



METASTASES FROM RENAL CELL CANCER TO THE THYROID GLAND: A SYSTEMATIC REVIEW OF 175 CASES BETWEEN 1964 AND 2016

F. D'ANGELO¹, P. MAGISTRI¹, L. ANTOLINO¹, F. SOCCIARELLI², T. OLIVIERI³, F. CANEGALLO³, L. BOLLANTI⁴, P. AURELLO¹, F. DI BENEDETTO³, G. RAMACCIATO¹

¹Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy.

²Department of Pathology, St. Andrea University Hospital, Rome, Italy.

³Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, University of Modena and Reggio Emilia, Modena, Italy

⁴Department of Endocrinology, St. Andrea University Hospital, Rome, Italy

Abstract – Background: Renal Cell Cancer (RCC) is the most common extra-thyroid cancer metastasizing to the thyroid gland and has been responsible for 48.1% metastases of Non-Thyroid Malignancies (NTMs) to the thyroid in the past decade. Metastases to the thyroid gland have been reported in 1.4%-3% of patients undergoing thyroid surgery for thyroid malignancies. We systematically reviewed the literature from 1964 to 2016 and herein present our experience.

Patients and Methods: The research was systematically performed on Pubmed, EMBase and Cochrane Library databases by entering the strings: "renal carcinoma AND thyroid metastasis" or "renal carcinoma AND thyroid metastases" or "hypernephroma AND thyroid metastasis (or metastases)".

Results: 175 cases were retrieved and 90 were included in the study since they fulfilled the inclusion criteria by reporting gender, age, latency of metastases presentation after nephrectomy, jugular vein infiltration and other sites of metastasis (when applicable). The mean age of thyroid metastases presentation is 64.4 years and the mean latency after a nephrectomy is 9.1 years (range 0-24). Fine needle aspiration biopsy (FNAB) failed to provide the correct diagnosis in 28.7% of patients with thyroid metastases from RCC.

Conclusions: Given the long latency, RCC follow-up program should be longer than recommended at present and implemented with an ultrasound scan of the neck.

KEYWORDS: Thyroid metastases, Renal cell carcinoma, RCC, RCC follow-up, RCC metastasis, Thyroidectomy, Thyroid surgery, Systematic review.

INTRODUCTION

Renal Cell Cancer (RCC) accounts for 2% of all malignancies¹ and 20% to 30% of resected patients with localized tumors experience relapse. Moreover, RCC is the most common extra-thyroid cancer metastasizing to the thyroid gland and has been responsible for 48.1% metastases of Non-Thyroid Malignancies (NTMs) to the thyroid in the past

decade. Also, colorectal cancer, lung cancer, breast cancer and melanoma can metastasize to the thyroid². Furthermore, autopsy studies demonstrated a prevalence of NTMs³ metastases to the thyroid gland²⁻⁴ ranging from 1.9% to 24%. Despite the findings of the previous studies⁵, thyroid is no longer considered a rare metastatic site from NTMs as they have been reported in 1.4% to 3% thyroidectomies for thyroid malignancies². Thus,



the presence of a thyroid nodule in a patient with a history of NTMs should be investigated as a possible metastasis.

We herein report a systematic review of the literature starting from 1964, when Wychulis et al⁶ described for the first time RCC metastasis to the thyroid gland. We also provide our experience describing the case of a patient who has undergone total thyroidectomy for a rapidly enlarging nodule that eventually resulted in a RCC metastasis.

PATIENTS AND METHODS

As previously described, PRISMA statement guidelines for conducting and reporting systematic reviews were followed. A systematic literature search was performed independently by two of the manuscript's authors (PM and TO) using PubMed, EMBASE, Scopus and the Cochrane Library Central. No restrictions were set for the type of publication, language or time interval. The following MESH search headings were used: "renal carcinoma AND thyroid metastasis" or "renal carcinoma AND thyroid metastases" or "hypernephroma AND thyroid metastasis (or metastases)". The same two authors independently screened the titles and abstracts of the primary studies that were identified in the electronic search. Duplicate studies were excluded. Title, abstract section, and keywords were screened in order to select studies for further assessment. A total of 175 cases published between 1964 and 2016 were retrieved. Two authors (LA and FC) extracted the main data as follows: (1) patients' gender and age, (2) interval between RCC diagnosis and thyroid metastases presentation, (3) jugular vein infiltration and (4) other metastatic sites. Studies not reporting enough information on the outcomes were not included. All relevant texts, tables and figures were reviewed for data extraction and whenever further information was required, the corresponding authors of the papers were contacted by e-mail.

RESULTS

According to the aforementioned criteria, 90 cases were included in this review^{2,6-88}: among them, there are fifty-one men (56.7%) and thirty-nine women (43.3%), with a mean age of 64.4 years (range 32-82). Eight patients (8.9%) had synchronous metastases. The majority of patients had late onset metastasis, with a mean interval of diagnosis after nephrectomy of 9.1 years. Jugular vein infiltration was present in 14 (15.6%) patients.

The most frequent synchronous extra-thyroid localization was the lung (32.8%) followed by pancreas (17.2%), bone (10.3%), adrenal gland (10.3%) and liver (10.3%) (Table 1).

CASE REPORT

A 57 years-old man was admitted to our department in October 2010 for a rapidly enlarging neck swelling. He previously underwent a thyroid ultrasound, which described a 7 cm single nodule in the left thyroid lobe. A cytological exam on fine needle aspiration was then performed resulting in an adenomatous follicular proliferation (a Thy 2 lesion, according to the Bethesda System⁸⁹). Preoperative chest X-ray did not demonstrate any parenchymal lesion. In agreement with the endocrinologist, a surgical procedure was scheduled and the patient underwent a total thyroidectomy. Two drainages and local hemostatic were used, as the thyroid was unusually easy to bleed during the procedure. The histological report described macroscopically a 5 cm nodule in the left lobe of the thyroid gland, that microscopically resulted in a macro-metastasis of a renal clear cell tumor, TTF-1 negative and CD 10 positive (Figure 1), infiltrating the thyroid capsule. The remaining thyroid parenchyma showed

TABLE 1. Review of case reports.^{2,6-88}

Number of cases	90
Male	51 (56.7%)
Female	39 (43.3%)
Mean age	64.4 years (range 32-82)
Synchronous metastases	8 (8.9%)
Total extra-thyroid localization	58
Lung	19 (32.8%)
Pancreas	10 (17.2%)
Bone	6 (10.3%)
Adrenal gland	6 (10.3%)
Liver	6 (10.3%)
Brain	3 (5.3%)
Nasal cavity	2 (3.5%)
Submandibular gland	1 (1.7%)
Supramandibular gland	1 (1.7%)
Ovary	1 (1.7%)
Abdominal	1 (1.7%)
Recurrence of RCC	2 (3.5%)
Mean interval after nephrectomy	9.1 years (range 0-24)
Jugular vein infiltration (including not specified widespread)	14 (15.6%)

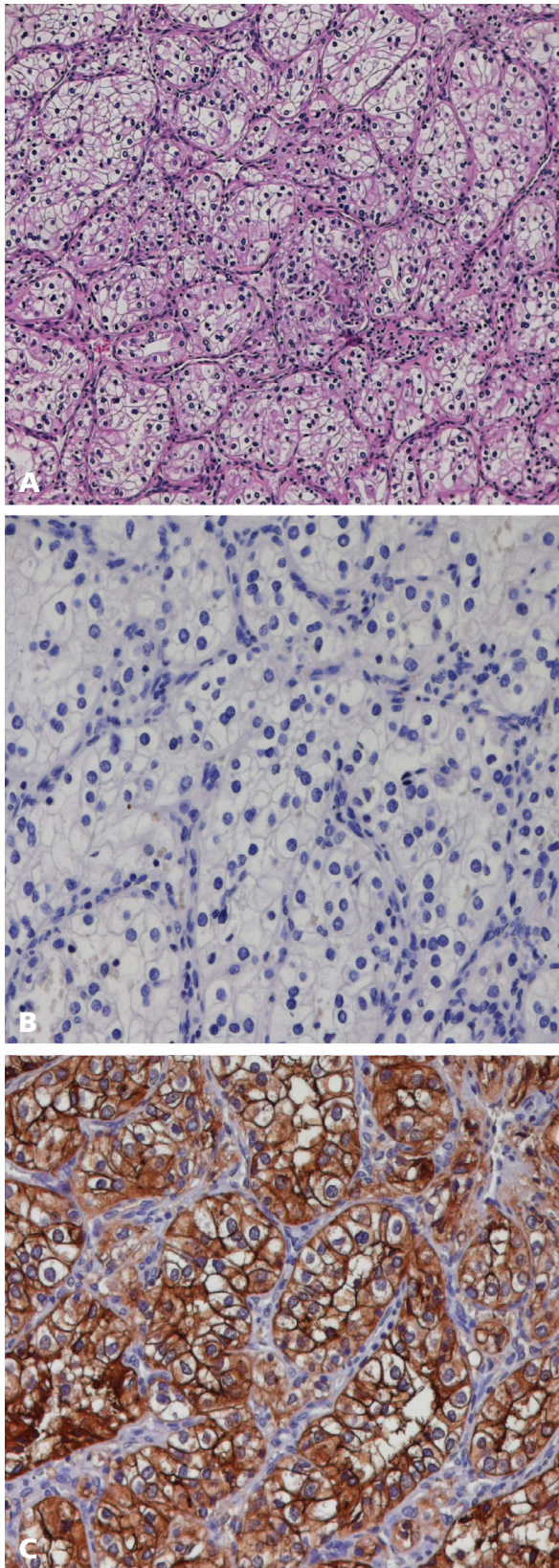


Fig. 1. *A*, Tumor cells are arranged on nest and cords, with a rich and sinusoid-like vasculature of support (H&E 100X). Cell cytoplasm is abundant and optically clear, nuclei are round and centrally located. *B*, Tumor cells are negative for TTF-1 (immunohistochemistry, 200X). *C*, Diffuse strong membrane positivity for CD10 (immunohistochemistry, 200X).

normo-macrofollicular proliferation. As a matter of fact, eleven years before the patient underwent a left nephrectomy for a clear cell tumor of the left kidney. He quit the follow-up program for renal cancer in 2006 and the last CT scan performed was negative. Thus, the patient underwent a post-operative total body CT scan that demonstrated the presence of other metastases affecting both the lungs and the body of the pancreas. Finally, a completion bone scintigraphy showed an irregular uptake of the radiotracer in the sternum. The patient started therapy with Sunitinib (Sutent[®], Pfizer Inc., NY, NY, USA), an oral multi-targeted receptor tyrosine kinase (RTK) inhibitor: up to now, five years after the total thyroidectomy, the patient is still under follow-up and the metastases did not progress. However, the therapy with Sunitinib has stopped due to a myocardial infarction 6 months ago.

HISTOPATHOLOGICAL FEATURES

The specimen was fixed in 10% buffered formalin (Carlo Erba Reagents, Italy). After 48 hours of fixation the specimen was measured (5x2.5x1 cm the right lobe, 2.5x2.5x2 cm the isthmus, and 5x4x3 cm the left lobe) and sectioned. In the left lobe, a yellowish nodule with a maximum diameter of 4.8 cm was observed. The right lobe presented a diffuse nodular pattern. After a hematoxylin-eosin staining (Carlo Erba Reagents, Cornaredo (MI), Italy), the section was observed at light microscope. The left lobe nodule was composed by a proliferation of large cells with a clear cytoplasm, a well-marked cytoplasm membrane and a central round nucleus without nucleoli. Cells were arranged in nests and cords, surrounded by a rich sinusoid-like vasculature. At immunohistochemistry, cells showed strong membrane positivity for CD10 (clone 56C6, Dako) and were completely negative for Thyroglobulin (polyclonal rabbit anti-human, DAKO) and TTF-1 (thyroid transcription factor 1, clone 8G7G3, DAKO). Both macrophages and multinucleated giant cells inside the granulomas were strongly positive for CD 68 (clone EBM11, Dako). The right lobe and isthmus showed only a mild nodular hyperplasia, without giant cell granulomas. On the basis of the clinical history, the morphological and immunophenotypical characterization, a diagnosis of metastasis of clear renal cell carcinoma of the kidney was formulated.

DISCUSSION

Renal Cell Carcinoma accounts for 2-3% of all malignancies, with a median age of 65 years at diagnosis, and 85% of RCC are clear cell tumors. The



incidence of RCC has increased by 2% each year in the past 65 years, but the reason of this increase is still unknown¹. The most frequently described risk factors are smoking and obesity, while von Hippel-Lindau disease, which is caused by an autosomal dominant constitutional mutation in the VHL gene, represents the most common type of hereditary RCC^{90,91}. Patients with RCC had a mean 5-year survival rate of 69.4%⁹². The most important prognostic factors affecting patients' survival are tumor grade, local extension of the tumor, presence of regional nodal metastases and evidence of metastatic disease at presentation, with a prevalence of lung, bone, brain, liver and adrenal gland metastases⁹¹. Thyroid metastases from RCC account for 48.1% of Non-thyroid Malignancies (NTMs) metastases to the thyroid gland between 2000 and 2010, with a propensity to extend into the jugular veins. Epidemiologically, our data show that the mean age of thyroid metastases presentation is 64.4 years, with a slightly higher incidence in male than in female (see Table 1). The most common signs and symptoms are the presence of a neck mass, neck swelling and compression-related symptoms, such as dysphagia and dyspnea. However, although 74.9% of cases initially present with the described clinical manifestation, all the others are incidentally discovered on physical examination or imaging studies². Moreover, differential diagnosis may be of concern, since metastatic lesions often occur several years after the treatment of the primary lesion⁸². As a matter of fact, other authors reported that development of clinical thyroid gland metastases from RCC occurred at an average of 9.4 years after resection of primary RCC⁹³, which is consistent with our results (mean interval of 9.1 years, see Table 1). Our findings also confirm that lung and pancreas represent a frequent metastatic localization, accounting respectively for 32.8% and 17.2% of extra thyroid metastases from RCC among patients with thyroid metastases. Chung et al² demonstrated that FNAB failed to provide the correct diagnosis in 28.7% of patients with thyroid metastases from RCC. They also underlined that although FNAB is the most reliable tool for the study of thyroid nodules, a negative or indeterminate FNAB should lead to surgical excision according to patients' history and clinical presentation². As observed by Pitale et al³³ the follow-up chest CT in neoplastic patients should be converted in a thyroid-chest CT in order to avoid missing thyroid metastases. However, in 2015 the National Comprehensive Cancer Network (NCCN) Guidelines for Kidney Cancer recommend follow-up every 6 months for the first 2 years after surgery (3-6 months for three years for stage II and III), then annually for the following five years, comprehensive of history and physical

examination and metabolic panel (e.g., blood urea nitrogen, serum creatinine, calcium levels, LDH, and liver function tests). Abdominal and chest imaging are indicated within 3-12 months of surgery (3-6 for stage II and III) and then annually for three years, based on individual risk factors (up to 5 years for stage II and III). In the case reported here, our patient underwent regular follow-up for RCC for 7 years after surgical treatment and then quit. Eleven years after nephrectomy, metastases to the thyroid, to the lung and to the pancreas were demonstrated. Up-to-now, a thyroid gland monitoring is still not included in the follow-up program of RCC patients, even if metastases to this site can occur several years after the primary surgical treatment. In contrast, it is known that a precocious surgical intervention on the thyroid may prevent local recurrence and extension into other regional structures like the recurrent laryngeal nerve and trachea, improving patients' quality of life². Notably, our review demonstrates that jugular vein infiltration and local widespread are found in 15.6% of cases of thyroid metastases from RCC. Finally, surgical treatment of patients with solitary thyroid gland metastases is recommended, since it demonstrated a favorable prognosis in patients treated with radical surgery (mean 5-year survival rate 30-60%)⁸⁶.

CONCLUSIONS

Given the long latency between primary neoplasm and metastases presentation, the rising question is which approach should be adopted for the follow-up of patients with a history of RCC. We suggest improving the current post-surgical RCC follow-up program with an ultrasound scan of the neck, which represents a reliable and affordable method to detect new nodules or other modifications of the thyroid⁹⁴. A thyroid scan, according to data in the literature, should be prolonged for at least ten years after surgery, since a precocious intervention can improve patients' survival.

CONFLICT OF INTERESTS:

The authors declare that they did not receive any financial support and they have no conflicts of interest to disclose.

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