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Clear Cell Renal Carcinoma Pituitary Recurrence Presenting as Panhypopituitarism Manifested as Chronic Diarrhea: A Case Report and Brief Literature Review

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ABSTRACT

Background: Clear cell renal carcinoma is the most common histologic subtype of renal cell carcinoma and has the worst overall survival. Metastatic disease may develop in 20 to 40% of patients after radical nephrectomy. Pituitary metastasis is a rare presentation.

Objective: To report a case of pituitary metastatic recurrence of clear cell renal carcinoma that presented as panhypopituitarism, with chronic diarrhea as the main manifestation.

Case description: A 70-year-old man with type 2 diabetes mellitus, hypertension, multifactorial chronic kidney disease, and a right radical nephrectomy one year earlier for clear cell renal carcinoma, with no evidence of recurrence on follow-up, presented to the emergency room with general malaise and chronic watery diarrhea, weight loss, fatigue, and diplopia. He had bitemporal hemianopsia, right third and sixth cranial nerve palsies, and a right pupil unresponsive to light, consistent with cavernous sinus syndrome and partial Horner syndrome. Magnetic resonance imaging showed an extra-axial mass infiltrating the hypophyseal fossa. Panhypopituitarism was documented (decreased morning cortisol, central hypothyroidism, hypogonadotropic hypogonadism, and elevated prolactin); with stress-dose hydrocortisone and levothyroxine, symptoms and blood pressure improved. A transnasal biopsy confirmed metastatic recurrence of clear cell renal carcinoma. Nivolumab and directed gamma knife radiotherapy were offered.

Conclusions: Pituitary metastases are rare. We report an unusual presentation: chronic diarrhea as the main sign of panhypopituitarism secondary to pituitary recurrence of clear cell renal carcinoma.

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Introduction:

Renal cell carcinoma accounts for 90% of all kidney cancers. Most cases are diagnosed in older adults (60 to 70 years), and it is twice as frequent in men as in women. The three main histological types are clear cell (75%), papillary (15 to 20%), and chromophobe (5%); clear cell renal carcinoma has the worst overall survival [1]. At the time of diagnosis, one-third of patients have metastatic disease, and 20 to 40% may develop it after radical nephrectomy; serial imaging is therefore used to monitor disease progression and treatment response [2].

Clear cell renal carcinoma tends to metastasize to the lungs, bone, lymph nodes, liver, adrenal glands, and brain. An isolated clival metastasis is a rare presentation, with only a few case reports found on literature review [3-5]. Management options for metastatic lesions range from radiotherapy to systemic treatment with immune checkpoint inhibitors (pembrolizumab), tyrosine kinase inhibitors (cabozantinib, axitinib, lenvatinib), and mTOR inhibitors (everolimus). With these new options, overall survival has improved from less than 1 year to more than 4 years [6-7].

The aim of this report is to describe a patient with pituitary recurrence of clear cell renal carcinoma that presented as panhypopituitarism, with chronic diarrhea as the main symptom, and to briefly review the literature.

CASE REPORT

A 70-year-old man presented to the emergency room with general malaise and chronic watery diarrhea. He had a history of type 2 diabetes mellitus, hypertension, and multifactorial chronic kidney disease. One year earlier he had been diagnosed with clear cell renal carcinoma and treated with right radical nephrectomy; follow-up imaging showed no evidence of recurrence.

He reported recent weight loss, fatigue, and diplopia. On arrival he was hypotensive and tachycardic, which improved after intravenous fluid administration; the other vital signs were within normal parameters.

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Physical examination revealed bitemporal hemianopsia, right third and sixth cranial nerve palsies, and a right pupil that was unresponsive to light, consistent with a cavernous sinus syndrome and a partial Horner syndrome. The rest of the physical examination was unremarkable.

Blood work (Table 1) showed normocytic anemia, increased creatinine without acute dialysis criteria, mild hyperkalemia, and a normal anion gap metabolic acidosis, best explained by the history of diarrhea. Based on these findings, a head magnetic resonance imaging study revealed an extra-axial mass infiltrating the hypophyseal fossa (Figure 1). Further workup demonstrated panhypopituitarism: decreased morning cortisol, central hypothyroidism, hypogonadotropic hypogonadism, and elevated prolactin (Table 2). Stress-dose hydrocortisone and levothyroxine were started, and the patient showed remarkable improvement in symptoms and blood pressure. The chronic diarrhea workup included a coprological examination, a coproparasitoscopic study, and a celiac disease antibody panel (Table 3); the coproparasitoscopic study and the celiac disease antibodies were negative.

A 30.0 × 26.2 × 23.8 mm extra-axial mass infiltrates the hypophyseal fossa and the anterior and posterior clinoid processes and surrounds the cavernous portion of the right carotid artery. There is gross rostral displacement of the anterior pituitary; the posterior pituitary could not be visualized with this method. Gadolinium was not used owing to stage IV chronic kidney disease with a solitary kidney.

A transnasal biopsy was performed. Immunohistochemistry showed expression of cytokeratin AE1/AE3, PAX8, CD10, and RCC, with a Ki-67 proliferation index of 40% (Figure 2). A metastatic recurrence of clear cell renal carcinoma was thus confirmed after the curative-intent nephrectomy performed the previous year. Systemic therapy with nivolumab and directed radiotherapy with gamma knife was offered.

DISCUSSION

Renal cell carcinoma has historically been called the "internist's tumor" because of its paraneoplastic presentations, such as anemia, erythrocytosis, hepatic dysfunction (also known as Stauffer syndrome), and hypercalcemia. Nowadays, it is mostly diagnosed as an organ-limited disease, usually as an incidental finding, owing to the wide availability of computed tomography. The classic but infrequent triad (less than 10% of patients) is hematuria, weight loss, and a palpable abdominal mass.

The imaging modalities of choice are abdominal contrast-enhanced computed tomography and magnetic resonance imaging, to evaluate the extent of the primary tumor and of metastatic disease. Clear cell renal carcinoma frequently shows avid arterial enhancement, which helps differentiate it from other renal cell subtypes. Histopathologic evaluation confirms the definitive diagnosis, but owing to its radiological characteristics it can be diagnosed by imaging with a fair amount of confidence, given its high sensitivity and specificity (greater than 88% each), so that curative treatment can be offered early and appropriately.

In a recent review, Moon and colleagues examined the time interval from the diagnosis of clear cell renal carcinoma to pituitary metastasis. In this review of 36 case reports, the median time between both events was 1 year, with an interval from 0 to 27 years. The most frequent clinical presentation was visual defects; almost 50% of the patients had biochemical results consistent with hypopituitarism, and around 30% had diabetes insipidus at presentation [5].

In contrast, the main clinical manifestation in our patient was chronic diarrhea, which was subsequently correlated with secondary adrenal insufficiency. Gastrointestinal manifestations of adrenal insufficiency are frequent, but persistent or chronic diarrhea is unusual, since patients are usually diagnosed during a hypotensive adrenal crisis [5].

This report portrays an elderly patient with a history of organ-limited clear cell renal carcinoma treated with radical nephrectomy 1 year earlier, who presented with chronic diarrhea as the main manifestation of panhypopituitarism secondary to a metastatic recurrence. We found several case reports showing that clear cell renal carcinoma has an important pituitary tropism and that the pituitary is an important site of recurrent disease, but none of them reported chronic diarrhea as the main manifestation.

Paraneoplastic diarrhea is a rare phenomenon that may be triggered by a variety of pathophysiological mechanisms [8]. However, it is mostly described in tumors of endocrine or gastrointestinal origin; added to the fact that panhypopituitarism and visual defect were the main clinical findings during our approach, this led to a low diagnostic suspicion and delayed the diagnosis in our patient. Case reports usually describe an elderly patient with progressive headache and loss of visual acuity, and with diabetes insipidus in one-third of patients [9,10]. In most cases of paraneoplastic diarrhea, diagnosis and treatment of the underlying disease is considered the only effective measure [8].

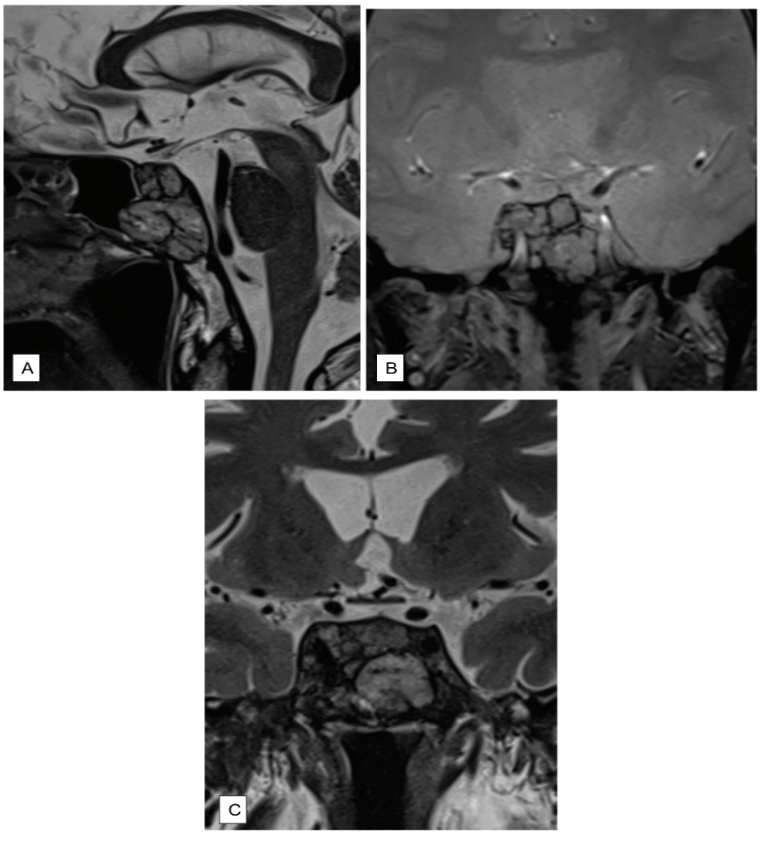


Figure 1: Head magnetic resonance imaging. A) Sagittal susceptibility-weighted imaging (SWI). B) Coronal SWI. C) Coronal T2-weighted sequence.

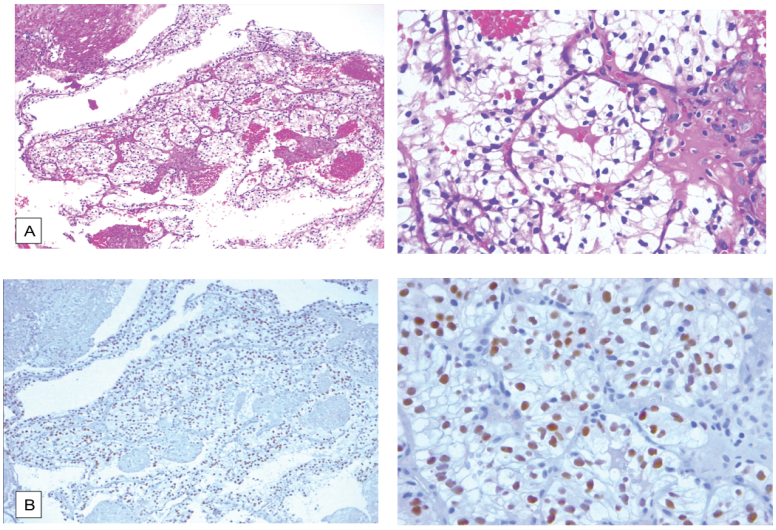


Figure 2: Transnasal biopsy. A) Conventional hematoxylin and eosin staining: clear cells arranged in nests surrounded by a delicate vascular network, suggestive of clear cell renal carcinoma. B) Nuclear expression of PAX8 supports the renal origin of the neoplasm based on the known history.

Table 1: General laboratory results.

Test	Results
Complete blood count	
Leukocytes	$8.9 \times 10^3/\mu L$
Hemoglobin	9.9 g/dL
Platelets	$262 \times 10^3/\mu L$
Blood chemistry and serum electrolytes	
Glucose	174 mg/dL
Blood urea nitrogen	45.8 mg/dL
Creatinine	3.61 mg/dL
Sodium	140 mmol/L
Potassium	5.7 mmol/L
Chloride	105 mmol/L
Total carbon dioxide	20.7 mmol/L
Calcium	9.35 mg/dL
Phosphate	4.3 mg/dL
Magnesium	2.17 mg/dL (1.70–2.30)
Uric acid	3.0 mg/dL
Urinary spot	
Prostate-specific antigen	85 ng/mL (0–7.2)

Table 2: Laboratory evaluation of the pituitary axes demonstrating panhypopituitarism.

Test	Results
Thyroid axis	
Thyroid-stimulating hormone	0.078 µIU/mL (0.300–4.20)
Triiodothyronine	1.77 ng/mL (0.80–2.0)
Total triiodothyronine	8.47 µg/dL (4.6–12)
Free thyroxine	1.17 ng/dL (0.93–1.70)
Parathyroid	
Parathyroid hormone	26.7 pg/mL (15.0–65.0)
Adrenal axis	
Corticotropin	16.3 pg/mL (7.30–64)
Serum cortisol	1.9 µg/dL (7–25)
Gonadotropic axis	
Follicle-stimulating hormone	1.5 mIU/mL (20–138)
Luteinizing hormone	<0.3 mIU/mL (1.7–12)
Serum testosterone	9.91 ng/dL (193–740)
Lactotropic axis	
Prolactin	155 ng/mL (4–15.2)
Growth hormone axis	
Insulin-like growth factor 1	11 ng/mL (32–200)

Table 3: Chronic diarrhea workup.

Test	Results
Coprological examination	
Amount	30 g
Consistency	Semisolid
Color	Yellow
Emulsion	Present
Food scraps	Present
Mucus	Absent
pH	6.0
Leukocytes	3–5
Occult blood	Negative
Gram stain	Diminished
Macroscopic parasites	Negative
Microscopic parasites	Negative
Coproparasitoscopic study	
Result	Negative
Celiac disease antibody panel	
Anti-endomysial	Negative
Anti-deamidated gliadin IgA	<2 U/mL (0–25)
Anti-deamidated gliadin IgG	<2 U/mL
Anti-transglutaminase IgA	<2 U/mL (0–25)
Anti-transglutaminase IgG	0.05 index (0–1)

CONCLUSION

Overall, pituitary metastases are rare. Several case reports demonstrate an evident tropism of clear cell renal carcinoma to tissues adjacent to the pituitary gland. In this report we present an elderly patient with the unusual presentation of chronic diarrhea as the main sign of panhypopituitarism secondary to a pituitary metastatic recurrence of clear cell renal carcinoma.

DECLARATIONS

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Informed consent.: Written informed consent was obtained from the patient for publication of the case and accompanying images.

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