Endocrinology, Diabetes & Metabolism CASE REPORTS

A M Lopes and others | Pituitary metastasis and lung adenocarcinoma

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Pituitary metastasis unveiling a lung adenocarcinoma

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Summary

Pituitary metastasis (PM) can be the initial presentation of an otherwise unknown malignancy. As PM has no clinical or radiological pathognomonic features, diagnosis is challenging. The authors describe the case of a symptomatic PM that revealed a primary lung adenocarcinoma. A 62-year-old woman with multiple sclerosis and no history of malignancy, incidentally presented with a diffusely enlarged and homogeneously enhancing pituitary gland associated with stalk enlargement. Clinical and biochemical evaluation revealed anterior hypopituitarism and diabetes insipidus. Hypophysitis was considered the most likely diagnosis. However, rapid visual deterioration and pituitary growth raised the suspicion of metastatic involvement. A search for systemic malignancy was performed, and CT revealed a lung mass, which proved to be a lung adenocarcinoma. Accordingly, the patient was started on immunotherapy. Resection of the pituitary lesion was performed, and histopathology analysis revealed metastatic lung adenocarcinoma. Following surgery, the patient underwent radiotherapy. More than 2 years after PM detection, the patient shows a clinically relevant response to antineoplastic therapy and no evidence of PM recurrence.

Learning points:

- Although rare, metastatic involvement of the pituitary gland has been reported with increasing frequency during the last decades.
- Pituitary metastasis can be the initial presentation of an otherwise unknown malignancy and should be considered in the differential diagnosis of pituitary lesions, irrespective of a history of malignancy.
- The sudden onset and rapid progression of visual or endocrine dysfunction from a pituitary lesion should strongly raise the suspicion of metastatic disease.
- MRI features of pituitary metastasis can overlap with those of other pituitary lesions, including hypophysitis; however, rapid pituitary growth is highly suggestive of metastatic disease.
- Survival after pituitary metastasis detection has improved over time, encouraging individualized interventions directed to metastasis to improve quality of life and increase survival.

Background

Metastatic involvement of the pituitary gland is rare and can be the first presentation of neoplastic disease. The authors report the case of a symptomatic PM that represented the first manifestation of a lung neoplasia, highlighting the importance of considering PM in the differential diagnosis of pituitary lesions, even in the absence of a prior

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history of malignancy. This case illustrates the diagnostic challenges of PM, as hypophysitis was the initial most likely diagnosis. Along with neoplasia targeted therapy, the patient underwent pituitary metastatic resection followed by radiotherapy, with a clinically relevant pulmonary response and no evidence of PM recurrence more than 2 years after diagnosis. Even though PM has been associated with reduced life expectancy, patients live longer now, and therefore multimodal therapeutic interventions directed for PM should be considered, as this case demonstrates.

Case presentation

A 62-year-old woman with multiple sclerosis (MS) and smoking habits was referred for a diffuse pituitary enlargement incidentally found on MRI. She was diagnosed with MS 20 years ago and was under treatment with fingolimod for 3 years. She had no history of malignancy. MRI performed during MS follow-up revealed a diffusely enlarged and homogeneously enhancing pituitary gland, associated with stalk enlargement (Fig. 1). When questioned, the patient reported a few weeks' history of fatigue, nausea, polydipsia, and nocturia, as well as headache and diminished visual acuity. There were no other complaints. On neurological examination, there was no evidence of cranial palsies or visual changes by confrontation test. Formal visual field testing was normal. Biochemical evaluation demonstrated central hypothyroidism, central hypocortisolism, hypogonadotrophic hypogonadism, an elevated prolactin, and a slightly elevated serum sodium (Table 1).

Investigation

Hypophysitis was considered the most likely diagnosis given the MRI findings and the fact that the patient had MS under immunosuppression therapy. Measurement of angiotensin-converting enzyme (ACE) and IgG4 in serum were performed and returned normal. Also, the patient underwent a lumbar puncture, with normal cell count and chemistry (glucose and protein) cerebrospinal fluid (CSF) examination. The patient was started on replacement therapy with prednisolone, and later with levothyroxine and desmopressin. Fingolimod was withdrawn, even though no known association with hypophysitis was found. High-dose glucocorticoid was administered for presumed hypophysitis. One month later, symptoms of fatigue and nausea had improved, but visual complaints and headaches had worsened. Imaging reassessment confirmed continued pituitary growth, extending to the suprasellar area along the pituitary stalk and abutting the optic chiasm. At this point, the hypothesis of metastatic involvement was considered. The patient underwent a whole-body CT scan that revealed a right lung mass and mediastinal adenopathy. Later, a PET scan confirmed hypermetabolic foci localized to the pulmonary mass and mediastinal adenopathy, but not to the pituitary. A transthoracic needle aspiration of the lung mass was performed, and histopathological analysis revealed a lung adenocarcinoma positive for thyroid transcription factor-1 (TTF-1) and for EGF receptor (EGFR).

Treatment

According to the characteristics of the lung adenocarcinoma, therapy with the tyrosine kinase inhibitor afatinib was initiated. Two months after the pituitary enlargement finding, sellar MRI was repeated and showed persistent pituitary symmetric growth and stalk thickening, with edema along the optic chiasm (Fig. 2). Given the ongoing visual loss and the uncertainty about the effect of immunotherapy on the presumed

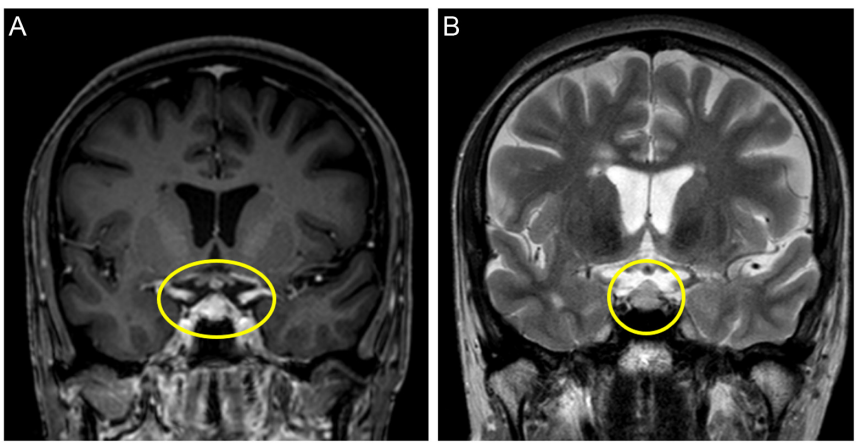

Figure 1
T1-weighted (A) and T2-weighted (B) images of the MRI performed during multiple sclerosis follow-up that revealed a diffusely enlarged and homogeneously enhancing pituitary gland associated with stalk enlargement.

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Table 1 Biochemical investigation at presentation.

Laboratory tests	Patient's values	Reference range
Serum sodium, mmol/L	147	135–145
Hormonal profile		
TSH, µIU/mL	0.35	0.30–3.94
FT4, pmol/L	8.75	12.2–20.2
Serum cortisol, nmol/L*	91.0	171.0–535.2
ACTH, pmol/L	1.43	1.98–11.45
FSH, mIU/mL	0.3	7.7–58.5
Prolactin, µg/L	114.4	4.79–23.3

*Morning sample.
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

pituitary metastasis (PM), surgery was decided for prompt symptomatic relief and histological diagnostic assessment. The patient underwent craniotomy considering the enlargement of the predominant suprasellar component toward the basal hypothalamus. At surgery, the lesion was found to be firm, vascular, and adherent to adjacent tissues. The histopathological report confirmed a metastatic adenocarcinoma with primary lung origin, positive for TTF-1, napsin, and cytokeratin 7. The postoperative course was uneventful. Visual symptoms improved significantly, but hypopituitarism persisted. Following surgery, the patient underwent intensity-modulated radiotherapy, completing 54 Gy for 6 weeks without complications.

Outcome and follow-up

Nearly 27 months after afatinib initiation and PM resection, the patient shows a clinically relevant pulmonary response and no evidence of PM recurrence (Fig. 3) or new metastatic disease. Currently, the patient is under replacement therapy with hydrocortisone 20 mg, levothyroxine 0.50 mg, and desmopressin 0.06 mg. Clinical, biochemical, and radiological follow-up continue as appropriate.

Discussion

Metastatic involvement of the pituitary gland is considered rare, accounting for less than 1% of all surgically treated pituitary lesions and less than 1% of all intracranial metastases (1, 2). However, the prevalence of PM in autopsy series was estimated to be higher, up to 5% (1). It is hypothesized that most cases remain asymptomatic due to limited time for symptoms to become evident, but systemic manifestations of malignancy may mask pituitary disease, and some cases likely remain undiagnosed (1). Notably, PM has been reported with increasing frequency during the past decades, reflecting not only longer survival of patients with metastatic malignancy but also increased recognition of pituitary involvement (3).

Breast and lung cancer account for approximately 60% of malignancies associated with PM (4). Even though PM tends to occur in patients with known metastatic cancer, symptomatic pituitary involvement may represent the initial presentation and the only metastatic site of an otherwise unknown malignancy (5). The frequency of such presentation varies in the literature, possibly influenced by the time of publication (6). Interestingly, different series found that most cases of PM preceding the diagnosis of malignancy originated from lung cancers, as the case we report (3, 6, 7, 8).

There is no definite clinical or radiological distinction between PM and other sellar lesions. Therefore, diagnosis can be challenging, particularly when a history of malignancy is absent. Clinical presentation is variable, depending on the extent of metastatic involvement. Although diabetes insipidus (DI) has been considered the endocrine hallmark of PM due to a high prevalence in the initial series, more recent data suggest a lower frequency (1). In series of cases diagnosed over the last two decades, DI was present in less than 30% of patients (3, 5, 6, 7). On the contrary, anterior hypopituitarism was considered uncommon in the setting of PM, but recent series found it to occur in more than 70% of patients (3, 6, 7). Visual dysfunction is frequently found in PM: a review of 289 cases of PM reported over 60 years found that visual impairment was the most common first manifestation, occurring in nearly half of cases (4). This high prevalence reflects the aggressiveness of metastatic lesions, with suprasellar and parasellar invasion causing

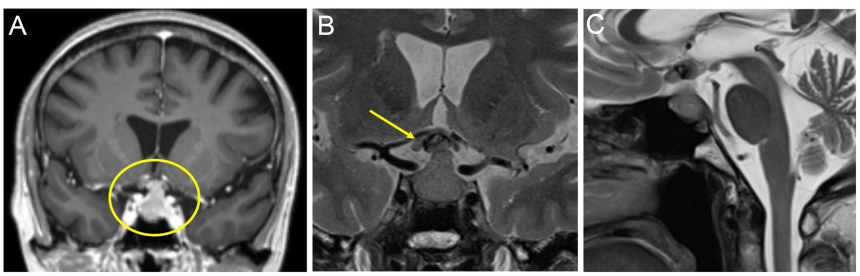

Figure 2
T1-weighted (A) and T2-weighted (B and C) images of the MRI performed 2 months after the pituitary enlargement finding, showing the suprasellar extension of the mass with edema of the optic chiasm (yellow arrow).

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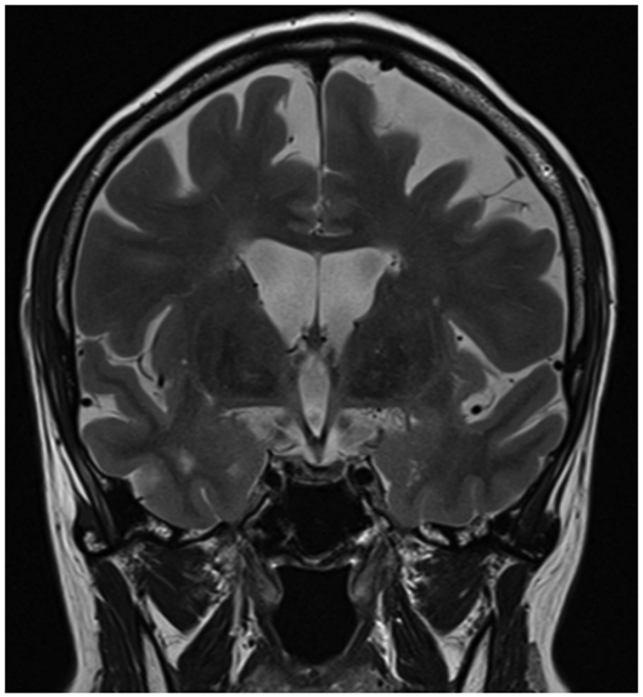

Figure 3
T2-weighted image of the last MRI performed during follow-up, with no evidence of metastatic recurrence on the sellar or parasellar area.

visual deficits and cranial palsies, respectively. Even though no single clinical feature can establish the diagnosis, the development of DI or ophthalmoplegia from any pituitary lesion should raise the suspicion of metastatic disease, irrespective of a history of malignancy (8). Of note, because of the potentially rapid growth of metastatic lesions, PM should be strongly suspected in patients with rapid onset and progression of any of these findings, such as in the case we describe.

The most common MRI finding in the setting of PM is an enhancing pituitary lesion with suprasellar extension (7). However, it is often difficult to reliably differentiate PM from other sellar lesions based on imaging alone. Importantly, the rapid growth of a sellar mass and aggressive invasion of parasellar structures, with bone erosion rather than remodeling, is highly suspicious of metastasis (7). Other findings that suggest the diagnosis of metastasis, although not specific, are a dumbbell-shaped appearance, stalk enhancement with thickening, and loss of the posterior lobe bright spot (7).

Our case demonstrates the challenges of PM diagnosis when a history of malignancy is absent. Given the MRI findings, paired with the history of MS, hypophysitis was initially the most likely diagnosis. Notably, our patient presented with symmetric enlargement and homogeneous enhancement of the pituitary associated with stalk enlargement, reflecting that MRI findings of PM can overlap with those of hypophysitis. Although thickening of the stalk is considered the most significant and characteristic radiological sign of hypophysitis, it should be noted that one-quarter of cases of stalk lesions represent metastasis (9), and tuberculosis and other granulomatous diseases can also present with stalk involvement (10). Close follow-up is strongly advised for presumed cases of hypophysitis and proved to be essential in this case: the continued and rapid pituitary growth suggested metastasis as a possible diagnosis and prompted the search for systemic malignancy.

PM has been associated with end-stage disease, and therefore with a poor prognosis (1). However, survival time from PM detection appears longer than previously reported, possibly reflecting improvements in the management of advanced malignancy (3, 5, 6). The management of PM depends on the symptoms and extent of the lesion, but also the stage of the primary malignancy and other comorbidities. The aim is to provide symptomatic relief and improve quality of life, while preventing further enlargement of the lesion. Surgery improves vision and cranial nerve dysfunction (3, 7), and provides an accurate histological diagnosis, allowing for the appropriate treatment. Importantly, even though most series report that surgery is not expected to increase survival, recently metastatic resection was suggested to provide a survival benefit (3). Stereotactic radiosurgery has proved to be safe and effective for growth control after diagnosis (5).

Overall, this case reflects the improved survival of patients with pituitary metastatic involvement and reinforces the importance of considering multimodal interventions directed to PM. Along with targeted therapy with afatinib, the patient underwent PM surgical resection followed by radiation. Surgery was decided given the ongoing visual loss and the uncertainty regarding the regression of visual deficits in response to the medical treatment alone. Also, surgery confirmed the diagnosis and supported further intervention with radiotherapy. After more than 2 years of follow-up, the patient exhibits a clinically relevant primary disease response and no evidence of PM recurrence. The prolonged survival of patients with pituitary metastatic involvement encourages individualized multimodal interventions directed to PM, but outcome-oriented studies will be necessary to elucidate the optimal therapeutic approach.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement
All authors were involved in the clinical care of the patient. A M L has performed the literature review and drafted the manuscript. All the other authors revised the manuscript and approved the final version to be published.

References

1 Komninos J, Vlassopoulou V, Protopapa D, Korfias S, Konogeorgos G, Sakas DE & Thalassinos NC. Tumors metastatic to the pituitary gland: case report and literature review. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 574–580. (https://doi.org/10.1210/jc.2003-030395)

2 He W, Chen F, Dalm B, Kirby PA & Greenlee JDW. Metastatic involvement of the pituitary gland: a systematic review with pooled individual patient data analysis. *Pituitary* 2015 **18** 159–168. (https://doi.org/10.1007/s11102-014-0552-2)

3 Patel KR, Zheng J, Tabar V, Cohen MA & Girotra M. Extended survival after surgical resection for pituitary metastases: clinical features, management, and outcomes of metastatic disease to the sella. *Oncologist* 2020 **25** e789–e797. (https://doi.org/10.1634/theoncologist.2019-0520)

4 Javabakht A, D'Apuzzo M, Badie B & Salehian B. Pituitary metastasis: a rare condition. *Endocrine Connections* 2018 **7** 1049–1057. (https://doi.org/10.1530/EC-18-0338)

5 Habu M, Tokimura H, Hirano H, Yasuda S, Nagatomo Y, Iwai Y, Kawagishi J, Tatewaki K, Yunoue S, Campos F, *et al*. Pituitary metastases: current practice in Japan. *Journal of Neurosurgery* 2015 **123** 998–1007. (https://doi.org/10.3171/2014.12.JNS14870)

6 Lithgow K, Siqueira I, Senthil L, Chew HS, Chavda SV, Ayuk J, Toogood A, Gittoes N, Matthews T, Batra R, *et al*. Pituitary metastases: presentation and outcomes from a pituitary center over the last decade. *Pituitary* 2020 **23** 258–265. (https://doi.org/10.1007/s11102-020-01034-2)

7 Schill F, Nilsson M, Olsson DS, Ragnarsson O, Berinder K, EngstrÖm BE, Dahlqvist P, Wahlberg J, Englund E & Burman P. Pituitary metastases: a nationwide study on current characteristics with special reference to breast cancer. *Journal of Clinical Endocrinology and Metabolism* 2019 **104** 3379–3388. (https://doi.org/10.1210/jc.2019-00012)

8 Al-Aridi R, Sibai KE, Fu P, Khan M, Selman WR & Arafah BM. Clinical and biochemical characteristic features of metastatic cancer to the sella turcica: an analytical review. *Pituitary* 2014 **17** 575–587. (https://doi.org/10.1007/s11102-013-0542-9)

9 Turcu AF, Erickson BJ, Lin E, Guadalix S, Schwartz K, Scheithauer BW, Atkinson JLD & Young Jr WF. Pituitary stalk lesions: the mayo clinic experience. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 1812–1818. (https://doi.org/10.1210/jc.2012-4171)

10 Pereira J, Vaz R, Carvalho D & Cruz C. Thickening of the pituitary stalk: a finding suggestive of intrasellar tuberculoma? Case report. *Neurosurgery* 1995 **36** 1013–1016. (https://doi.org/10.1227/00006123-199505000-00019)

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