Received: 1 December 2023 | Revised: 15 December 2023 | Accepted: 19 January 2024

DOI: 10.1002/ccr3.8595

CASE REPORT

Clinical Case Reports Open Access WILEY

Metastatic pituitary neuroendocrine neoplasms: A case report of a malignant prolactinoma

Inês Manique[1] | **Sara Amaral**[1] | **Teresa Rego**[2] | **Andreia Coelho**[3] | **Andreia Ponte**[4] | **Margarida Brito**[5] | **Ana Palha**[1] | **Luísa Cortez**[1] | **Dalila Forte**[6] | **Amets Sagarribay**[6] | **Luís Cerqueira**[7] | **Carlos Pontinha**[8] | **Manuela Mafra**[8] | **José Silva-Nunes**[1]

[1]Endocrinology, Diabetes and Metabolism Department, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

[2]Endocrinology and Nutrition Department, Hospital de Santo Espírito da Ilha Terceira, Azores, Portugal

[3]Oncology Department, Hospital de Santo Espírito da Ilha Terceira, Azores, Portugal

[4]Radiation Oncology Department, Hospital de Santo Espírito da Ilha Terceira, Azores, Portugal

[5]Oncology Department, Instituto Português de Oncologia, Lisboa, Portugal

[6]Neurosurgery Department, Hospital de São José, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

[7]Neuroradiology, Hospital de São José, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

[8]Anatomical Pathology, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal

Correspondence
Inês Manique, Endocrinology, Diabetes and Metabolism Department, Hospital Curry Cabral, Centro Hospitalar Universitário Lisboa Central, Lisbon, Portugal.
Email: inesjmf@gmail.com

Funding information
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Key Clinical Message

We report a rare clinical case of a malignant prolactinoma in which the exponential increase of prolactin levels with minimal tumor growth and no response to treatment led to diagnosis of abdominal, thoracic, and vertebral metastases.

KEYWORDS

metastatic pituitary neuroendocrine tumor, prolactinoma, radiotherapy, surgery, temozolomide

1 | INTRODUCTION

Majority of pituitary neoplasms are benign adenomas. However, 30%–45% of pituitary adenomas can be invasive, and 15% may have an aggressive behavior.[1,2] This aggressiveness is defined imagiologically by an invasive tumor with clinically relevant growth despite the use of optimal standard therapies (combination of medical therapies, surgery, and/or radiotherapy).[1]

In 0.1%–0.2% of cases, these aggressive pituitary tumors may metastasize. The most common metastatic sites are brain, spinal cord, and meninges.[3] There is not a reliable way to predict which pituitary adenomas may evolve to malignancy. However, a high mitotic index, Ki67 and p53 immunoreactivity, may suggest a higher metastatic potential.[1,4] According to the published 2022 World Health Organization Classification of Pituitary Tumours, the terminology "metastatic pituitary

neuroendocrine tumours" (metastatic PitNET) is advocated to replace the previous one "pituitary carcinoma." This move was decided to distinguish this tumor from neuroendocrine carcinoma (a poorly differentiated epithelial neuroendocrine neoplasm).[5] More than 70% of metastatic PitNET present with functionality, with corticotroph and lactotroph tumors being the most common.[4]

The exact prevalence of malignant prolactinomas is not described. Malignant prolactinomas may be histologically indistinguishable from aggressive prolactinomas. Therefore, the diagnosis cannot be made until a metastasis appears.[1,4,6] The management of a malignant prolactinoma is challenging, given the unpredictable clinical course, and the frequent unsustainable response to the treatment (including dopamin agonists, surgery, radiotherapy, and chemotherapy). Due to its complexity, the approach of these tumors should be discussed in multidisciplinary tumor board.[1]

We present a case of a male patient with a malignant prolactinoma with vertebral, lung, and abdominal metastases identified 4 years after initial diagnosis of a macroprolactinoma with an aggressive behavior.

2 | CASE HISTORY

A 53-year-old man with a history of dyslipidemia and nodular thyroid disease was diagnosed in January 2019 with a macroprolactinoma. The diagnosis was made in the context of a clinical condition characterized by erectile sexual dysfunction, tiredness, holocranial headaches, and diplopia. Magnetic resonance imaging (MRI) revealed a pituitary macroadenoma with 27 mm in the anteroposterior (AP), 29 mm in the transversal (T), and 25 mm in the vertical (V) diameters, with supra and infrasellar growth, as well as right cavernous sinus invasion, without optic chiasm compression or deviation (Figure 1). The blood analysis revealed a hyperprolactinemia of 470 ng/mL (reference 4.04–15.2 ng/mL) with an associated hipogonadotrophic hypogonadism. Remaining pituitary function was unremarkable.

3 | DIFFERENTIAL DIAGNOSIS AND TREATMENT

The diagnosis of a macroprolactinoma was made, and cabergoline was initiated on a dosage of 0.5 mg twice

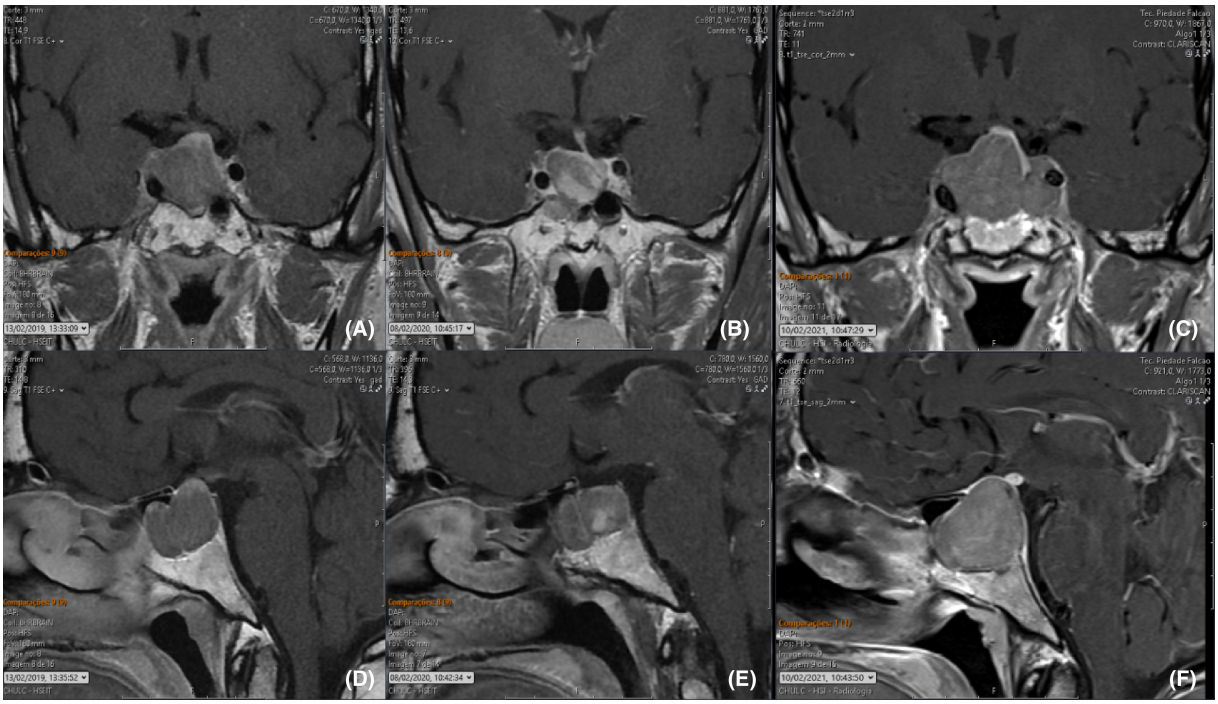
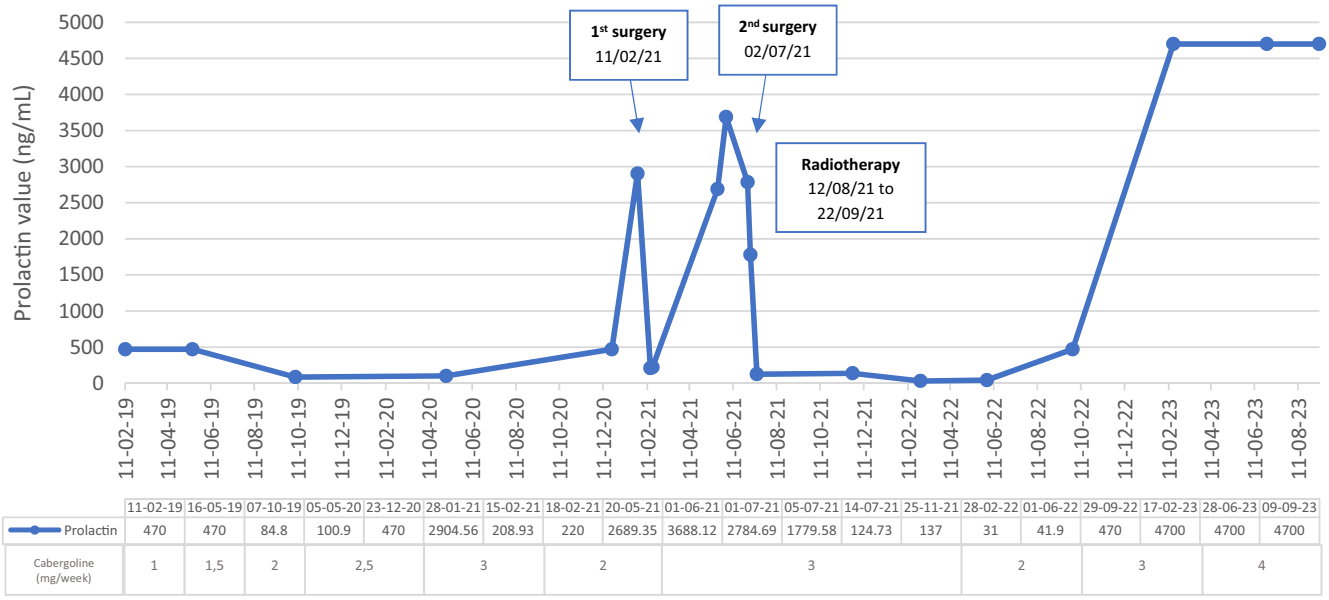


FIGURE 1 Presurgical evolution after diagnosis. MR T1 TSE coronal (A, C, E) and sagital (B, D, F) sections after gadolinium administration. In the 1st MR (a and b), a sellar and suprasellar pituitary lesion with suprasellar growth displacing the optic chiasm upwards, invading the right cavernous sinus (Knosp 3A). One year after initiation of medical treatment, a follow-up study (c and d) shows a clear reduction of the tumoral size and resolution of the chiasmatic compression. Follow-up MRI 1 year latter (e and f) shows lesion regrowth, now larger than before starting the treatment, invading both cavernous sinus and compressing the optic chiasm.



	11-02-19	16-05-19	07-10-19	05-05-20	23-12-20	28-01-21	15-02-21	18-02-21	20-05-21	01-06-21	01-07-21	05-07-21	14-07-21	25-11-21	28-02-22	01-06-22	29-09-22	17-02-23	28-06-23	09-09-23
Prolactin	470	470	84.8	100.9	470	2904.56	208.93	220	2689.35	3688.12	2784.69	1779.58	124.73	137	31	41.9	470	4700	4700	4700
Cabergoline (mg/week)	1	1,5	2	2,5		3		2		3					2		3		4	

FIGURE 2 Prolactin evolution and cabergoline doses.

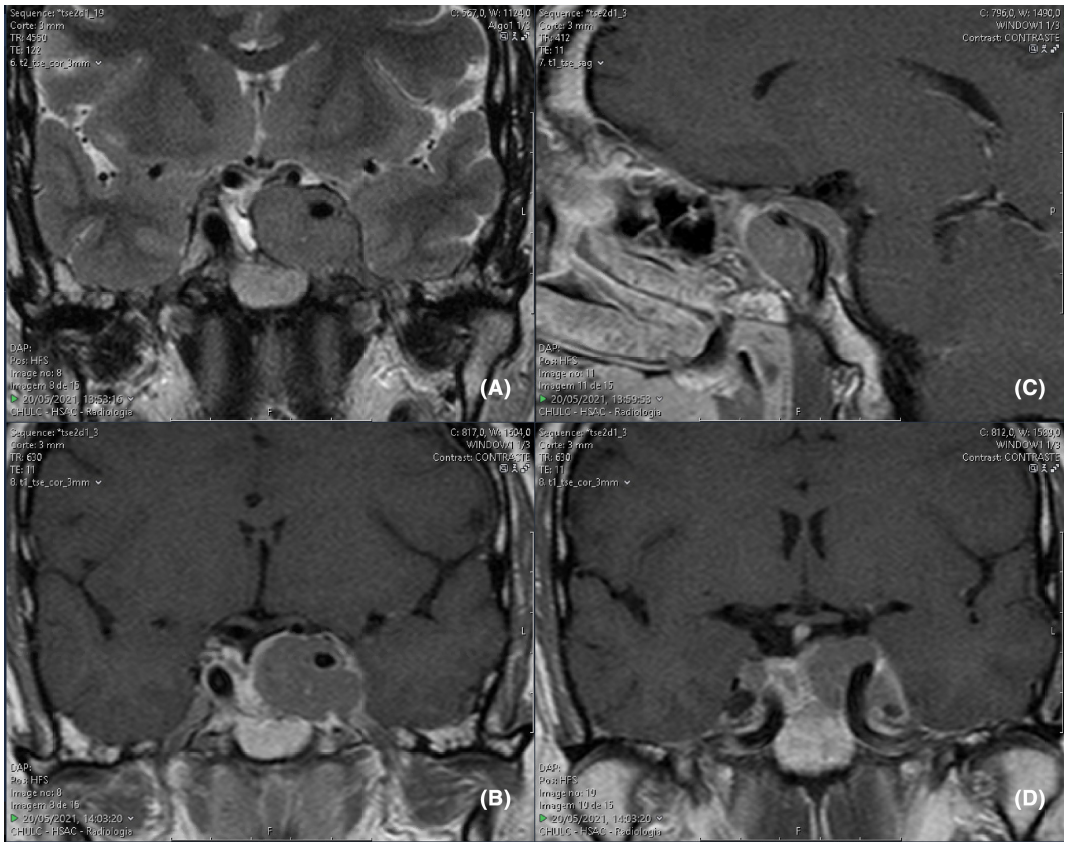


FIGURE 3 Postsurgical evolution (first surgery). MR coronal T2 TSE (A) and T1 TSE after gadolinium (B and D) and sagital T1 TSE after gadolinium (C) sections. Large lesion remnant filling and expanding the left cavernous sinus and encarcerating the internal carotid (Knosp 4). The supra-sellar extension contact (without displacing) the optic chiasm on the left side.

a week. Figure 2 reports prolactin levels evolution. The minimum prolactin level was 84.8 ng/mL (reference 4.04–15.2 ng/mL) under carbergoline 2.5 mg per week achieved 8 months after starting therapy and MRI showed a tumoral size reduction (20 mm [AP] × 25 mm [T] × 20 mm [V]).

In the next 2 years, the prolactin values rapidly increased achieving 2904.56 ng/mL (reference 3.46–19.4 ng/mL),

despite the maximum dose of cabergoline (3 mg per week). Compressive symptoms got worse during this time with severe holocranial headaches and reappearence of diplopia with ptosis (left sixth cranial nerve palsy and incomplete third cranial nerve palsy). In February 2021, MRI revealed a predominantly solid sellar lesion with 29 mm (AP) × 32 mm(T) × 30 mm (V) molding the optic chiasm, with sphenoidal sinus and bilateral cavernous sinus invasion (Knosp 4; Figure 1). Panhypopituitarism was diagnosed during this period, and patient started therapy with hidrocortisone (30 mg/day) and levothyroxine (50 µg/day).

Due to tumor growth and new symptoms of tumor mass effect, after multidisciplinary discussion (Endocrinology, Neuroradiology, Neuro-opthalmology, and Neurosurgery), the patient underwent transsphenoidal surgery, in February 2021, without complications. Histological examination revealed a solid PitNET immunoreactive for for prolactin, a Ki67/mib1 of 20%–30%, 2 mitosis/10 High-Power Fields (HPF), without cytologic atypia.

After surgery, the patient reported clinical improvement and the minimum prolactin level at that time was 203,93 mg/mL. However, levels progressively raised during the next 4 months to a maximum of 3688,12 ng/mL under cabergoline 3 mg per week.

Given the agressiveness of this prolactinoma, a thoraco-abdominal-pelvic CT and an 18-FDG PET/CT were performed; nevertheless, no abnormalities were found.

In July 2021, trigeminal nevralgia and left eye ophtalmoplegia with complete ptosis stood out. At that time, MRI revealed a residual pituitary tumor with 26 mm (AP) × 26 mm(T) × 22 mm (V) with increasing of the left cavernous sinus invasion (Figure 3). The patient underwent surgical reintervention in July 2021. The histology revealed a prolactinoma with a Ki67/mib1 of 25% and 5/10 mitosis/HPF. The patient reported clinical improvement after this surgery. The prolactin levels after the second surgery were 124.73 ng/mL (reference 3.46–19.4 ng/mL), and the multidisciplinary team decided to perform radiotherapy. The patient underwent fracctionated radiation therapy (total dose of 54 Gy in 30 fractions) between August and September 2021.

Six months after he finished radiotherapy treatment, prolactin level was 31 ng/mL under cabergoline 2 mg/week and MRI revealed a little residual tumor in the left cavernous sinus (Figure 4). In September 2022, prolactin levels started to increase (maximum >4700 ng/dL), and cabergoline was adjusted until 4 mg per week. At this time, an echocardiogram was performed revealing preserved

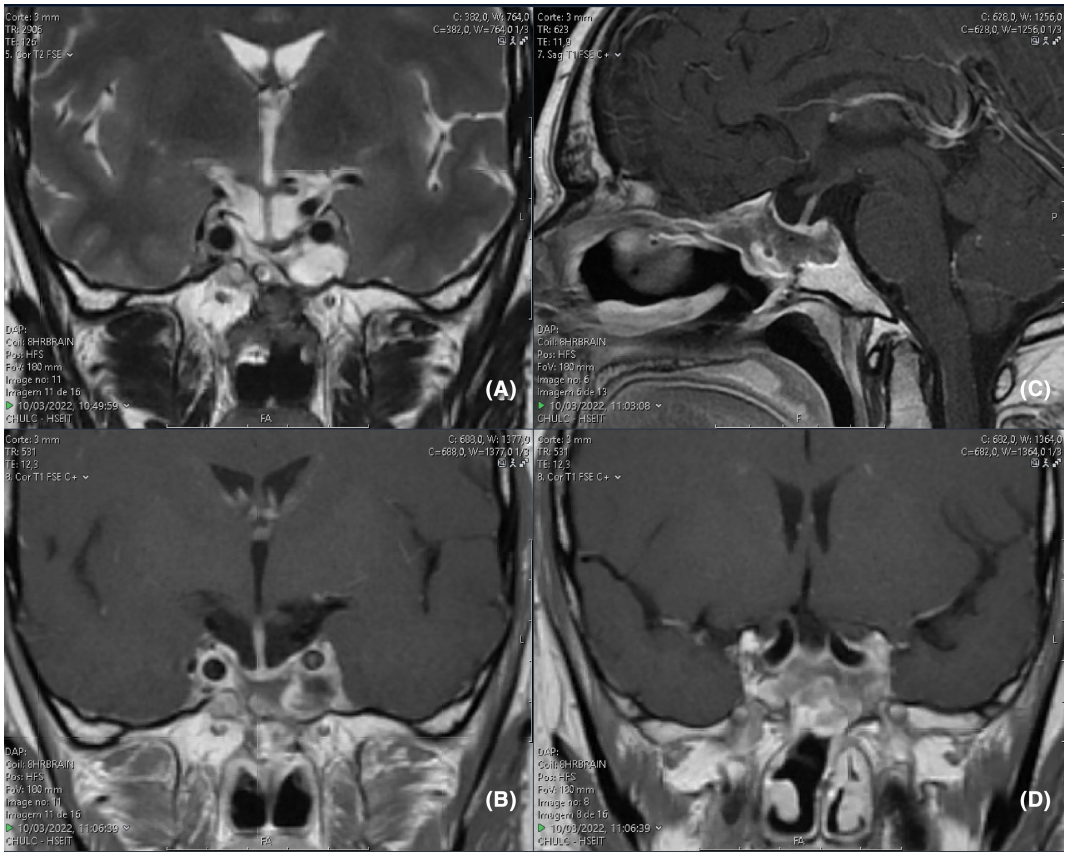


FIGURE 4 Postsurgical (second surgery) and radiosurgical MR coronal T2 TSE (A) and T1 TSE after gadolinium (B and D) and sagital T1 TSE after gadolinium (C) sections. Extensive tumoral ressection and necrosis with visible small remnant at the left cavernous sinus. Slight chiasmatic ptosis without signal or caliber anomalies.

global systolic function (ejection fraction 66%) with a slight mitral and tricuspid regurgitation. MRI showed a slightly discrete dimensional increase of the partially cystic component in the region of the sella turcica with extension to the lower part of the inferior cavernous sinus with 15.5 mm in its transverse axis.

Due to the exponential increase in prolactin levels with minimal tumor growth and no response to cabergoline, a CT was performed revealing two suspicious juxtapleural lung lesions; an heterogeneous and lobulated abdominal mass (78 × 57.5 mm) between left flank and left iliac fossa, in relation with left rectus muscle and ileal loops; and osteolytic lesions of the D7 vertebral body, 8th rib and S1 right and S2 left sided encarcerating the first sacral roots bilaterally and the 2nd sacral root on the left side. A spine MRI was performed showing osteocondensant suspicious lesions in C4, D8, D4, D5 vertebrae and an osteocondensant lesion involving both sacral wings, with a soft-tissue component that had an endocanal expression with compression of the roots of the cauda equina (Figure 5).

Biopsy of the referred intra-abdominal mass revealed a metastatic PitNET of lactotrophic type (immunoreactive for CK CAM 5.2, Synaptophysin, CD56, Pit1, Prolactin, estrogen receptor) with a Ki67 between 40% and 50% (Figure 6).

4 | OUTCOME AND FOLLOW-UP

The patient was referred to the Oncology Department. The pain control was only achieved after optimizing analgesia with transdermic fentanyl (maximum dose needed 150 μg/h), transdermic buprenorphine (140 μg/h), oral tapentadol 100 mg (2 pills/day) and pregabalin (100 mg every 8 h) and palliative sacral region volumetric arc radiotherapy (30 Gy in 10 fractions). Chemotherapy was initiated with temozolamide (150 mg twice a day, from D10 until D14) and capecitabine (1000 mg, twice a day, from D1 until D14) every 28 days.

5 | DISCUSSION

Prolactinomas are the most common functional pituitary tumors (47%–66%).[2] Usually, they respond to the first-line treatment with dopamine agonists, due to its abundant expression of dopamine type 2 receptor (D2).[1,2] Resistance

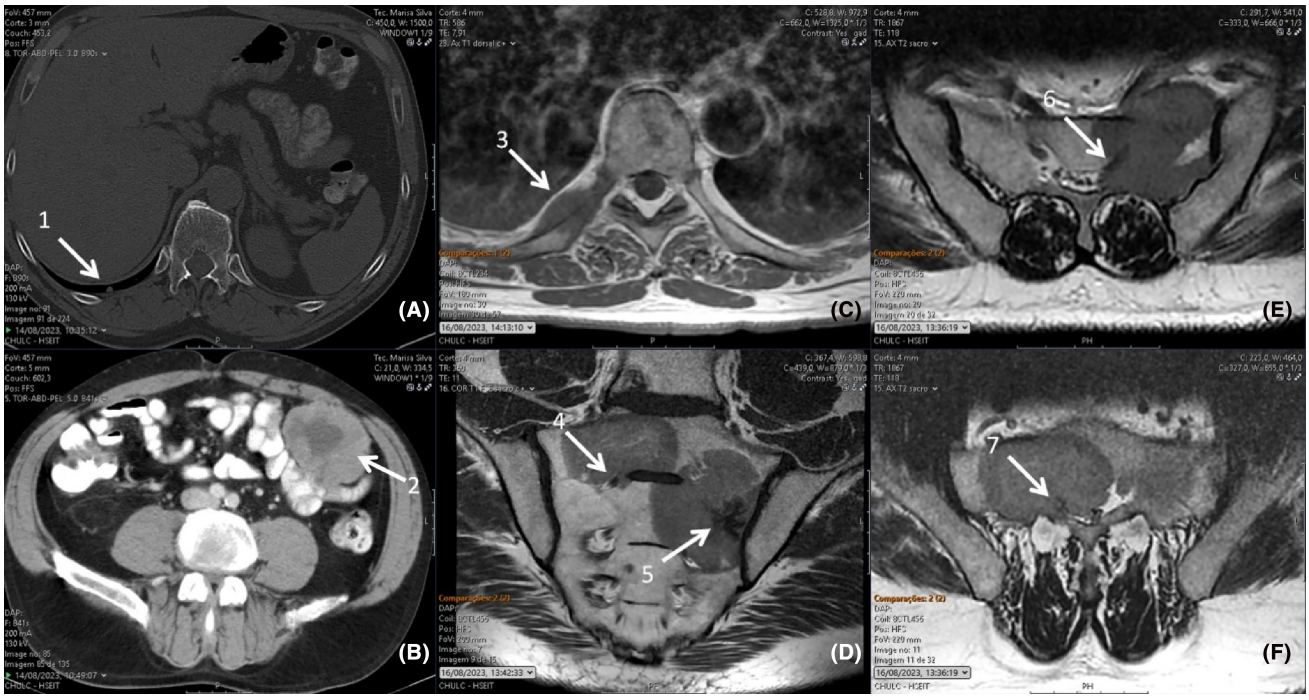


FIGURE 5 Abdomino-pelvic CT scan (A and B), dorsal (C) and lumbo-sacral MRI (D, E, F). MRI: dorsal axial T1 TSE (C), sacral coronal T1 TSE FS (D) and axial T2 TSE (E and F) weighted images. The CT scan shows a small juxta-pleural lesion on the right side and a large anterior abdominal mass on the left side. The MRI scan shows osteolytic lesions of the 8th rib on the right side and S1 right and S2 left sided lesions encarcerating the 1st sacral roots bilaterally and the 2nd sacral root on the left side. Notice the epidural extension at the S1 level with root encarceration (S1) and displacement (S2). Smaller D7 body posterior lateral justa-pedicular lesion not shown. 1—juxta-pleural lung lesion; 2—abdominal mass; 3—Osteolytic lesion of the 8th right rib; 4—incarcerated right S1 right root; 5 and 6—incarcerated left S2 root; 7—right sided epidural invasion of the S1 bone lesion incarcerating the S1 right root.

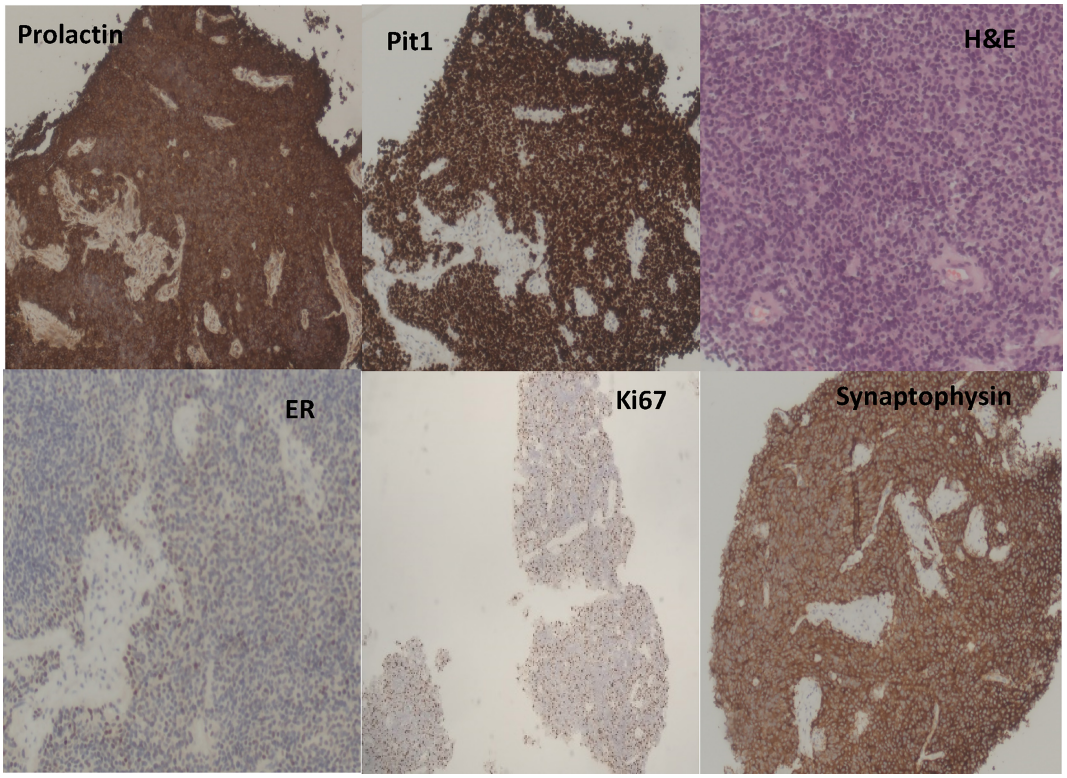


FIGURE 6 Histopathology revealing a metastatic pituitary neuroendocrine tumor of lactotrophic type immunoreactive for Synaptophysin, Pit 1, Prolactin and Estrogen Receptor (ER). The neoplasm has a high Ki67 value between 40%–50%.

to cabergoline and bromocriptine is described in 10% and 25% of the prolactinomas, respectively.[1] There is no consensus on the definition of dopamin agonists resistance.[1,7] European Society of Endocrinology (ESE) Guidelines for the management of aggressive pituitary tumors and carcinomas define dopamin agonists resistant prolactinomas as a failure to normalize prolactin levels and less than a 50% reduction in tumor size, under doses of cabergoline up to 3.5 mg/week.

Aggressive prolactinomas are usually invasive macroadenomas, resistant to dopamin agonists, and occur in men. Our patient presented with all of these features. Potential predictors of aggressiveness are Ki67 index ≥3%, p53 immunodetection and mitotic count >2. Some authors suggest that Ki67 >10% is a sign of malignancy; however, there is no clear consensus and validation. No marker alone is sufficient to predict the prognosis.[1] The relevance and the clinical impact of studies on predictive biomarkers are not discussed in the most recent World Health Organization classification of PitNET.[5] In the presented patient, despite increasing doses of cabergoline, prolactin levels did not normalize; additionally, there was a marked increase of tumor dimension and invasiveness. This pattern of aggressive behavior persists even after the surgeries. Ki67 and mitotic index revealed greater tumor aggressiveness and metastatic potential.

It is difficult to predict metastatic potential of aggressive pituitary prolactinomas. The latency time until the detection of metastasis is in average 4.7 years (2 months to 22 years).[1] This latency period was similar to what we observed in the presented clinical report.

Pathogenesis of metastatic PitNET is not fully understood; yet the mechanism of invasion is similar to other malignancies.[6,8]

Regardless of the rarity, in the setting of site-specific symptoms, and/or when prolactin value are discordant with the known pituitary disease (namely when there is not a corresponding increase in tumor size), appropriate imaging studies should be considered to investigate possible metastases.[1] This was the case for our patient, with metastases found when prolactin levels had an exponential increase despite a minimal tumor growth.

After the medical therapy failure in dopamine agonists resistant prolactinomas, surgery may have a role to manage local mass effects or offer control of hormone hypersecretion.[1] Enclosed macroprolactinomas resistant to dopamin agonists show cure or control rate higher than invasive prolactinomas (60% vs. <10%, respectively).[9,10]

Radiotherapy may be an effective therapeutic option in prolactinomas after medical and surgical treatment failure.[8,11] Adjuvant radiotherapy should be considered for

patients with a clinically relevant invasive tumor remnant with pathological agressive markers. The decision between fractionated external beam radiation therapy or stereotactic radiosurgery must take into consideration tumor characteristics (size, location, prior radiotherapy treatment, and pathology). For stereotactic radiosurgery, tumor target should be at least 3–5 mm distant from the optic chiasm and less than 3 cm in diameter. Fractionated external beam radiation therapy has a low risk of optic neuropathy (1% at 10 years) and is the preferential modality in tumors with diffuse local invasion and suprasselar or brainstem extension.[1] Radiotherapy in the treatment of aggressive prolactinomas is associated with a cumulative percentage for tumor control range from 68% to 100%, and hormonal control rates over 50%. A recent review suggested the use of radiotherapy in growing, clinically aggressive, or dopamin agonists resistant prolactinomas.[11]

Temozolamide monotherapy is the first-line therapy for metastatic PitNET and aggressive tumors refractory to other treatment modalities.[1] Temozolamide is an oral alkylating agent that promotes DNA damage by base mismatch repair and cause cell death.[8,12] European Society of Endocrinology recommends standard doses of 150 mg/m^2 in the first cycle and 200 mg/m^2 in the subsequent cycles. A biochemical and/or radiological effect usually is observed within 3–6 months. If response is verified after 3 cycles, treatment can be continued for at least 6 months.[1]

An ESE survey involving aggressive pituitary tumors or carcinomas (40 prolactinomas, 15 of them malignant) treated with temozolamide for 10 years revealed an efficacy of 37%. Clinically functional pituitary tumors respond better.[1,12] In a meta-analysis with aggressive pituitary tumors and carcinomas, a median progression-free survival duration of 20 months was verified, with a 41% radiologic response (at least 30% reduction in tumor dimension) and a 53% biochemical response (>50% decrease of secreting hormone). The imagiological response improved up to 60% of cases with chemoradiotherapy comparing to chemotherapy alone.[13] European Society of Endocrinology guidelines suggests that in patients with rapid tumor growth in whom maximal doses of radiotherapy have not been reached, combining temozolamide with radiotherapy should be considered.[1]

There is a substantial number of cases of metastatic PitNET that do not respond to temozolamide or recurs.[4] High expression of O^6-methylguanine-DNA methyltransferase (MGMT) and others DNA repair enzymes such as MSH6, that counteract the alkylating effects of temozolamide have been associated with chemoresistance in pituitary aggressive tumors or carcinomas. ESE guidelines recommends determining immunohistochemically MGMT status to guide therapy (however, it is a low-evidence recommendation).[1,4,14] Tumor proliferative markers such as Ki67, mitotic rate and p53 expression have not been shown to be useful predictors for the response to temozolamide.[1]

Possible combinations with other drugs for the treatment of malignant prolactinomas are being studied. Partial responses have been found in some patients with temozolamide associated with capecitabine (CAPTEM), especially when capecitabine is given previously to temozolamide in aggressive pituitary tumors/carcinomas.[1] Capecitabine is a prodrug of 5-FU that have a synergistic effect with temozolamide in the treatment of NET.[4] In an ESE survey, the use of CAPTEM led to a partial response in one patient and stabilization of the disease in another one.[1] In an ex vivo culture from two patients with refractory prolactinomas, CAPTEM significantly reduced tumor size in one of the patients.[15] CAPTEM may also improve progression-free survival in patients with high-risk corticotroph tumors/carcinomas. Nakano-Tateno T. et al reported a patient with a metastatic PitNET of corticotroph type that 12 cycles of CAPTEM resulted in tumor control associated with clinical and radiological improvement; however, 27 months later CAPTEM was restarted for disease recurrence.[16] Despite the little evidence in metastatic PitNET, more evidence exists for the benefits of CAPTEM in NET of other origins, namely at the digestive system and lungs.[17]

Although scarce evidence exists supporting this regimen, our patient underwent a combination of temozolamide and capecitabine given the aggressiveness of the metastatic tumor.

Prolactinomas express somatostatin receptors (SSTRs), predominantly SST5 and with a lesser extent SST1 and SST2.[18] As in most NETs, somatostatin receptor scintigraphy (SRS) and ^{68}Ga-DOTA peptide PET imaging may have potential therapeutic implication on molecular-targeted therapy using somatostatin analogues and peptide receptor radionuclide therapy (PRRT) targeting the SSTRs. ^{68}Ga-DOTA peptide PET imaging has been applicated in the diagnosis and monitoring of pituitary carcinoma, with advantage in the detection of brain metastases compared with ^{18}F-FDG PET/CT and enhanced MRI. It has been used also for monitoring of ^{177}Lu-DOTATATE therapy in metastatic PitNET.[19] Octreotide long-acting release (LAR) or pasireotide may be an option in dopamine-resistant or aggressive prolactinomas, namely in association of temozolamide. However, their contribution could not be determined, given the small numbers of cases examined.[20,21] There are already five case reports of metastatic PitNET treated with PRRT; but none of them corresponding to a prolactinoma.[1,22]

If failure of temozolamide, other cytotoxic therapies can be tried; however, ESE does not suggest any regimen

in particular.[1] There are case reports of aggressive pituitary tumors/carcinomas, sometimes with partial regression, when treated with chemotherapy regimens including lomustine combinated with 5-FU, lomustine and doxorubicin, lomustine with procarbazine and etoposide, cisplatin and etoposide, cyclophosphamide with adryamicin, and 5-FU.[1]

Promising results are being observed in patients treated with tyrosine kinase inhibitors or antibody targeting the VEGFR pathway (lapatinib, sunitinib, erlotinib, and bevacizumab).[1] There is a case of a lactotroph carcinoma treated with ipilimumab (anti-CTLA-4) and nivolumab (anti PD1) with complete, sustained remission 24 months after the initiation of therapy. However, evidence suggests that corticotroph tumors may be more responsive to immunotherapy than prolactinomas.[4]

Loco-regional therapies are suggested in patients with isolated metastasis, independent of systemic treatment prescribed.[1] In our patient, besides the presence of multiple possible metastases (only one confirmed histologically) we considered palliative treatment to sacral lesion, given the intense functional limitation and associated pain.

In conclusion, aggressive PitNET may evolve to malignancy (metastasize) years after the diagnosis, and long-term follow-up is needed. In the presented patient, the discrepancy between the prolactin levels and the pituitary tumor size variation raised suspicion for the presence of metastases. We also highlight the dissociation between the aggressiveness of the metastatic disease (multiple metastases) and the stability of pituitary tumor. Currently, there are promising results with some treatment modalities. However, there is a lack of randomized studies for the management of metastatic PitNET; therefore, they are treated similarly to aggressive PitNET.

AUTHOR CONTRIBUTIONS

Inês Manique: Conceptualization; methodology; writing – original draft; writing – review and editing. **Sara Amaral:** Conceptualization; resources; supervision; validation; writing – review and editing. **Teresa Rego:** Conceptualization; resources; supervision; validation; writing – review and editing. **Andreia Coelho:** Resources; validation; visualization; writing – review and editing. **Andreia Sofia de Lima Ponte:** Validation; visualization; writing – review and editing. **Margarida Brito:** Validation; visualization; writing – review and editing. **Ana Palha:** Validation; visualization; writing – review and editing. **Luísa Cortez:** Validation; visualization; writing – review and editing. **Dalila Forte:** Validation; visualization; writing – review and editing. **Amets Sagarribay:** Validation; visualization; writing – review and editing. **Luís Cerqueira:** Resources; validation; visualization; writing – review and editing. **Carlos Pontinha:** Resources; validation; visualization; writing – review and editing. **Manuela Mafra:** Resources; validation; visualization; writing – review and editing. **José Silva-Nunes:** Validation; visualization; writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Inês Manique https://orcid.org/0000-0002-3728-9229
Sara Amaral https://orcid.org/0000-0002-2911-9270
Margarida Brito https://orcid.org/0000-0002-6104-5902
Ana Palha https://orcid.org/0000-0002-7689-1378
Luísa Cortez https://orcid.org/0000-0002-9821-5389
Dalila Forte https://orcid.org/0009-0008-8065-6590
Amets Sagarribay https://orcid.org/0000-0003-2280-8417
Carlos Pontinha https://orcid.org/0000-0002-1265-949X
Manuela Mafra https://orcid.org/0000-0002-0623-4102
José Silva-Nunes https://orcid.org/0000-0002-4728-1220

REFERENCES

1. Raverot G, Burman P, McCormack A, et al. European Society of Endocrinology Clinical Practice Guidelines for the management of aggressive pituitary tumours and carcinomas. *Eur J Endocrinol*. 2018;178(1):G1-G24.
2. Olarescu NC, Perez-Rivas LG, Gatto F, et al. Aggressive and malignant Prolactinomas. *Neuroendocrinology*. 2019;109(1):57-69.
3. Sansur CA, Oldfield EH. Pituitary Carcinoma. *Semin Oncol*. 2010;37(6):591-593.
4. Robertson IJ, Gregory TA, Waguespack SG, Penas-Prado M, Majd NK. Recent therapeutic advances in pituitary carcinoma. *J Immunother Precis Oncol*. 2023;6(2):74-83.
5. Asa SL, Mete O, Perry A, Osamura RY. Overview of the 2022 WHO classification of pituitary tumors. *Endocr Pathol*. 2022;33(1):6-26.
6. Hong AR, Yoon JH, Kim HK, Kang HC. Malignant Prolactinoma with liver metastases masquerading as metastatic

gastrointestinal stromal tumor: a case report and literature review. *Front Endocrinol*. 2020;11:451.
7. Melmed S, Casanueva FF, Hoffman AR, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273-288.
8. Du Four S, Van Der Veken J, Duerinck J, et al. Pituitary carcinoma - case series and review of the literature. *Front Endocrinol*. 2022;13:968692.
9. Primeau V, Raftopoulos C, Maiter D. Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. *Eur J Endocrinol*. 2012;166(5):779-786.
10. Raverot G, Wierinckx A, Dantony E, et al. Prognostic factors in prolactin pituitary tumors: clinical, histological, and molecular Data from a series of 94 patients with a long postoperative follow-up. *J Clin Endocrinol Metab*. 2010;95(4):1708-1716.
11. Niculescu DA, Gheorghiu ML, Poiana C. Radiotherapy in aggressive or dopamine agonists resistant prolactinomas; is it still worthwhile? *Eur J Endocrinol*. 2023;188(4):R88-R97.
12. McCormack A, Dekkers OM, Petersenn S, et al. Treatment of aggressive pituitary tumours and carcinomas: results of a European Society of Endocrinology (ESE) survey 2016. *Eur J Endocrinol*. 2018;178(3):265-276.
13. Luo M, Tan Y, Chen W, et al. Clinical efficacy of Temozolomide and its predictors in aggressive pituitary tumors and pituitary carcinomas: a systematic review and meta-analysis. *Front Neurol*. 2021;12:700007.
14. Murakami M, Mizutani A, Asano S, et al. A mechanism of acquiring Temozolomide resistance during transformation of atypical Prolactinoma into prolactin-producing pituitary carcinoma: case report. *Neurosurgery*. 2011;68(6):E1761-E1767.
15. Ishida A, Shichi H, Fukuoka H, Inoshita N, Ogawa W, Yamada S. Efficacy of temozolomide combined with capecitabine (CAPTEM) on refractory prolactinomas as assessed using an ex vivo 3D spheroid assay. *Pituitary*. 2022;25(2):238-245.
16. Nakano-Tateno T, Satou M, Inoshita N, et al. Effects of CAPTEM (Capecitabine and Temozolomide) on a Corticotroph carcinoma and an aggressive Corticotroph tumor. *Endocr Pathol*. 2021;32(3):418-426.
17. Ünal Ç, Azizy A, Karabulut S, et al. Efficacy of Capecitabine and Temozolomide regimen in neuroendocrine tumors: data from the Turkish oncology group. *Oncologist*. 2023;28(10):875-884.
18. Thodou E. Mapping of somatostatin receptor types in GH or/and PRL producing pituitary adenomas. *J Clin Pathol*. 2006;59(3):274-279.
19. Iglesias P, Cardona J, Díez JJ. The pituitary in nuclear medicine imaging. *Eur J Intern Med*. 2019;68:6-12.
20. Sosa-Eroza E, Espinosa E, Ramírez-Rentería C, Mendoza V, Arreola R, Mercado M. Treatment of multiresistant prolactinomas with a combination of cabergoline and octreotide LAR. *Endocrine*. 2018;61(2):343-348.
21. Lasolle H, Vasiljevic A, Borson-Chazot F, Raverot G. Pasireotide: a potential therapeutic alternative for resistant prolactinoma. *Ann Endocrinol*. 2019;80(2):84-88.
22. Marques P. The effects of peptide receptor radionuclide therapy on the neoplastic and Normal pituitary. *Cancer*. 2023;15(10):2710.

How to cite this article: Manique I, Amaral S, Rego T, et al. Metastatic pituitary neuroendocrine neoplasms: A case report of a malignant prolactinoma. *Clin Case Rep*. 2024;12:e8595. doi:10.1002/ccr3.8595