



Case Report

Solitary Metastasis of Clear Renal Cell Carcinoma to Thyroid Gland: Three reported cases with review of the literature

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Abstract

Metastasis to the head and neck and more specifically to the thyroid gland from distant primary tumors is less common in comparison to the local regional metastasis of squamous cell carcinomas of the upper aero-digestive tract. Preoperative diagnosis of these cases can be difficult. The authors present three cases with distant solitary metastases of clear renal cell carcinoma to the thyroid gland with ambiguous mechanism of tumor spread to the thyroid. Solitary metastases of clear renal cell carcinomas are an uncommon variant of metastasis of this tumor and may imitate thyroid well differentiated carcinoma which

most commonly affects the thyroid gland. Therefore, thorough endocrinological investigation of the thyroid gland is necessary. The recommended therapy of renal cell carcinoma metastasis includes surgical removal of all cancerous tissues – i.e. of the gland with the possibly infiltrated adjacent tissues, as well as removal of the affected lymph nodes – selective radical neck dissection. In our study, we discuss the clinical picture, pathology, diagnosis, differential diagnosis and prognosis together with literature review.

Keywords: distant metastases, clear renal cell carcinoma, thyroid gland, histopathology, therapy

Introduction

Solitary distant metastasis of clear renal cell carcinoma (CRCC) is a very rare variant of metastases. Distant metastasis as secondary malignant tumors to the head and neck are rarely encountered. Most of the literature describes individual cases only.

The diagnosis is made from clinical presentation, anamnesis, histological and radiological findings coupled with a confirmation of renal origin of the tumor. Metastasis of the CRCC to the thyroid gland may be characterised by the presence of renal cell carcinoma. Thyroid gland is a rare metastasis site for CRCC. Differentiating between the metastatic lesion and primary thyroid neoplasm can be difficult. Histologically, CRCC is characterised by the presence of clear cell carcinoma (variously differentiated). The possibility of a primary thyroid tumor is excluded by

immunohistochemical negative thyroglobulin staining and facultatively the glycogen PAS and/or amylase – PAS (a–PAS) positive staining.¹

Pitale et al. reported three cases of CRCC metastases among 941 patients after thyroidectomy during a 10-year period. In the literature, no more than 30 cases of CRCC metastases to the thyroid gland have been described.²

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The biological behavior of a primary tumor of the kidney mostly is aggressive – characterised by frequent metastatic involvement of the lymph nodes. Distant metastases to the bones and lungs are also observed. Radical therapy for solitary CRCC metastasis usually is considered the treatment of choice.

The aim of the current study is to analyze our experience in the management of CRCC metastases to thyroid gland.

Case series

Case No. 1

A 61 year–old–man presented with a palpable lump in the right lobe of the thyroid gland. He was euthyroid at the time of examination. Nephrectomy was carried out ten years ago for CRCC (Grawitz tumor).

Ultrasonography revealed homogeneously enhanced echogenicity without substantial gland enlargement, nodules in the right lobe with hypoechogenic area. The right lobe was 71x41x42 mm, and the left lobe was 28x14x12mm in size. The lymph nodes were not suspicious. Fine needle aspiration biopsy (FNAB) yielded atypical cells with carcinomatous features, the cells from the biopsy (cytology) were suspicious and expressed as parathyroid cells. Subtotal thyroidectomy was done as definitive treatment. Histopathology showed a firm thyroid gland, with clear cell carcinoma in the right lobe. Within the right lobe of the thyroid, there was an accessory tumor. Glycogen test was positive in the right lobe and the test for thyroglobulin and parathormone were negative (Figures 1 and 2).

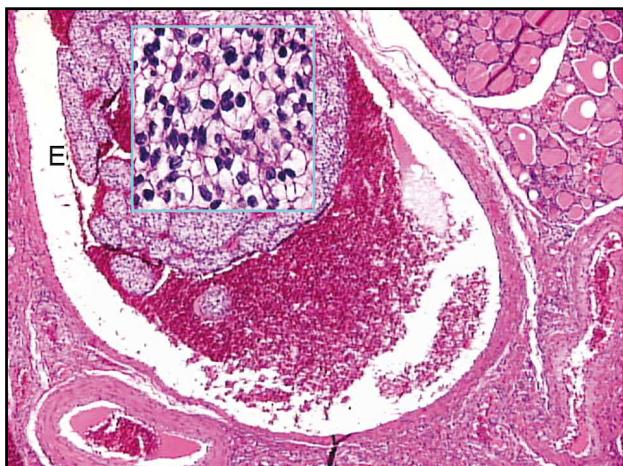


Figure 1. Neoplastic embolus /E/ of the clear cell kidney carcinoma in the dilated thyroid vessel. H&E staining, magnifying. 10x. Inset: detail of the CCRCC cytoplasm.

After surgery, hypocalcemia was not observed and vocal cord mobility was reserved. Substitution therapy with synthetic thyroid hormones subsequently was started. Postoperative long term follow–up was planned, no recurrence was seen, and it involved the Urology Centre, Otolaryngology Department and Endocrinology Clinic.

Case No. 2

A 73 year–old–female presented with an enlarged thyroid gland with multiple nodes and jugular vein thrombosis on the left side. The symptoms were observed 3 months ago and have been progressive since then. She was euthyroid at the time of examination. She had a hysterectomy carried out due to a benign tumor 12 years ago prior to presentation with the enlarged thyroid gland. At the time of hysterectomy, she had no evidence of renal cell carcinoma.

Ultrasonography of the neck region revealed multiple hypoechogenic tumor in both lobes of the thyroid gland. In the left lobe, we noted a hypoechogenic tumor with infiltration around the lobe structures. In the jugular vein, there was a hyperechogenic thrombosis with complete obstruction of the lumen. Guided FNAB was carried out from the left lobe and yielded a few suspicious clear carcinomatous cells. Surgery was recommended for multinodular goitre with uncertain biology.

The patient underwent total thyroidectomy with removal of the left jugular vein. There was tumor growth around the thyroid gland and down into the upper mediastinum. These severe tumor invasion limited the extent of the surgery. Histopathology of thyroid gland confirmed the diagnosis of clear cell carcinoma in both

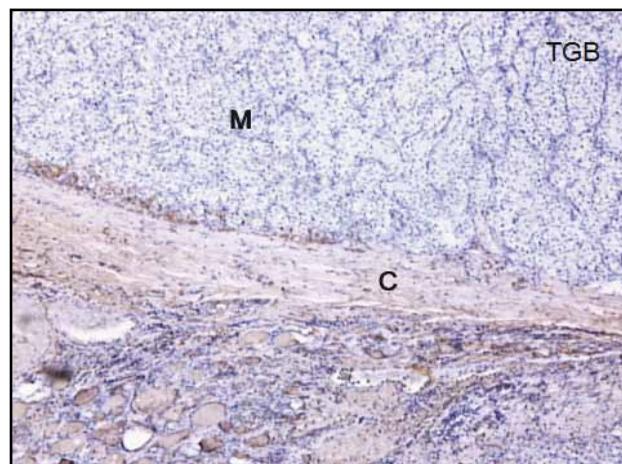


Figure 2. Thyroglobulin /TGB/ Immunohisto– chemistry. Positive in the lower part of the view –non neoplastic thyroid, and in a narrow rim under the capsule /C/. Metastatic nodule /M/ of the CCRCC negative. Anti TGB, magnifying 10x.

lobes. Glycogen test and PAS plus amylase PAS test were positive in the tumor.

After surgery, she did not develop hypocalcaemia but the vocal cord remained paralyzed on the left side. She was subsequently started on thyroid hormone replacement therapy.

Ultrasonography of the kidney showed a hypoechogenic suspicious tumor on the left kidney. Computed tomography scan of the kidney showed a tumor in the inferior parts – suspicious Grawitz tumor, avascular type on the left side. Nephrectomy was then carried out.

Nine months later, progression of the tumor in the neck was observed and ten months later there were solitary metastases in the lungs and bones. The patient died ten months after thyroid surgery due to progression of RCC.

Case No. 3

A 78 year-old-man, had right nephrectomy done 13 years ago due to RCC. 7 years later, he presented with a thyroid tumor on the right thyroid lobe. He also had slightly enlarged and histologically positive lymph nodes on the same side of the tumor. We advised total thyroidectomy with neck dissection. He declined the management and was sent home on palliative care. A year later, he presented to our clinic with complaints of difficulty swallowing and mechanical compression symptoms in the neck. He was euthyroid at the time of examination. Chest X-ray and scintigraphy of the bony skeleton revealed no metastasis. Ultrasonography of the kidney revealed no evidence of tumor in the right kidney but the left kidney had a cystic tumor.

Ultrasonography of the neck showed an enlarged right lobe of the thyroid gland with a tumor. There was enhancement of echogenicity with structural homogeneity of the tumor. A single enlarged lymph node located under the carotid bifurcation with suspicious features of the tumor infiltration was also seen. The other lymph nodes were described as tumor free.

FNAB was carried out and yielded a few suspicious cells of clear renal cell carcinoma. The patient underwent total thyroidectomy with selective neck dissection on the right side. A biopsy confirmed a firm thyroid gland, with clear cell carcinoma in the right lobe (alveolar subtype). Within the right lobe of the thyroid gland, a growing accessory tumour was seen.

Postoperatively, he did well as he did not develop hypocalcaemia and the vocal cords were unaffected. Substitution therapy with synthetic thyroid hormones was initiated and the patient remained on follow up in urology, otolaryngology and endocrinology clinics. Two years later during follow up, he had submandibular salivary gland

enlargement but was tumor free with no evidence of metastasis. The patient died 3 years later from recurrence of solitary metastasis and dissemination of the renal cell carcinoma to the bones and the lungs.

Discussion

Distant metastasis to the thyroid may occur by direct extension from malignant tumors in adjacent structures or by retrograde lymphatic spread. The metastasis of renal cell carcinoma (RCC) is a rare variant of solitary metastases to the thyroid gland. Kennel et al. 1991³ described four cases of renal cell carcinoma (Grawitz's tumor) that metastasized to the head and neck region at different stages of its evolution. The authors discussed the difficulties of the preoperative and histopathological diagnosis.

Kovacs et al.¹ presents the classification of renal cell tumors based on current genetic knowledge that correlates with recognizable histological findings. The classification that was adopted in Heidelberg in October 1996 includes: Benign renal tumors, are subclassified into: metanephric adenoma and adenofibroma, papillary renal cell adenoma, and renal oncocytoma. Malignant renal tumors are subclassified into: common or conventional renal cell carcinoma; papillary renal cell carcinoma; chromophobe renal cell carcinoma; collecting duct carcinoma, with medullary carcinoma of the kidney; and renal cell carcinoma, and unclassified tumors. The clinicopathological characteristics of RCC "well-differentiated carcinoma" includes the following:

- a) A renal origin of the tumor primaries.
- b) Radical nephrectomy earlier.
- c) Older age of presentation.
- d) Solitary presence of distant metastases.

The clinical history of the patient and the histological findings should be consistent with a renal origin of the tumor and that the history should be characterised by the presence of renal cell carcinoma or nephrectomy years ago. Other findings applicable to routine diagnostic practice are: ultrasonography, fine needle biopsy, other imaging methods (CT, MRI) and a histological classification with immunohistochemical staining.

The routine diagnostic protocol for primary and secondary neoplasms in the head and neck areas includes ultrasonography, fine needle biopsy, other imaging methods (CT, MRI) and a histological classification with immunohistochemical staining, the molecular classification based on current genetic knowledge.^{4,5}

Ultrasonography often reveals a mass in the thyroid gland with/without lymph nodes enlargement (cancerous infiltration of lymph nodes).

FNAB have shown suspicious or tumor cells, but the immunohistochemical differentiation of these lesions from the primary thyroid neoplasm can be difficult. Renshaw et al. studied the cytological features of each subtype of renal cell carcinoma (RCC) for separating the various subtypes. Seventy-four percent of the primary renal lesions were correctly classified. All metastases were correctly identified. Subclassification of RCC by FNAB is relatively accurate. In this study⁵, the most common error was to misclassify papillary and sarcomatoid RCC as clear cell RCC. While in our patients clear cell RCC was misclassified as papillary carcinoma of the thyroid gland.

Histologically, the tumor is characterised by the presence of clear cells carcinoma.¹ The histopathologic distinction between a clear cell thyroid tumor and a RCC metastasis in the thyroid gland may be difficult. The possibility of a primary thyroid tumor must be ruled out by immunohistochemical thyroglobulin staining and glycogen and PAS positive and a-PAS negative staining. All of the tumours in this study except one lymph node metastasis contained cells expressing vimentin intermediate filaments, generally a marker of mesodermally-derived tissues and their tumours, the sarcomas. In addition, the primary renal tumours and lymph node metastases contained cells that may express keratin proteins. Using a monoclonal antibody to keratins specific for glandular epithelial cells, it has been shown that some of the tumor cells resemble adenocarcinomas, at least in this respect. Double immunofluorescence labelling demonstrated that some of the vimentin-containing cells contained keratin while others did not. Grawitz tumor cells express intermediate filament types which are generally biological markers of both sarcomatous and carcinomatous tumours.

The biological behaviour of the primary kidney tumour is mostly aggressive – characterised by angiogenic metastases. Also, the presence of distant metastases in bones, lungs and lymph nodes have been observed.

Surgery for solitary RCC metastasis primarily is considered the treatment of choice. However, some patients survive without local recurrence or distant metastasis after the metachronous distant metastasis resection. Total or partial thyroidectomy, as well as excision of the affected lymph nodes with selective modified neck dissection was carried out in our patients. Some authors report to have used a non-radical surgery in cases of RCC distant metastases.^{2,6,7} Surgical removal of solitary metastases of RCC has been the only effective method of treatment. Prognosis of RCC after distant solitary metastasis is generally good. On the other hand partial dissection of metastases of RCC achieved good palliative results.

Radiochemotherapy in the treatment of metastatic renal cell carcinoma have been described as having good results too. Enhancement of radiation effects with drugs has been noted in some literature. Oncology treatment (radiotherapy, chemotherapy) improves the prognosis in selected cases

Surgical removal of a solitary metastasis of RCC has been discussed in the literature. We found that FNAB can be used to verify the tumor type of solitary metastases. Ultrasonography and other imaging methods (CT, MRI) can be used to assess for other metastases in the neck region. Investigation of the mediastinum and abdomen must be included and ruling out large metastatic disease is necessary prior to thyroid surgery. The prognosis for patients with solitary metastases of RCC is relatively good while the prognosis for patients with large metastatic disease is unclear.^{8,9,10}

Solitary metastases to thyroid gland are rarely described and recognition of RCC from differentiated clear cell thyroid carcinoma in cytology is difficult. Therefore complete analysis (including cytoblock, immunohistology, PAS a.o.) on the biopsy is necessary. On the other hand, thyroid metastases may be the prior manifestation of RCC and the only spread of the disease.

Conclusion

The difficulty of early recognition of this variant of RCC metastases lies in the ability to clinically simulate differentiated carcinoma (clear cell carcinoma) of thyroid gland. The practical importance of the correct RCC diagnosis pertains to the widely accepted requirement of the more therapeutic measures needed to eradicate the disease.

The treatment of metastases of RCC includes surgical excision of all cancerous tissues and removal of the affected lymph nodes. On the other hand, partial dissection of metastases of RCC in some individuals can achieve good palliative results. Follow up in the respective speciality clinic is important while oncology treatment is necessary.

The authors recommend radical surgery determined by tumor extent, location of the tumor, patient's general condition and age. The goals of surgical treatment were accomplished in the majority of the cases which included pain relief, improved and better quality of life. Prognosis of the patient with solitary distant metastases of RCC after complete removal is still controversial.

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