal carcinoma to the thyroid should be considered in any patient presenting with a thyroid mass and a medical history of operated renal cell carcinoma (4).

We describe a clinical case of a single metastasis of clear cell renal carcinoma in the thyroid occurring 16 years after nephrectomy.

CASE PRESENTATION

An 82-year-old woman from an endemic goiter area was referred to our thyroid department for a right thyroid nodule (August 2015). A recent growth of the right thyroid nodule was noticed during the last months before admission in our department. Sixteen years before (1999) the patient had undergone a right nephrectomy for a clear cell renal carcinoma. She has a 3 years history of right thyroid nodule, known from 2012, a 10 years history of type 2 diabetes mellitus and a 4 years history of atrial fibrillation. The patient had no family history of thyroid disorder or a personal history of previous exposure to radiation on the head or neck areas. Interestingly, a fine needle aspiration biopsy

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(FNAB) performed in another medical institution (2012) found a “benign cytology” within the thyroid gland, suggesting a well-differentiated follicular thyroid adenoma.

The patient was symptomatic (10 kg weight loss in 9 months) and clinically euthyroid. The clinical examination at admission indicated an atrial fibrillation (heart rate 84 beats/min) and a normal blood pressure (130/80 mm Hg), the height was 153 cm and the body weight was 49 kg (body mass index 20.9 kg/sqm) and a normal body temperature.

The right lobe goiter was painless, firm and mobile with deglutition, without signs of local compression and without latero-cervical lymphadenopathies. The rest of the clinical examination was normal.

Thyroid ultrasonography revealed a significant increase in the volume of the right thyroid lobe (197.6 mL), which was completely transformed into a well-defined macronodule (53/72/99 mm - Fig. 1) with mixed echostructure, with many intranodular cystic areas, the largest one measuring 17.7 / 13.2 mm. The solid component was slightly hypoechoic and inhomogeneous. The nodule had a predominant peripheral Doppler signal. TIRADS score was appreciated as 4A, i.e. a low (5-10%) suspicion of malignancy (5). The left thyroid lobe was small (volume = 1.8 mL), slightly hypoechoic and inhomogeneous, with normal vascularization. No suspicious cervical lymph nodes were noted. The ultrasound examination also revealed intraluminal echoes inside the upper third of the right internal jugular vein consistent with an intravenous thrombosis (Fig. 2).

Thyroid function tests revealed normal thyroid function: serum TSH was 2.04 μ IU/mL (normal range

0.5 – 4.5 μ IU/mL) and serum FT4 was 16.50 pmol/L (9 – 19 pmol/L). Biochemistry investigations revealed increased serum glucose 159 mg/dL (70 – 110 mg/dL) and increased serum creatinine 1.27 mg/dL (normal range 0.5 – 1 mg/dL); thorax X-ray was normal.

The patient was suspected of thyroid carcinoma and referred to a surgical department. Surgical therapy was performed in “Sf. Ioan” Clinical Hospital from Bucharest in September 2015 (near total thyroidectomy).

The thyroid was approached through a Kocher incision with transversal sectioning of the strap muscles on the right side. The left thyroid lobe appeared normal, while the right one was totally replaced by a bulky tumoral nodule of about 10/ 6/ 5 cm, very firm and adherent to the strap muscles, inferior constrictor of pharynx and esophagus, with hard, whitish, tumoral buds on its posterior and lateral surfaces in the vicinity of the tracheo-esophageal groove. The peritumoral vasculature was highly abundant, making the dissection very bloody and thus the identification of the recurrent laryngeal nerve and parathyroid glands was impossible on the right. On the cross section the nodule was very heterogeneous, with zones of liquid necrosis alternating with solid ones, with thick, whitish septa.

Histopathology examination showed a normal left thyroid lobe, while the right lobe (8.5/5/5 cm) was entirely transformed in a tumoral, solid, multinodular mass, with haemorrhage areas, which proved to be a metastasis of clear cell renal carcinoma (important proliferation of epithelial malignant cells, with clear cytoplasm, in an alveolar, solid, acinar and even microcystic pattern, nearby fibrosis and calcification).

There was a well-defined distinction between the tumor cells and the adjacent thyroid gland.

Figure 1. Thyroid ultrasound showing in the right lobe a well- defined macronodule (53/72/99 mm) with mixed echostructure, with many intranodular cystic areas, the solid component was slightly hypoechoic and inhomogeneous.

Figure 2. Thyroid ultrasound showing intraluminal echoes inside the upper third of the right internal jugular vein (VIJ) consistent with an intravenous thrombosis.

No lymph nodes were detected (Figs 3, 4).

Postoperatively, the patient was treated with levothyroxine 100 mcg/day and has been referred to an oncology department where computed tomography imaging of the head, thorax and upper and lower abdomen did not reveal any primary kidney tumor or other metastases. The patient started chemotherapy with Tensirolimus (intravenous infusion once a week). Tensirolimus is converted to Rapamycin in vivo and acts as amTOR inhibitor, being helpful in the therapy of advanced renal cell carcinoma. The patient declared that her general status improved and she regained 2 kg.

Figure 3. Well-demarcated metastasis of CCRC in the thyroid; the border between thyroid follicles and the tumor tissue is indicated by arrow (Hematoxylin-eosin - HE, 4x).

Figure 4. Nuclear and cytoplasmic details of the intrathyroidal epithelial malignant tumor (carcinoma): clear cytoplasm (because of glycogen and lipids content) and pleomorphism and hyperchromasia of the nuclei. A: HE, 20x. B: HE, 40x.

DISCUSSION

Metastatic disease into the thyroid gland is a rare event, usually up to 2% of thyroid malignancies (6). In a Romanian series of 288 patients with thyroid cancer, thyroid metastases were found in 2.7% (7). Thyroid metastases are found in 0–13% of patients who have undergone thyroidectomy and in 0–13% of patients submitted to fine needle aspiration biopsy (FNAB). At autopsy, thyroid metastases may occur in 1.2–24% of patients with widespread malignant lesions (3).

Clear cell renal carcinoma is the most common malignancy of the kidney and usually has already metastases at the time of diagnosis (6). However, metachronous metastases appear in over 50% of patients who were treated with radical nephrectomy (8).

Clear cell renal carcinoma is also the most common origin for secondary malignancies in the thyroid (3, 9, 10). Metastatic disease from the kidney to the thyroid gland can occur more than 20 years after nephrectomy, with the average time interval between 7.5 – 8.7 years (4, 11, 12). In a review of 113 patients with renal cell carcinoma intrathyroidal metastases, over 90% of them have been metachronous (12), like in our patient. Most of these metastases are single unilateral nodules (over 70% of cases), hypoechoic on ultrasound, and are discovered in the 6–7th decade of life (12), in some patients even after the age of 70 years (13), as in our case.

It must be added that the thyroid gland is one of the most vascularized organs in the body and one would expect it to be the site of metastatic disease.

The presence of a solitary renal cell carcinoma metastasis suggests the ability of the host to destroy the majority of the circulating neoplastic cells (2).

We can speculate that in our patient the ability of the host to destroy the majority of the circulating neoplastic cells might be decreased due to a secondary immunodeficiency (14), explained by the age of the patient (82 years) associated with a frequent comorbidity (type 2 diabetes mellitus).

There are several hypotheses explaining the relatively high incidence of metastases from the kidney to the thyroid gland. Although a popular theory claims that the proclivity of metastasis to the thyroid gland is related to its rich blood supply, some researchers have suggested that an abnormal thyroid gland is vulnerable to metastatic growth due to a decrease in oxygen and iodine content alteration (15). Renal cell carcinoma can metastasize to the thyroid bypassing the lungs via the valveless paravertebral venous plexus of Batson (15).

However, in a metaanalysis of 113 cases, the concordance between the lateralization of the renal cell carcinoma and of the thyroid metastasis, as in our patient, occurred only in 40 to 50% of the patients (12). Although renal cell carcinoma metastasis to the thyroid gland can be suspected in patients with a history of renal tumors, preoperative diagnosis of a primary versus secondary thyroid tumor is difficult. The preoperative FNAB, usually considered an accurate diagnostic tool for thyroid tumors, may lead to high false negative rates in thyroid metastases: 28.7% (16) or about 50% in patients with metastasis of clear cell renal carcinoma (13, 17). Thus, one should remain suspicious for metastatic disease to the thyroid gland when FNAB is negative or indeterminate for malignant cells (16), as has been the case in our patient. Ancillary methods (as immunohistochemistry) may improve the diagnostic accuracy, a renal cell carcinoma metastasis usually showing positive immunostaining for renal cell carcinoma antigen, CD10 or vimentin and negative immunostaining for thyroglobulin or thyroid transcription factor-1 (TTF-1) (10).

In 27% of the patients with renal cell carcinoma and thyroid metastases, other nonthyroidal metastases have been reported in lungs, pancreas, skeleton, lymph nodes, liver or adrenal glands (12).

Surgical resection of the thyroid metastasis of renal cell carcinoma has a clear survival benefit, with a mean 5-year survival rate of 30–60% (12, 17, 18).

The prognostic factors for low survival are age over 70 years, invasion of adjacent cervical structures, current or past evidence of metastases to nonendocrine

organs (17). Conversely, presence of an isolated metastasis, a longer time interval between the diagnosis of renal cell carcinoma and the appearance of thyroid metastasis, and treatment are good prognostic factors (2, 12, 19, 20).

In our patient the anterior cervical ultrasound has suggested an intravenous thrombosis, possibly tumoral, in the homolateral internal jugular vein. Such a vein tumor thrombus, usually detected preoperatively as an incidental finding, is a rare complication of thyroid cancer, and those tumors behave aggressively (21). However, it has been observed in 2 of 10 patients with renal cell carcinoma metastases in the thyroid (“echogenic tongue”) (13).

It is not clear whether a total thyroidectomy leads to a better prognosis than a subtotal thyroidectomy in patients with metastatic renal cell carcinoma. No differences were observed between total and subtotal thyroidectomy in several studies (2, 3, 20). Medical therapy may be used: immunotherapy (e.g., interferon- α), multikinase inhibitors (sunitinib, sorafenib, axitinib, pazopanib), antivascular endothelial growth factor agents (bevacizumab), and mammalian target of rapamycin inhibitors (temsirolimus, everolimus) (12).

Survival is short (mean of 8 months) for patients with synchronous thyroid metastases, but it is quite longer (mean of 10 years) for patients with metachronous thyroid metastases (20). The clinician should however keep in mind that thyroid metastases in renal cell carcinoma indicate advanced disease and the patient should be evaluated for the presence of other metastases.

In conclusion, metastatic renal cell carcinoma to the thyroid should be considered in a patient presenting with a thyroid nodule and a history of operated renal cell carcinoma, since an isolated thyroid metastasis can occur up to 25 years after nephrectomy. Surgical treatment of solitary thyroid metastases is recommended, because it has a clear survival benefit.

Conflict of interest

The authors declare that they have no conflict of interest concerning this paper.

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