CASE REPORT

Diagnosis and management of isolated pituitary metastasis from adenocarcinoma of unknown origin presenting as loss of libido

Julien Feghaly,¹ George Astras²

¹St George's University of London, Cyprus, Nicosia, Cyprus

²Department of Oncology, American Medical Center, Nicosia, Cyprus

Correspondence to
Julien Feghaly,
feghaly.julien@gmail.com

Accepted 4 March 2015

SUMMARY

Pituitary gland metastasis from primary tumours is uncommon on its own. Rarely, some of these primary tumours may be of unknown origin. This metastasis to the pituitary gland could manifest as diabetes insipidus, cranial nerve palsies, headaches, fatigue and other symptoms. In rare cases, it could present as loss of libido. We describe here this rare presentation, loss of libido, examine the diagnosis and management undertaken, and provide a systematic review of the literature for similar cases.

BACKGROUND

It is a rare case with a rare presentation that shows the importance of a good clinical examination and tests that help us reach a final diagnosis in order to provide the definitive treatment for it.

CASE PRESENTATION

A 37-year-old man originally presented in June 2007 with left axillary lymphadenopathy. He went on to have axillary clearance. The pathology report only revealed reactive lymphadenopathy. The tumour marker profile before radical axillary dissection was unremarkable. Physical examination, including breast examination, apart from the lymphadenopathy, was otherwise unremarkable. Testicular ultrasound examination showed an abnormal small right testicle with a diffuse pathology. He subsequently had a right orchidectomy in July 2007; however, his testes only showed atrophic changes. Following the orchidectomy, a positron emission tomography scan in July 2007 failed to identify a primary site of the adenocarcinoma.

In September 2008, this patient had left axillary and skin recurrence in the same area and block dissection for residual ER/PR/HER2 negative adenocarcinoma. He was later also treated with six cycles of Mitomycin C, Cisplatin, 5-Fluorouracil (MCF) chemotherapy for an unknown primary tumour starting in February 2009, and received radiotherapy to the nodal region and tumour bed. He was subsequently well and placed in follow-up. The MCF protocol consisted of a combination of mitomycin C (7 mg/m² on day 1 of cycles 1, 3 and 5), cisplatin (50 mg/m² on day 1) and 5-fluorouracil (600 mg/m² on day 1), delivered as a 21-day cycle.

He was regularly followed up with CT scans which showed that, apart from a stable plaque of thickening in his left axillary scar, there was no evidence of recurrence until January 2014. In January

2014, he presented to his general practitioner with loss of libido and impotence. He was investigated with a hormone profile, which showed low testosterone 1.2 ng/mL (2.8–8.0 ng/mL), low T3 1.5 pg/mL (2.3–4.2 pg/mL), low free T4 0.5 ng/L (0.8–1.8 ng/L), normal thyroid-stimulating hormone TSH 3.3 U/mL (0.3–5.0 U/mL), low morning cortisol 4.2 µg/dL (4.3–22.4 µg/dL), normal afternoon cortisol 3.5 µg/dL (3.1–16.7 µg/dL), low follicle stimulating hormone (FSH) 1.0 mIU/mL (1.6–8.0 mIU/mL), low luteinising hormone (LH) 1.1 mIU/mL (1.5–9.3 mIU/mL) and low prolactin 0.7 ng/mL (2.0–18.0 ng/mL), consistent with pituitary failure. The patient was not checked for diabetes insipidus.

He was started on hormone replacement therapy and further investigated. His treatment was comprised of levothyroxine, 75 mg orally once daily, and hydrocortisone, 20 mg orally two times a day, both continuously. On February 2014, a CT scan of his chest, abdomen and pelvis showed no recurrent disease, while his MRI scan showed a 19 mm pituitary tumour extending superiorly into the suprasellar cistern ([figure 1](#)). An endoscopic resection of pituitary of pituitary fossa tumour was performed in June 2014, with the biopsy showing a morphology that was the same as his original presentation of adenocarcinoma. However, it now slightly had a changed profile in that it was now very mildly estrogen receptor/progesterone receptor positive

Figure 1 Brain MRI (sagittal) dated February 2014; showing 19 mm pituitary fossa metastasis.

To cite: Feghaly J, Astras G. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-208735

Figure 2 Brain MRI (sagittal) dated June 2014 pre-surgery; showing a nodule measuring 10×7.5×6.3 mm involving predominantly the stalk of the pituitary gland.

and definitely HER2 positive. MRI scans were performed pre-surgery and postsurgery (figures 2 and 3).

OUTCOME AND FOLLOW-UP

Further investigation did not reveal any primary pathology and he is currently on adjuvant trastuzumab for a year and Hormonal manipulation for 5 years. After completion of trastuzumab, he will be under regular surveillance.

DISCUSSION

Literature searches were performed for articles looking at the metastatic involvement of the pituitary gland in different cancers and the types of symptoms that manifest when metastasis to the pituitary gland is present. The literature reviewed included the years 1975–2011. The literature included reports of cases or case-series involving metastatic disease of the

Figure 3 Brain MRI (sagittal) dated September 2014 postsurgery; showing a nodule measuring 4×4×2 mm at the size of the original tumour immediately related to the infundibulum.

pituitary gland, with specific emphasis on presentation, disease progression, treatment and prognosis.

Metastasis of the pituitary gland is uncommon with signs and symptoms being detected at a much later time in the disease progression.¹ Pituitary gland metastasis has been reported from almost every tissue type,^{2–3} however, breast and lung cancer are the commonest sites of the primary tumour and account for two-thirds of the cases, but metastasis from lymphoma, leukaemia, melanoma, kidney, colon and prostate cancer are also reported. In approximately 3% of cases, the primary tumour remains undetected despite intensive investigations (figure 4).^{2–34} In cancers with unknown primaries, the median survival is 4–12 months, with about 50% survival at 1-year and about 10% survival at 5 years from diagnosis.³⁵ The incidence of metastatic cancers of unknown origins is not known.

Reviewing the location of metastases in 201 cases, McCormick *et al*⁴ found an involvement of the posterior lobe either alone or in combination with the anterior lobe in 84.6% of cases, whereas the anterior lobe was affected in 15.4% of cases.

The predilection for metastasis to the posterior lobe is mainly attributed to the lack of direct arterial blood supply to the anterior lobe.^{4–7 36 37} The posterior lobe is supplied by the hypophyseal arteries, whereas the anterior lobe is nourished by the portal vessel system and secondarily by the lower infundibular stem, which partly arises from the posterior lobe. Another contributing factor is that the posterior lobe has a large area of contact with adjacent dura.⁷ Metastatic deposits in the anterior lobe are usually the result of a contiguous spread from the posterior lobe. The anterior lobe seems to be susceptible to ischaemic infarcts and is associated with a large metastatic lesion of the posterior lobe.^{7 36}

In most of the patients, the signs and symptoms of metastasis to other parts of the body such as lymph node, lung or bone are the first manifestations and metastasis to the pituitary gland occurs later.¹ At the time of diagnosis of the pituitary metastasis, many patients have widespread evidence of the disease; however, pituitary dysfunction as the first presentation of the primary breast cancer and infundibular involvement occurs rarely.³⁸

The present case presented with symptoms of feeling unwell, decreased libido and an inability to achieve erection, which implied anterior hyperphysical involvement. A review of the literature suggested that clinical presentation of decreased libido is a rare event, approximately 1%. The patient was not checked for diabetes insipidus, which presents in approximately 45% of pituitary metastasis, not confirming if metastasis was limited to the anterior pituitary lobe (figure 5).^{2–34}

The patient's hormone profile clearly indicated hypopituitarism with testosterone, T3, free T4, FSH, LH, prolactin and morning cortisol all being low and he was subsequently commenced on levothyroxine and hydrocortisone therapy.

Pituitary MRI of the patient revealed a 19 mm pituitary tumour extending superiorly to the suprasellar cistern (figure 1). The location of tumour in imaging provided a higher possibility of differentiation between malignant and benign disease. Clinical and radiological features of pituitary metastasis can be indistinguishable from benign suprasellar lesions such as pituitary adenoma. Histopathology remains the key to the diagnosis of pituitary metastasis. Luu *et al*³⁹ reported four patients with sellar lesions presenting with anterior visual pathway compression initially diagnosed as pituitary adenoma who on immunohistochemistry were found to have metastasis to the pituitary.

Figure 4 Origin of primary tumour metastatic to pituitary in 380 cases; in 3% of cases, the primary tumour is of unknown origin.²⁻³⁴

Classification of the cell histology determined the primary site of origin in some patients.

This case underwent endoscopic resection of the pituitary fossa tumour which showed ER/PR reactivity, 3+ HER2 status and appearance consistent with metastatic carcinoma. The previous immunohistochemistry obtained from the left axillary/skin recurrence in 2008 was found to be ER/PR/HER2 negative. In men, 1.7–45% of breast cancers are HER2 positive.⁴⁰ Sari *et al*⁶ reported a comparative study of the immunohistochemical detection of hormone receptor status and HER2 expression in primary and paired recurrent/metastatic lesions of patients with breast cancer. Analysis was made on 78 patients with metastatic breast carcinoma whose ER, PR and/or HER2 status was known both on the tissue samples of primary and recurrent metastatic lesions (RML).

Among the RML sites, 20.5% were locoregional and 70.5% were distant metastatic sites. Among 61 patients with known HER2 expression on both primary and RML, 14.7% (n=9) had

discordant results. Among these discordant cases, three had positive primaries and negative RML; six had negative primaries and positive RML. Among 18 patients who had HER2 positive primaries, 16.6% (n=3) had HER2 negative metastasis. Among 43 patients who had HER2 negative primaries, 14% (n=6) had HER2 positive metastasis.

Recent reports suggest that the receptor status of metastatic lesions may occasionally change compared to the primary tumour. The mechanisms underlying these discordant findings between the primary and RML are not very clear. As these discordant results make changes in treatment decision, a biopsy of the metastatic lesion is highly recommended in patients with metastatic breast cancer when feasible.

Treatment of malignant pituitary involvement consists of transcranial and transphenoidal surgeries, chemotherapy and radiotherapy. The regression of metastasis is achieved after each of these treatments.

Figure 5 Graph showing clinical presentation of 180 symptomatic pituitary metastases; clinical presentation of decreased libido is a rare event, <1%. diabetes insipidus is the most common presentation, 45%.²⁻³⁴

Learning points

- To summarise, this report clearly demonstrates that pituitary metastasis should be considered on differential diagnosis of unusual pituitary tumours, especially in patients with and without a history of malignant disease.
- Tumours of the sellar and parasellar regions in the case presented can easily be confused with pituitary adenoma.
- Change in ER, PR, and HER2 status between previous axillary tumour and metastatic carcinoma in pituitary has greatly influenced the management and prognosis.

Competing interests None.

Patient consent Not obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Kurkjian C, Armor JF, Kamble R, *et al.* Symptomatic metastases to pituitary infundibulum resulting from primary breast cancer. *Int J Clin Oncol* 2005;10:191–4.
- Sioutos P, Yen V, Arbit E. Pituitary gland metastases. *Ann Surg Oncol* 1996;3:94–9.
- Max MB, Deck MD, Rottenberg DA. Pituitary metastasis: incidence in cancer patients and clinical differentiation from pituitary adenoma. *Neurology* 1981;31:998–1002.
- McCormick PC, Post KD, Kandji AD, *et al.* Metastatic carcinoma to the pituitary gland. *Br J Neurosurg* 1989;3:71–9.
- Morita A, Meyer FB, Laws Jr ER. Symptomatic pituitary metastases. *J Neurosurg* 1998;89:69–73.
- Sari E, Guller G, Hayran M, *et al.* Comparative study of the immunohistochemical detection of hormone receptor status and HER-2 expression in primary and paired recurrent / metastatic lesions of patients with breast cancer. *Med Oncol* 2011;28:57–63.
- Teears RJ, Silverman EM. Clinicopathologic review of 88 cases of carcinoma metastatic to the pituitary gland. *Cancer* 1975;36:216–20.
- Van Seters AP, Bots GT, Van Dulken H, *et al.* Metastasis of an occult gastric carcinoma suggesting growth of a prolactinoma during bromocriptine therapy: a case report with a review of the literature. *Neurosurgery* 1985;16:813–17.
- Freda PU, Post KD. Differential diagnosis of sellar masses. *Endocrinol Metab Clin North Am* 1999;28:81–117.
- Ntyonga-Pono MP, Thomopoulos P, Luton JP. Pituitary metastases. Three cases. *Presse Med* 1999;28:1567–71.
- Ito I, Ishida T, Hashimoto T, *et al.* Hypopituitarism due to pituitary metastasis of lung cancer: case of a 21-year-old man. *Intern Med* 2001;40:414–17.
- Neroni M, Artico M, Pastore FS, *et al.* Diaphragma sellae metastasis from colon carcinoma mimicking a meningioma. A case report. *Neurochirurgie* 1999;45:160–3.
- Hanna FW, Williams OM, Davies JS, *et al.* Pituitary apoplexy following metastasis of bronchogenic adenocarcinoma to a prolactinoma. *Clin Endocrinol (Oxf)* 1999;51:377–81.
- Furuta S, Hatakeyama T, Zenke K, *et al.* Pituitary metastasis from carcinoma of the urinary bladder mimicking pituitary apoplexy—case report. *Neural Med Chir (Tokyo)* 1999;39:165–8.
- McEvoy AW, Khan N, Kitchen ND. Bitemporal hemianopia caused by metastatic carcinoma in a patient with Wegener's granulomatosis: an unexpected finding. *Br J Neurosurg* 1997;11:579–81.
- Aung TH, Po YC, Wong WK. Hepatocellular carcinoma with metastasis to the skull base, pituitary gland, sphenoid sinus, and cavernous sinus. *Hong Kong Med J* 2002;8:48–51.
- De Merlier Y, Duprez T, Maiter D, *et al.* MR features of pituitary metastases in two patients with central diabetes insipidus. *Acta Neurol Belg* 1996;96:141–2.
- Yamazaki T, Suzuki H, Tobe T, *et al.* Prostate adenocarcinoma producing syndrome of inappropriate secretion of antidiuretic hormone. *Int J Urol* 2001;8:513–16.
- Noga C, Prayson RA, Kowalski R, *et al.* Metastatic adenocarcinoma to a pituitary adenoma. *Ann Diagn Pathol* 2001;5:354–60.
- Pinet C, Raholimina V, Ferri RM, *et al.* Panhypopituitarism secondary to pituitary metastases. *Presse Med* 2000;29:17–18.
- Bell CD, Kovacs K, Horvath E, *et al.* Papillary carcinoma of thyroid metastatic to the pituitary gland. *Arch Pathol Lab Med* 2001;125:935–8.
- Nomizu T, Kanno M, Watanabe T, *et al.* A case of breast cancer metastatic to the pituitary gland. *Breast Cancer* 1996;3:71–4.
- Beckett DJ, Gama R, Wright J, *et al.* Renal carcinoma presenting with adrenocortical insufficiency due to a pituitary metastasis. *Ann Clin Biochem* 1998;35:542–4.
- Van de Velde A, Wassenaar H, Strubbe A, *et al.* Metastatic breast cancer presenting with diabetes insipidus. *JBR-BTR* 2000;83:68–70.
- Takatsugi K, Komuta K, Hosen N, *et al.* Metastasis of small cell lung cancer to the parotid gland as the initial clinical manifestation, followed by metastases to the pituitary gland and lumbar spinal cord. *Nihon Kokyuki Gakkai Zasshi* 1998;36:246–50. Japanese.
- Quevedo I, Rodríguez Portales JA, Rosenberg H, *et al.* Apoplexy in pituitary metastasis of renal cell carcinoma. Clinical case followed for 7 years. *Rev Med Chil* 2000;128:1015–18.
- Tomita H, Urui S, Kokunai T, *et al.* A case of metastatic tumor of the pituitary gland presenting as a subarachnoid hemorrhage. *No Shinkei Geka* 2000;28:1117–20. Japanese.
- Izumi Y, Sakaguchi K, Uda F, *et al.* A patient with meningeal carcinomatosis accompanied by a small pituitary metastatic lesion from gastric cancer who developed cerebral salt wasting syndrome. *Nippon Ronen Igakkai Zasshi* 1999;36:657–62. Japanese.
- Salpietro FM, Romano A, Alafaci C, *et al.* Pituitary metastasis from uterine cervical carcinoma: a case presenting as diabetes insipidus. *Br J Neurosurg* 2000;14:156–9.
- McCutcheon IE, Kitagawa RH, Sherman SI, *et al.* Adenocarcinoma of the salivary gland metastatic to the pituitary gland: case report. *Neurosurgery* 2001;48:1161–5.
- Suchkova EN, Panova TN, Korshunova MP. Diabetes insipidus syndrome in bile duct adenocarcinoma metastasis to the hypophysis. *Klin Med (Mosk)* 1978;56:128–9. Russian.
- Masiukiewicz US, Nakchbandi IA, Stewart AF, *et al.* Papillary thyroid carcinoma metastatic to the pituitary gland. *Thyroid* 1999;9:1023–7.
- Tchenio X, Mornex F, Sassolas G, *et al.* Symptomatic hypothalamohypophyseal metastasis revealing a small-cell bronchial carcinoma. Study of two cases. *Rev Mal Respir* 2000;17:1107–9. French.
- Stalder G, Molina HA, Antelo N, *et al.* Hypopituitarism caused by colonic carcinoma metastasis associated with hypophysial aspergillosis. *Medicina (B Aires)* 1994;54:248–52. Spanish.
- Hainsworth JD, Gerec FA. Treatment of patients with cancer of unknown primary site. *N Engl J Med* 1993;329:257–63.
- Leramo OB, Booth JD, Zinman B, *et al.* Hyperprolactinemia, hypopituitarism, and chiasmal compression due to carcinoma metastatic to the pituitary. *Neurosurgery* 1981;8:477–80.
- Chandra V, McDonald LW, Anderson RJ. Metastatic small cell carcinoma of the lung presenting as pituitary apoplexy and Cushing's syndrome. *J Neurooncol* 1984;2:59–66.
- Chaudhuri R, Twelves C, Cox TC, *et al.* MRI in diabetes insipidus due to metastatic breast carcinoma. *Clin Radiol* 1992;46:184–8.
- Luu ST, Billing K, Crompton JL, *et al.* Clinicopathological correlation in pituitary gland metastasis presenting as anterior visual pathway compression. *J Clin Neurosci* 2010;17:790–3.
- Wang-Rodríguez J, Cross K, Gallagher S, *et al.* Male Breast carcinoma: correlation of ER, PR, Ki-67, Her2-Neu, and p53 with treatment and survival, a study of 65 cases. *Mod Pathol* 2002;15:853–61.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow