




# Pituitary Metastasis of Clear Cell Renal Carcinoma Mimicking Pituitary Macroadenoma – Case Report

## *Metástase de carcinoma renal de células claras em sela túrcica simulando macroadenoma hipofisário – relato de caso*

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### Abstract

**Introduction** Pituitary tumors account for 25% of all primary brain tumors and for 15% of overall intracranial expansive masses. Pituitary metastases, in contrast, are a rare condition, estimated as 1.8% of all resected sellar lesions. We present here a rare case of clear cell renal carcinoma metastasis to the pituitary gland.

**Case Report** A 65-year-old patient with holocranial headache and diplopia, whose physical examination showed right eye abduction palsy and ipsilateral anisocoria. Magnetic resonance imaging (MRI) of the pituitary revealed a heterogeneous mass in T1 weighted imaging with mild peripheral contrast enhancement and considerable growth during follow-up. Prolactin levels were high and dropped to normal after use of cabergoline, but remained normal even after the medication was halted. Biopsy was compatible with clear cell renal carcinoma. After surgery, the patient underwent radiotherapy, which was effective in reducing the volume of the lesion.

**Discussion** Only 25 cases of pituitary metastasis arising from the kidney were reported in the literature between the years of 1957 and 2018. Metastases can reach the pituitary through hematogenous spread, cerebrospinal fluid, and contiguous bony lesions. Clinical presentation varies from vague complaints such as fatigue or headache to more specific signs like polyuria and polydipsia, and ~ 60% of cases have clinical manifestations.

**Conclusion** Case reports of pituitary metastases are low worldwide, with only 25 case reports of kidney metastases in over a 60-year period. The rarity of the lesions and hormonal alterations due to pituitary stalk compression can mislead diagnosis, and some patients may even never be diagnosed regarding their lower life span. In this report, radiotherapy was effective postresection, and accounts for a treatment option. All these issues account for the relevance of these case reports.

### Keywords

- pituitary metastasis
- renal clear cell carcinoma
- skull base
- sellar tumor
- neurosurgical oncology

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## Introduction

Approximately 25% of primary benign brain tumors and 15% of all primary brain neoplasms are pituitary tumors. The annual incidence lies in an estimated range of 3 to 11 cases per 100,000 individuals, and they represent the third most common primary intracranial tumor, after gliomas and meningiomas.<sup>1</sup> On the other hand, pituitary metastases are rare, estimated to be 1.8% of all surgically resected sellar masses. In addition, only 25 cases of renal cell carcinoma metastasized to the pituitary were described between 1957 and 2018 in the largest meta-analysis to date, reinforcing the significance of the present case report.<sup>2</sup>

Regarding renal cell carcinoma, it accounts globally for 2 to 3% of all malignancies, with 338,000 new cases per year worldwide. Between 20 to 30% of the patients already have metastases at diagnosis.<sup>3</sup>

Autopsy studies demonstrated a prevalence of 1 to 4% of pituitary metastases in patients with advanced cancer, suggesting a higher prevalence than the diagnosed cases. These may be increasing due to enhancements in neuroimaging, laboratory testing, and higher lifespan of cancer patients over time. Treatment involves surgical decompression, chemotherapy, immunotherapy, radiotherapy, or even conservative approach.<sup>2</sup> The mostly described symptoms are visual field defects, panhypopituitarism, headache, and even diabetes insipidus (DI), but appear in only 7% of cases, as the rest of them are asymptomatic.<sup>4</sup>

## Case Report

We present a female patient, 65 years old, reporting a holocranial headache and diplopia of insidious start and gradual worsening over 1 month. In physical examination, it was noted right abducens nerve palsy alongside anisocoria, whereas the right pupil was moderately more dilated and less reactive than the left pupil. Neuroimaging revealed a sellar mass, and laboratory testing presented elevated serum levels of prolactin (141 ng/mL, reference values 3 to 20 ng/mL). Cabergolin was initiated, and prolactin levels reduced (1.4 ng/mL), dropping to normal rates even though the dopaminergic agonist was halted.

Past medical history of the patient involved left nephrectomy and adrenalectomy 11 years before due to clear cell renal carcinoma, and right adrenalectomy 7 years later due to another metastasis. The patient sought medical assistance before neuroimaging due to upper abdominal pain in a band-like pattern, exams showing elevated lipase and amylase serum levels. Abdominal imaging revealed a mass lesion invading the head of the pancreas causing pancreatitis, and biopsy confirmed it to be another site of metastasis of renal cell carcinoma. The comorbidities of the patient were type 2 diabetes mellitus and primary hypertensive disease.

Magnetic resonance imaging (MRI) of the brain of the patient revealed a heterogeneous mass in T1 weighted imaging with partial peripheral contrast enhancement (►Fig. 1). During follow-up and investigation, there was

considerable growth in a period of 2 months, from 2.0 cm<sup>3</sup> to 3.1 cm<sup>3</sup> (►Fig. 2). The lesion extends lateral to the lateral tangent between the supracavernous and intracavernous internal carotid artery segments, advancing into the superior cavernous sinus compartment, therefore being classified as modified Knosp 3A.<sup>5</sup>

The patient underwent surgery with partial resection of the tumor because of its hardened consistency and involvement of cavernous sinus alongside the carotid artery. Nevertheless, there was progressive visual improvement, reported by the patient as reduction in diplopia. Immunohistochemistry was positive for PAX8 transcription factor and CD10 marker, both typically found in this type of tumor.<sup>6</sup> Histological study showed an epithelial neoplasm with clear cells (►Fig. 3), as correlated to the rarefied cytoplasm of a clear cell carcinoma usually described.<sup>7</sup>

Postoperative computed tomography scan (CT) soon after surgery showed hemostatic material inside the sella and sphenoid sinus. A small amount of residual tumor can be identified on the right side, but major reduction of the lesion volume is observed (►Fig. 4).

Oncologic follow-up after the procedure included chemotherapy with Axitinib and Pembrolizumab. Radiosurgery was performed 3 months after surgical resection aiming for the residual tumor involving the right internal carotid artery, with even more reduction of its volume (►Fig. 5).

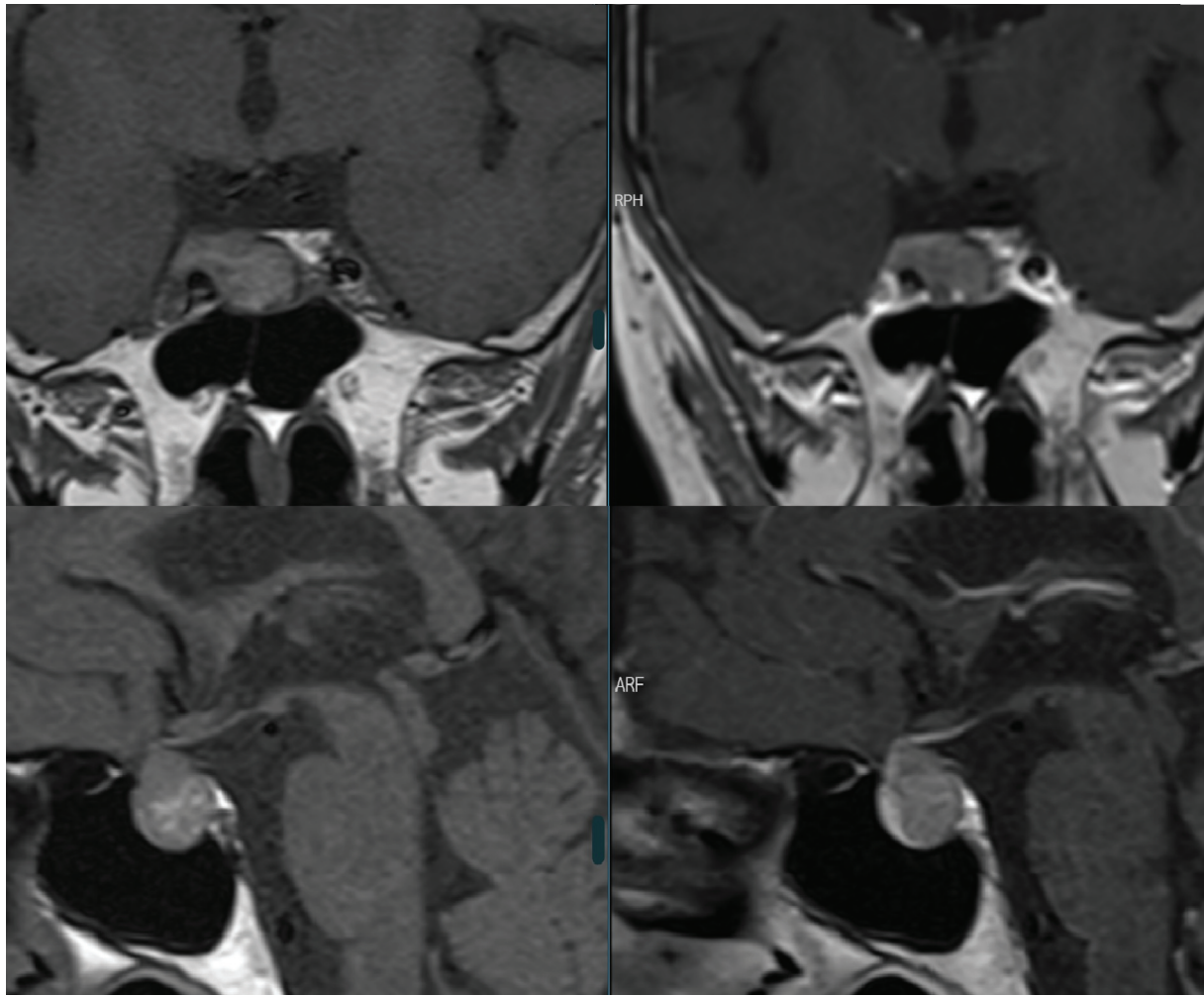
## Discussion

According to a recent meta-analysis, only 25 cases of pituitary metastasis from kidney were reported from 1957 to 2018. The incidence of pituitary mass due to renal cell carcinoma is low worldwide, despite standing as the fourth most common primary site. The reported cases arise the possibility of interactions between the metastasis and renal cancers contributing to dissemination to the sella.<sup>2</sup>

Among patients with renal cell carcinoma in general, 21% have distant metastasis at the moment of diagnosis. Studies concur regarding frequency of the metastases, and according to an important prospective series, the most frequent sites of metastases from renal cell carcinoma were lung (54%), lymph nodes (22%), and bone (20%). Moreover, 17% of patients without metastasis at diagnosis were affected by metastatic spread during follow-up.<sup>3</sup>

Breast and lung correspond to more than half of original tumor sites in all reported cases of pituitary metastasis. Kidney, prostate, and colon stand for 3 to 5% of the cases. Other rare causes include melanoma, thyroid, pancreas, hematologic neoplasms, and unknown primary cancers.<sup>4</sup>

There are four main ways of metastases to spread to the pituitary. Two of them involve conventional hematogenous spread, through the hypophyseal arteries supplying the posterior lobe and through the hypophyseal portal system of the anterior lobe. Cerebrospinal fluid can also carry malignant cells, and the final mechanism is direct



**Fig. 1** First MRI of the patient, in coronal (superior half) and sagittal (inferior half) sections, precontrast T1 weighted images on the left and T1 postcontrast on the right. A sellar mass is observed with parasellar extension on the right over the cavernous carotid artery and surpassing it, therefore being classified as Knosp 3A. It is a heterogeneous lesion, with sparse high intensity spots in T1 and less postcontrast enhancement than the pituitary parenchyma surrounding it.

compression or invasion of the gland by bony metastases of the skull base.<sup>4</sup>

Involvement of the posterior lobe alone occurs in 50.8% of cases, whereas only the anterior lobe is affected in 15.4%, and both of them in 33.8%.<sup>7</sup> The diminished flow of the portal system serves as a protection against dissemination to the adenohypophysis, while increased supply of the neurohypophysis favors its susceptibility when compared with the former. The posterior lobe is also smaller than the anterior, being more vulnerable to dysfunction than the anterior. Therefore, symptoms would be easier to identify through compression, leading to more cases diagnosed and accounted for. Another factor is that the posterior lobe has a larger surface area in contact with the adjacent dura, so cerebrospinal fluid dissemination is more prone to occur. Anterior lobe involvement is usually the result of a larger lesion of the posterior lobe or metastatic deposits through contiguous spread. The anterior lobe also seems to be susceptible to ischemic infarcts.<sup>4,8</sup>

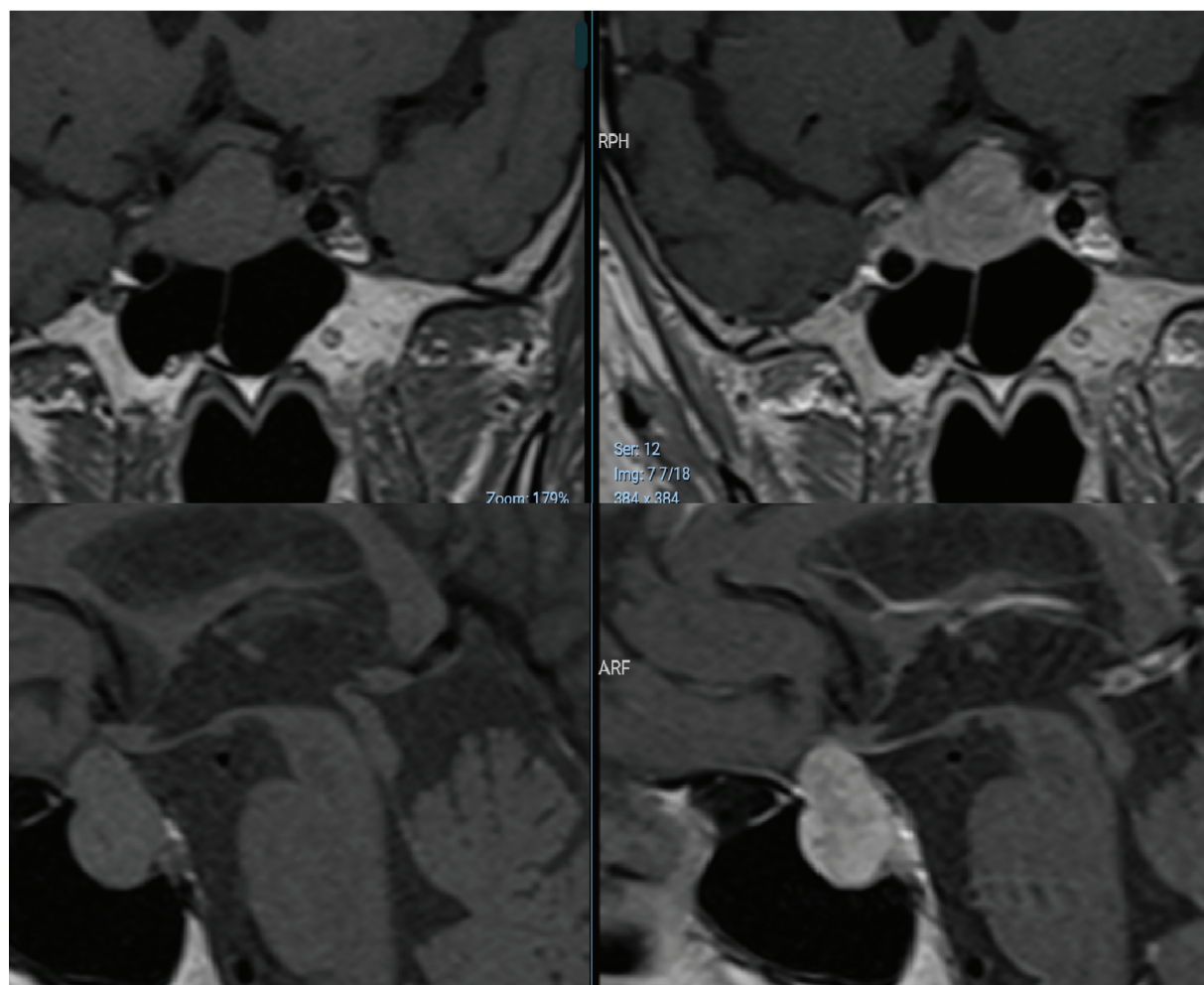
Symptoms vary from vague complaints such as fatigue or headache to more specific signs like polyuria and polydipsia,

and ~ 60% of cases have clinical manifestations. Primary symptoms in descending order of importance with their respective frequencies are visual impairment (48.8%), DI (38.4%), panhypopituitarism (37.7%), and headache (35.3%). Extension of an infiltrating tumor to supraoptic and paraventricular nuclei in the hypothalamus can cause DI, as it is where the synthesis of neurohypophysis hormones takes place. It is also caused by compromised tracks convergence originating from hypothalamic nuclei, at the base of the hypothalamus at the origin of the pituitary stalk.<sup>2</sup>

The patient also presented high prolactin levels. It is known that nonadenomatous pituitary or parasellar masses can cause hyperprolactinemia through inhibition of the release of hypothalamic dopamine, by compression of the infundibular stalk.<sup>9</sup> This can lead to misdiagnosis of the sellar mass, as prolactinoma would be considered a feasible diagnosis without proper care in propaedeutics. In this case, it was actually considered a differential diagnosis in a former investigation.

Surgery is a treatment option for confirming diagnosis and decreasing symptoms, but complete resection is difficult

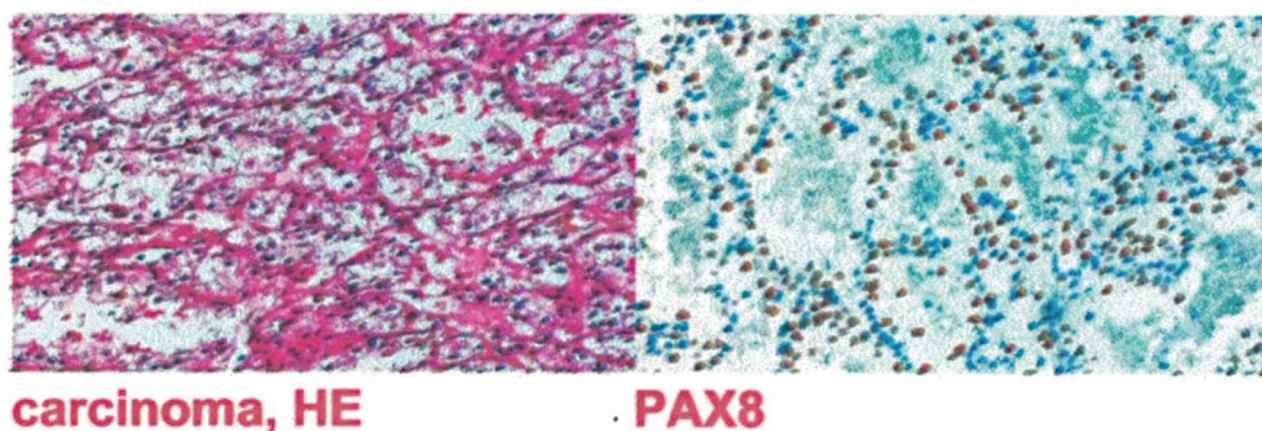




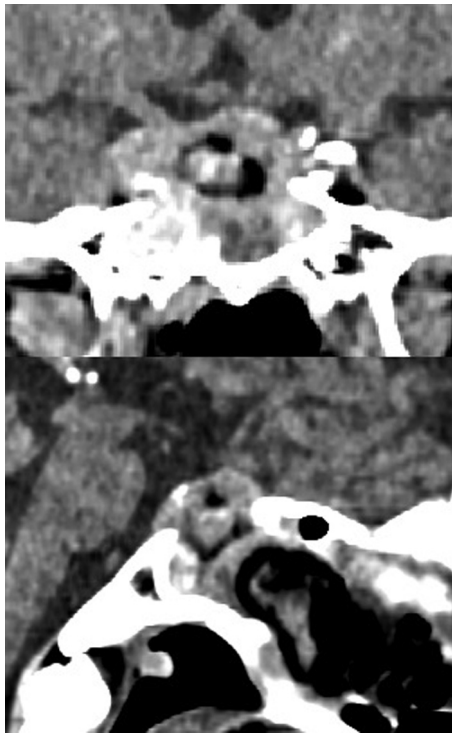
**Fig. 2** MRI 2 months after initial imaging revealing growth of the tumor. Sagittal sections disposed inferiorly and coronal superiorly, in noncontrast T1 weighted images on the left and postcontrast on the right. It is noted higher contrast enhancement and growth of the lesion toward the suprasellar compartment with optic chiasm compression. Also, there is expansion bilaterally with greater involvement of the right cavernous sinus and extension to the left internal carotid artery. The mass grew from 2.0 cm<sup>3</sup> to 3.1 cm<sup>3</sup>.

and may be risky when there is hypervascularization, invasion of nearby organs or even of the cavernous sinus,<sup>2</sup> which was the situation of this patient.

Even with current treatment, pituitary metastasis has poor prognosis, as metastases in other sites are commonly present at the moment of diagnosis. The estimated lifespan of



**Fig. 3** Histological samples of anatomopathological and immunohistochemistry study of the lesion, where it is observed the presence of clear cells with scarce cytoplasm, typical of the clear cell renal carcinoma. There was expression of CD10 (not shown in the picture) and PAX8 factors, which corroborated the diagnosis.



**Fig. 4** Immediate postoperative CT scan with hemostatic material inside the sella and significant tumor reduction.

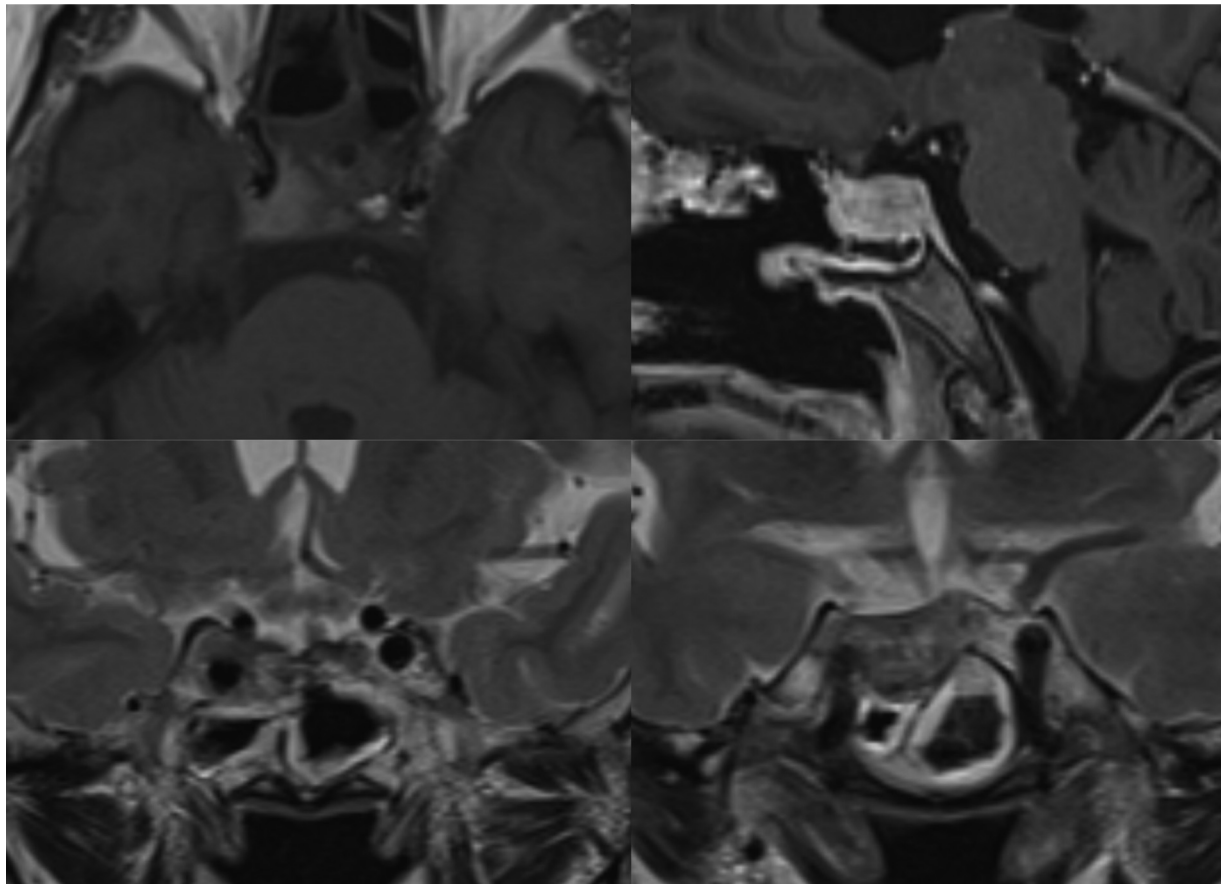
the patients lies between 6 and 22 months, and no treatment has yet shown effectiveness in improving it. Factors that may lead to longer survival rates include younger age at presentation, smaller lesions, and less time between primary disease diagnosis and pituitary metastasis presentation<sup>4</sup>.

### Conclusion

Pituitary metastases are known as rare conditions, but of increasing awareness in spite of its rise in incidence favored by the improvement in diagnostic techniques. Metastases from clear cell renal carcinoma are even more rare, with only 25 described cases until 2018 from a large meta-analysis<sup>2</sup>. We present a case report of a 65-year-old woman with visual impairment and a sellar mass from which biopsy was consistent with clear cell renal carcinoma. Acknowledging these cases is significant due to their rarity worldwide, their increasing incidence with the development of diagnostic tools and the pathogenesis of the disease, which is yet to be elucidated.

### Conflict of Interests

The authors have no conflict of interests to declare.



**Fig. 5** MRI of the patient 4 months following radiotherapy. It is possible to note significant reduction of the volume of the metastasis, and therefore its responsiveness to the therapy. There is a smaller residual lesion hyperintense on T1 imaging in the upper left image that shows contrast enhancement in T1 postcontrast in the upper right picture, predominantly on the right side in close relation with the carotid artery in T2 images, in the lower half of the figure.

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