

Rare Case of Clear Cell Renal Cell Carcinoma Metastasizing to Contralateral Kidney and Ipsilateral Parotid more than five Years following Nephrectomy

SUMMARY

Background/Aim: Salivary gland malignancies are rare, with only a fraction due to metastases. We report a rare case of the Clear Cell Renal Cell Carcinoma (CCRCC), a subtype of the Renal Cell Carcinoma (RCC), metastasizing to the parotid gland more than five years following nephrectomy. **Case report:** A 75-year-old female presented with a unilateral left parotid mass that was growing over the period of 18 months. After clinical and laboratory examinations, the patient underwent left partial superficial parotidectomy with preservation of the facial nerve. The significance of the patient's history of the CCRCC was pivotal to the histopathological diagnosis of a metastatic CCRCC to the parotid. **Conclusions:** The unpredictable nature of the RCC results in the need for a long period of follow-up, as well as having a high degree of suspicion of metastasis in a patient presenting with a medical history of the RCC and a parotid mass.

Key words: Renal Cell Carcinoma, Clear Cell Renal Cell Carcinoma, Parotid Metastases, Nephrectomy, Parotidectomy

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CASE REPORT (CR)

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Introduction

Salivary gland malignancies are rare, with only a fraction of these due to metastases^{1,2}. Affecting mostly males, malignancy of the parotid gland typically presents as a mass. Eighty per cent of secondary tumours involving the parotid gland originate from the head and neck region. Other origins include the lung, breast and kidney².

The RCC is the most common form of kidney malignancy, with a global incidence of 15 per 100,000 of which males are more commonly affected³. Risk factors for developing the RCC include smoking, obesity, hypertension, end stage renal disease and tuberous sclerosis⁴. The CCRCC, the most prevalent subtype of the RCC, was recently found to be associated with the Von Hippel-Lindau (VHL) mutation⁵. Although flank pain, gross hematuria and a palpable abdominal mass constitute the classical triad of the RCC, more than 50% of cases are incidentally detected⁴.

The RCC is recognized for its unique metastasis pattern owing to its ability to spread by mainly vascular, yet also lymphatic channels^{5,6}. Well established sites for metastasis are bone, adrenals, lung and the contralateral kidney; however, metastasis to the head and neck is extremely rare⁶. We report a rare case of the CCRCC metastasizing to the parotid gland more than five years following nephrectomy.

Case Report

A 75-year-old female presented to the Oral and Maxillofacial Clinic with a left parotid mass, which had been present and growing over the period of 18 months (Figure 1 a). The patient did not report local or systemic symptoms, such as facial paresis, change in salivation, weight loss, fever or hypertension. When acquiring past medical history, the patient reported the RCC of the left

kidney in 2010, which presented as a one-time painless hematuria, without prior change in urination, or flank pain. Following urological assessment, the patient then underwent a left total nephrectomy. A subsequent RCC of the right kidney three years later was incidentally found during a routine follow-up examination. The

patient underwent right partial nephrectomy and auto-transplantation. The patient reported a smoking history, as well as alcohol consumption, which began in her late 20s and increased to a current consumption of 3 units of alcohol per day. Clinical examination revealed a painless, hard, mobile parotid mass, measuring 4x4 cm.

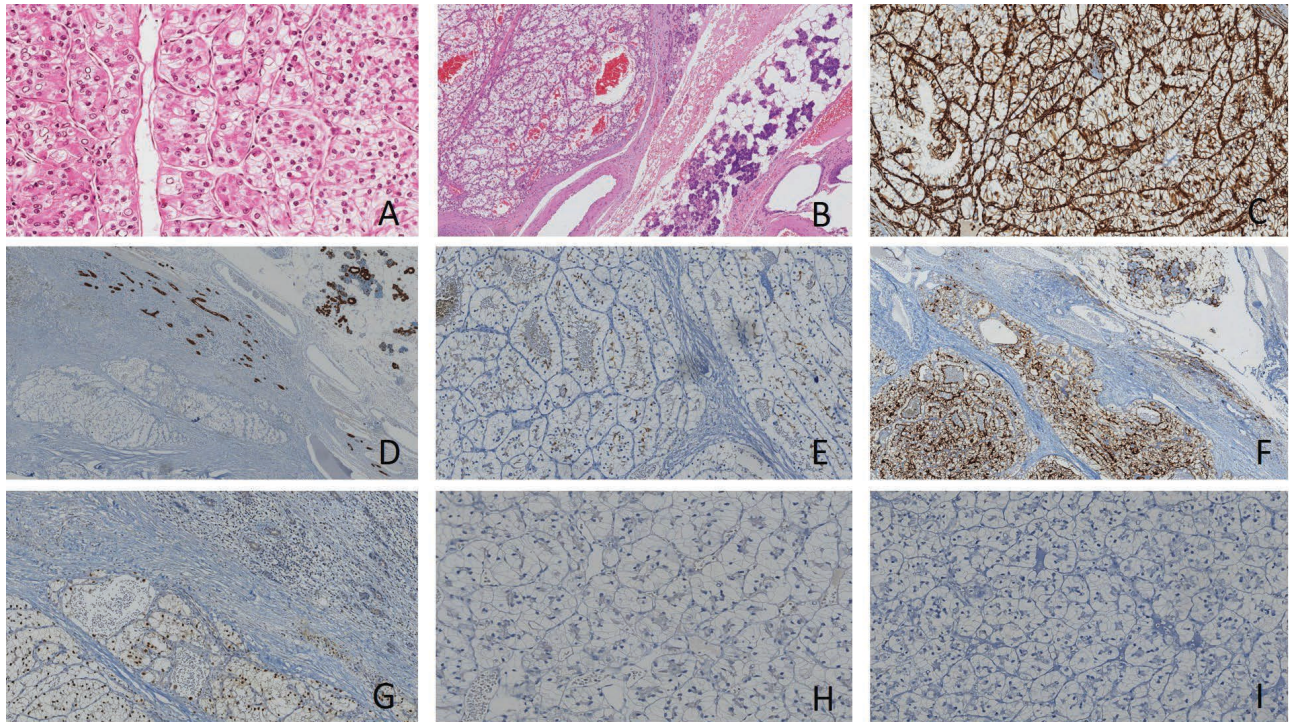


Figure 1. a) Clinical presentation of the enlarged left parotid gland; b) Transverse CT scan indicating the enlarged left parotid mass, with prominent nearby lymph nodes; c) Surgical field for left parotidectomy with preservation of the facial nerve; d) Excised parotid mass measuring 5x4x3cm, with regional lymph nodes.

Imaging

Neck ultrasonography (US) performed five months prior to the patient's visit to the Oral and Maxillofacial Clinic revealed a round hypoechoic lesion within the parotid gland, with well-defined borders. The lesion exhibited intense peripheral vascularization, in addition to inner vascularization at a lesser degree. The lesion at that time measured 1.6x1.6cm. Pleomorphic adenoma was suspected, but further investigation was suggested. All other salivary glands appeared normal and no enlarged lymph nodes were detected. A computer tomography (CT) scan of the upper neck and the parotids was performed four months later, without contrast, owing to the patient's allergy to the contrast media (Figure 1 b). The scan revealed a large 4.1x3.8x3.5cm solid lesion of the left parotid gland's superficial lobe, with mild lobulation and speculation of its borders at its upper margin, as well as signs of infiltrative growth to the deep lobe of the left parotid. There were prominent lymph nodes from the left upper lateral group of the neck (IIa) up to 2x1cm. Small lymph nodes from other groups of the neck were also present. No obvious infiltration of deep or superficial

fat planes of the neck were seen. The right parotid and submandibular glands appeared normal. Fine needle aspiration biopsy (FNAB) of the left parotid that was subsequently performed was suspicious for malignancy.

Surgery

It was decided to perform partial superficial left parotidectomy, which included excision of the tumor and lower parotid lobe, with preservation of the facial nerve (Figures 1 c and d). Regional lymph nodes were additionally resected.

Pathology

Pathological evaluation of the excised parotid gland revealed a blanched surgical specimen of hard consistency, comprised of connective and fatty tissue, measuring 5x4x3 cm, and surrounded by a thin fibrous capsule, with focal disruption and evidence of brown-irred foci. Immunohistochemistry was performed (Figure 2), yielding CD10 (+), vimentin (+), PAX8 (+), RCC focally (+), CK7 (-), S100 (-), and Melan A (-). The final diagnosis of the renal metastatic CCRCC was established.

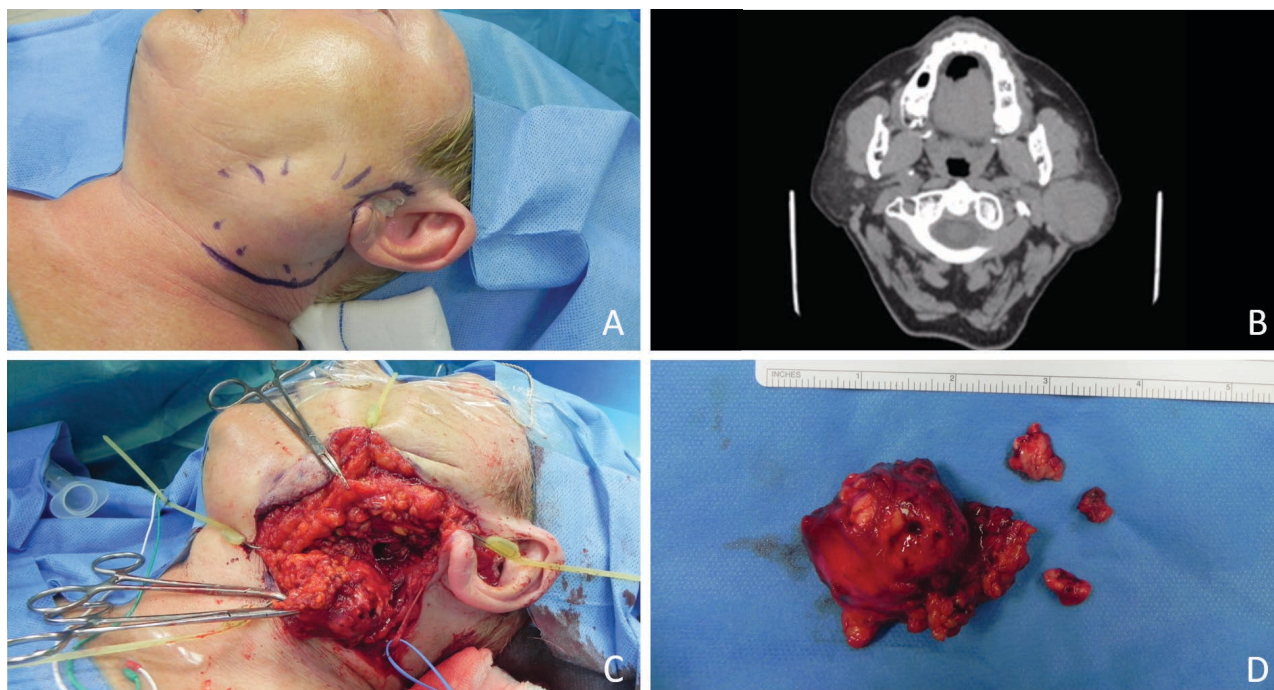


Figure 2. a) Primary renal cell carcinoma, clear cell type (H&E, x200); b) Parotid gland metastasis from renal cell carcinoma. The physiological parotid tissue can clearly be distinguished on the right of the slide, from the clear cell renal tissue on the left, through which vessels are also seen (H&E, x40); c) Positive vimentin immunostaining (Vimentin, x100); d) No expression of cytokeratin 7 in neoplastic cells but positive staining in normal parotid tissue (CK7, x100); e) Positive RCC immunostaining (RCC, x100); f) Expression of CD 10 (CD10, x40); g) Nuclear staining of PAX 8 (PAX8, x100); h) Negative staining of Melan A (Melan A, x100); i) No expression of S100 (S100, x100).

Discussion

We report a rare case of the CCRCC, a subtype of the RCC, metastasizing to the parotid gland more than five years following nephrectomy. The patient presented with a unilateral left parotid mass that was growing over the period of 18 months. After imaging investigation *via* US and CT, the initial impression concerning diagnosis was pleomorphic adenoma, although FNAB, as well as preceding imaging modalities were suspicious for malignancy and assisted in the planning of the operation. The patient underwent partial, left superficial parotidectomy with preservation of the facial nerve and the excised specimen was sent for pathological evaluation. The patient's history of CCRCC was considered central for the final diagnosis of metastatic CCRCC to the parotid, even after more than five years following nephrectomy. The patient remains under close-follow-up.

Due to its ability to spread *via* vascular, in addition to lymphatic channels, the RCC carries the ability to metastasize to distant and unpredictable locations of which metastasis to the parotid gland is extremely rare. The first cases of parotid involvement due to RCC metastases were reported by Patey *et al.* in 1965⁷. Since then, there have been limited reported cases of this phenomenon^{6,8-16}. In their review of the literature, Lawlor *et al.* reported 45 cases of RCC metastasizing

to the parotid, of which only 31 were complete case presentations⁶. They also reported that when FNAB was performed, it was diagnostic in only 3 of the cases. In 10 cases FNAB was non-diagnostic, while 18 cases did not mention the use of FNAB. In their case series, Park *et al.* reported that 33% of cases with a parotid mass suspicious for RCC metastasis, were negative for malignancy or had a non-diagnostic yield *via* FNAB¹⁷.

Eight of the articles reviewed by Lowler *et al.* stained positive for proximal nephron renal antigen, vimentin, CD10 and cytokeratin (CAM 5,2)⁶. CEA and cytokeratin 7 (CK7) were negative⁶. Similarly, the present patient was positive for CD10 and vimentin; while negative for CK7, excluding parotid origin of the tumour, as well as lung cancer metastases. The pathologist additionally assessed Melan A and S100, excluding melanoma metastases. Furthermore, this patient was positive for PAX8 and RCC, owing to a renal origin.

Since the initial diagnostic suspicion in this case was a primary parotid tumour, a pathological assessment of CK7, a highly important marker staining positive in primary parotid gland tumours, was performed. A few examples of these are clear cell carcinoma of the salivary glands, clear cell epithelial-myoeplithelial carcinoma, clear cell myoeplithelial carcinoma, and sebaceous carcinoma. Thus, by initially examining CK7, a parotid origin could be excluded.

According to Williamson *et al*, who compared international guidelines and surveillance protocols for post-nephrectomy RCC, the longest surveillance period post-nephrectomy was 5 years¹⁸. Lawlor *et al*. further reported that in their reviewed cases, metastases of the RCC to the parotid ranged from 5 months to 19 years post-excision⁶. Due to delay in diagnosis, 30% of patients first presented with pre-existing metastatic disease. Among those with localized RCC, 25% of patients that underwent a nephrectomy later presented with relapse and distant metastases^{5,6}, demonstrating that there is significant justification for continuous follow-up due to the long-spanning metastatic potential of the RCC. A follow-up protocol lasting longer than 5 years should be considered.

Conclusions

RCC metastases may be present several years after the excision of the primary tumour, resulting in the need for a multidisciplinary team approach in the management and close follow-up. When a patient presents with a parotid mass, clinical and laboratory investigations must follow, which should be accompanied by a detailed past medical history. In the case that the latter includes an RCC diagnosis, a high degree of suspicion for metastasis to the parotid should be considered.

References

- Speight P, Barrett A. Salivary gland tumours. *Oral Dis*, 2002;8:229-240.
- Barnes L, Eveson JW, Reichart P, Sidransky D. WHO Organization Classification of Tumors. Pathology and Genetics of Head and Neck Tumors. IARC Press, Lyon 2005; pp:430.
- Graves A, Hessamodini H, Wong G, Lim WH. Metastatic renal cell carcinoma: update on epidemiology, genetics, and therapeutic modalities. *Immunotargets Ther*, 2013;2:73-90.
- Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*, 2016;27(Suppl. 5):v58-v68.
- Choueiri T, Motzer R. Systemic Therapy for Metastatic Renal-Cell Carcinoma. *New Engl J Med*, 2017;376:354-366.
- Lawlor C, Wein R. Parotid Metastasis of Renal Cell Carcinoma: A Case Report and Review of the Literature. *J Can Ther Res*, 2012;1:15.
- Patey D, Thackray A, Keeling D. Malignant disease of the parotid. *Br J Cancer*, 1965;19:712-737.
- Lieder A, Guenzel T, Lebentrau S, Schneider C, Franzen A. Diagnostic relevance of metastatic renal cell carcinoma in the head and neck: An evaluation of 22 cases in 671 patients. *Int Braz J Urol*, 2017;43:202-208.
- Hussain F, Yedavalli N, Loeffler D, Kajdacsy-Balla A. Solitary parotid metastasis 8 years after a nephrectomy for renal cell carcinoma. *J Community Hosp Intern Med Perspect*, 2016; 6:31950.
- Majewska H, Skálová A, Radecka K, Stodulski D, Hyrcza M, Stankiewicz C, et al. Renal clear cell carcinoma metastasis to salivary glands - a series of 9 cases: clinicopathological study. *Pol J Pathol*, 2016;1:39-45.
- Balaban M, Vudali Dogruyol S, Idilman I, Unal O, Ipek A. Renal Cell Carcinoma Metastasis to Ipsilateral Parotid and Submandibular Glands: Report of a Case with Sonoelastographic Findings. *Pol J Radiol*, 2016;81:17-20.
- Franzen A, Günzel T, Lieder A. Parotid gland metastases of distant primary tumours: A diagnostic challenge. *Auris Nasus Larynx*, 2016;43:187-191.
- Shi J, Zhou J, Li J. Renal clear cell carcinoma with thyroid and parotid metastases: A case report. *Oncol Lett*, 2015;10:2617-2619.
- Udager A, Rungta S. Metastatic renal cell carcinoma, clear cell type, of the parotid gland. *Diagn Cytopathol* 2014;42:974-983.
- Hosn-Centenero SA, Coll-Anglada M, Pradillos-Garcés A, Salinas-Duffo D. A Rare Case of Renal Cell Carcinoma Metastasis in the Parotid Gland Eleven Years after the Initial Diagnosis. *Acta Otorrinolaringol*, 2014;65:375-377.
- Yanlan C, Liping S, Shaomin C, Zi L, Liping S. Metastasis to the parotid region as an initial presentation of renal cell carcinoma: A case report. *Oncol Lett*, 2013;5:997-999.
- Park YW, Hlivko TJ. Parotid gland metastasis from renal cell carcinoma. *Laryngoscope*, 2002;112:453-455.
- Williamson TJ, Pearson JR, Ischia J, Bolton DM, Lawrentschuk N. Guideline of guidelines: follow-up after nephrectomy for renal cell carcinoma. *BJU Int*, 2016;117:555-562.

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