Pituitary Metastasis: Central Diabetes Insipidus unmasked by Corticosteroids – Case Series and Review of Literature

Shree Vidhya N¹, Tan J.K², Raja Nurazni R.A², Masni M¹.

¹Endocrine Unit, Department of Medicine, Putrajaya Hospital
²Oncology Department, Institute Kanser Negara, Putrajaya Malaysia

Background

Metastasis to the pituitary gland is rare encounter and is more common amongst the elderly population with advanced malignancy. An estimated 1% of all pituitary tumour resections are metastatic. Primary sites that frequently metastasize include breast and lung carcinomas. In the recent decade, advancement in the field of oncology with multiple modalities of therapy has led to prolonged survival of patients with advanced stages of malignancy. Herein, we present three cases and review of literature of pituitary metastasis presenting as central diabetes insipidus (CDI) incidentally unmasked following administration of corticosteroids.

Objective

To establish the common clinical features, establish variations in clinical presentations and natural progression of disease in patients with pituitary metastasis.

Methods

Three cases of central diabetes insipidus unmasked by corticosteroids in pituitary metastasis were presented. A total of 9 other cases with central diabetes insipidus as first clinical manifestation unmasked by corticosteroid published from 2007-2017 were reviewed. Pertinent references were searched using windows remote search model on PubMed. The key words “pituitary metastasis” and “diabetes insipidus” searched in all fields resulted in 161 articles, of which articles of cranial diabetes insipidus as initial presentation without the use of corticosteroids were excluded. Searching “central diabetes unmasked by steroids” retrieved 8 additional references. Searching “metastatic carcinoma of pituitary” retrieved 35 additional references. About 20 new references were identified from the bibliographies of the articles reviewed. Ultimately, we identified a total of 18 references relevant to this research from the search terms. All references were reviewed to retrieve relevant references for this study. Non-English articles were excluded.

Results

A compilation of 9 previously reported cases of central DI unmasked by corticosteroids from 2007 to 2017 along with the present 3 cases were performed (Table 1). There was equal gender prevalence with a mean age of 61 (range 56-80 years old). More than 75% of the cases described here had previously been diagnosed with advanced malignancies of varying primary sites. The remaining 25% presented with varying symptoms of hypopituitarism as the harbinger to the discovery of the primary neoplasm. Amongst the literature review and cases presented, primary malignancies with pituitary metastasis included lung adenocarcinoma (33%), breast carcinoma (25%), nasopharyngeal carcinoma (16%), renal cell carcinoma (8%), hepatocellular carcinoma (8%) and gastric adenocarcinoma (8%). It is noteworthy that two of three present cases identified, were the result of direct infiltration of nasopharyngeal carcinoma to the pituitary gland. There is limited data documenting the prevalence of nasopharyngeal carcinoma with pituitary metastasis within the Asian population.

Conclusion

Central diabetes insipidus unmasked by corticosteroids is a less recognized, potentially lethal but fully reversible complication of pituitary metastasis. Symptoms or signs of central diabetes insipidus should be sought in all
patient with advanced malignancies presenting with polyuria and hypernatremia. Prompt restoration of pituitary hormones is warranted in affected patients to allow timely restoration of hormonal balance and preventing endocrine emergencies.

Introduction

Metastasis to the pituitary gland is a rare encounter representing less than 1% of all pituitary lesions. The first reported case of metastasis to the pituitary gland was identified and reported (in German) by Benjamin L. in 1857 discovered during an autopsy of a patient with disseminated melanoma (1, 5, 17). The increased prevalence in detection of pituitary metastasis denotes advancement in oncology treatment and options. These pituitary metastasis in advanced malignancies are most typically identified in the elderly population with diffuse malignancy. The most common primary tumours with metastasis to the pituitary gland are breast, lung and gastrointestinal malignancies. Their scarcity and usually indolent course, as well as the lack of specific clinical and radiological features, impede their differentiation from other more common sellar area lesions, particularly when history of malignancy is absent. Advancement in the field of oncology within the last decade has progressed with enhanced imaging modalities, improved surgical techniques, radical radio- and chemo-therapeutics for the treatment for systemic malignancies. This has led to augmented diagnosis of pituitary metastasis from primary tumours. Despite that, pituitary metastasis remains a challenge for diagnosis and remains poorly recognised and under reported. These pituitary metastasis are often discovered incidentally presenting with central diabetes insipidus having become unmasked after initiation of corticosteroids.

We report 3 clinical cases of pituitary metastasis diagnosed after incidental presentation of central diabetes insipidus after corticosteroid administration. A review of 9 other reported cases from 2007-2017 along with the current three cases were reviewed to establish common clinical features and clinical course of pituitary metastasis.

Case 1

Madam L, 67 year old lady diagnosed three years ago with stage four lung adenocarcinoma with extensive metastases to liver and bone presented to our centre with history of poor oral intake, generalised lethargy and reduced urine output for the past three days. She was admitted and treated as community acquired pneumonia. Biochemical markers supported the diagnosis of central diabetes insipidus with serum Na 156mmol/L, serum Osmolarity 309mmol/L and urine Osmolarity 145mmol/L. She was treated with subcutaneous desmopressin and intravenous fluids. Further tests demonstrated panhypopituitarism and oral desmopressin, thyroxine and hydrocortisone was initiated. Patient opted for palliative care succumbing to 3 months after admission.

Case 2

Madam S, 56 year old lady diagnosed with stage four nasopharyngeal carcinoma presented to us with symptomatic hyponatremia in March 2017 having undergone combined chemo-radiotherapy the previous year. She was dehydrated with sodium of 115 mmol/L and potassium 3.9mmol/L. She responded to hydration as sodium increased to 128 mmol/L. However, a week later sodium levels dropped to 119mmol/L despite hydration. CT brain revealed increasing size of primary tumour with intracranial extension involving cavernous sinus, pituitary fossa and left temporal and pontine infiltration. Other investigations support the diagnosis of syndrome of inappropriate antidiuretic hormone secretion and she responded to fluid restriction. In addition, she was diagnosed with hypocortisolism (9am: 26nmol/L) and commenced on oral hydrocortisone 10mg twice daily replacement. Repeat CT staging on revealed disease progression and a pituitary mass of 1.7 x 1.4 x 1.7cm. She was readmitted for chemotherapy but discharged without hydrocortisone in June 2017. In July 2017, she was admitted for her third cycle of chemotherapy with sodium of 123mmol/L, potassium 3.4mmol/L and was restarted on oral hydrocortisone 25mg tds. Unfortunately, she developed thirst and polyuria the same day with increasing sodium trend. Laboratory investigations revealed low urine osmolality and high serum osmolality with increasing serum sodium levels supported the diagnosis of central diabetes insipidus and subcutaneous desmopressin was administered. Complete pituitary hormonal panels support pan-hypopituitarism. She was discharged with hydrocortisone, thyroxine replacement and oral desmopressin but readmitted in September 2017 as her condition deteriorated. Ct brain showed disease progression with enlarging pituitary metastasis. Patient opted for palliative care and succumbed within 1 month.

Case 3
Mr C, a 55 year gentleman was diagnosed with advanced nasopharyngeal carcinoma, undifferentiated type, NOS. TNM: T4 N1 M0, Stage: IVA. He had completed combined chemo-radiotherapy in December 2017. Reassessment CT done in June 2018 revealed residual tumour at left inferior orbital fissure, left optic canal and left pterygopalatine fossa with local infiltration into the left cavernous sinus, pituitary sella and right sphenoid sinus. He was subsequently planned for chemotherapy with Paclitaxel/Carboplatin by the oncologist. He was admitted with symptoms of feeling unwell, vomiting, hypotension and hypoglycaemia. Morning serum cortisol and thyroid function revealed hypopituitarism. He was initiated on oral hydrocortisone and thyroid replacement and was discharge home. He presented 4 weeks later via emergency with symptoms of polyuria, with inability to compensate and with documented urine output of more than 200mls per hour. Investigations and water deprivation test confirmed the diagnosis of central diabetes insipidus with serum osmolarity of 291, serum sodium of 149 and urine osmolarity 164μmol/L. Further history revealed that the onset of polyuria was soon after initiation of steroids however patient was able to compensate with large volumes of fluid intake, up to 4L/day. He was discharged home with oral desmopressin 0.1mg daily in combination with other pituitary hormone replacement. He is planned for palliative chemotherapy in view of inoperable advance malignancy.

Discussion

The pituitary gland is an uncommon location for metastatic disease, although neoplasms from almost every tissue have been reported to metastasise there. In approximately two third cases of advanced malignancies, the patients were known to have metastatic disease prior to the discovery of pituitary metastasis. On the contrary, a third of patients, pituitary symptoms were the harbinger to the discovery of the primary neoplasm. The most frequent sources of metastases are: breast carcinoma (53% of pituitary metastatic lesions) and lung carcinoma (19%) (2, 3, 5). Metastatic spread is more common to the pituitary posterior lobe. A review of 201 cases of pituitary metastases demonstrated that the posterior lobe was involved in 84.6% (n = 170), with isolated posterior and anterior lobe lesions seen in 50.8 and 15.4% of cases respectively (3, 5). Many explanations for this predilection have been proposed. The posterior lobe is perfused directly by the inferior hypophysial arteries, while the anterior lobe is supplied by a portal system around the infundibulum from the superior hypophysial arteries, thus direct haematogenous spread may be more likely to seed to the capillaries of the stalk and posterior lobe. A further contributing factor is the fact the posterior lobe has a larger contact area with adjacent dura, facilitating meningeal spread though the suprasellar cistern (5). Central diabetes insipidus (DI) is relatively common in pituitary metastasis, present in 42.3% (95% CI 36.2–48.8) of patients at presentation in one pooled study (n = 248) (3). Moreover, in a patient with known metastatic disease, the development of DI and radiographic evidence of a pituitary mass is strongly suggestive of a pituitary metastasis. DI in the setting of metastasis may be associated with a thickened pituitary stalk in combination with absence of the normal high T1 signal intensity in the posterior lobe (27). The high incidence of DI in metastatic lesions is consistent with the similarly high incidence of posterior lobe involvement.

Our study described three cases of occult ADH deficiency masked by concurrent ACTH deficiency, only once glucocorticoid replacement therapy had been administered did the symptoms diabetes insipidus appear. This ‘masking’ phenomenon could be due to a multitude of factors, both from ADH-dependent and ADH-independent mechanisms, resulting in impaired renal-free water clearance. Recognition of this phenomenon in patients with adrenal deficiency and risk factors for developing CDI is important in early diagnosis and management of this phenomenon (9).

The reasons for this are complex. Firstly, cortisol induces resistance of the V2 receptor (or at a post-receptor level) to ADH, thus in states of glucocorticoid deficiency, the effects of ADH are amplified (8). Secondly, Corticotrophin Releasing Hormone (CRH) stimulates ACTH and ADH release, thus glucocorticoid deficiency upregulates CRH and thus ADH release (7, 8). Lastly, hypocortisolaemia results in renal sodium loss and volume depletion, potent stimulators for increased (but “appropriate”) ADH release. As such, when glucocorticoid deficiency is ameliorated, these compensatory mechanisms fail, and DI ensues. The high rate of DI in our study relative to the literature may be partly explained by our assessment of ADH function both before and after glucocorticoid replacement. Half of our cases had DI on initial assessment, similar to the prevalence in other studies, however the prevalence in our cohort increased to 75% after correction of glucocorticoid deficiency masked by concurrent ACTH deficiency; only once glucocorticoid replacement therapy had been administered did the symptoms diabetes insipidus appear. Recognition of this phenomenon in patients with adrenal deficiency and risk factors for developing CDI is important in early diagnosis and management of this phenomenon (9).

A compilation of 9 previously reported cases of central DI unmasked by corticosteroids from 2007 to 2017 along with the present 3 cases were performed (Table 1). There was equal gender prevalence with a mean age of 61 (range 56-80 years old). More than 75% of the cases described here had previously been diagnosed with advanced malignancies of varying primary sites. The remaining 25% presented with varying symptoms of hypopituitarism as the harbinger to the discovery of the primary neoplasm. Amongst the literature review and cases presented, primary malignancies with pituitary metastasis included lung adenocarcinoma (33%), breast carcinoma (25%), nasopharyngeal carcinoma (16%), renal cell carcinoma (8%), hepatocellular carcinoma (8%) and gastric adenocarcinoma (8%).
Previous studies have reported a high prevalence of breast carcinoma and lung carcinoma, however the Asian population shows a significant predilection for pituitary metastasis of nasopharyngeal carcinoma. The prevalence of NPC combined with the progression of disease with direct infiltration of the pituitary gland accounts for the presentation. However, there are no comparable studies looking into the frequency of nasopharyngeal carcinoma with pituitary metastasis.

The common presenting features in the present case series included significant polyuria, polydipsia with some patients presenting with an acute confusional state with the inability to compensate after the initiation of corticosteroids for pan-hypopituitarism. Symptoms of central diabetes insipidus was masked by the relative ADH deficiency. Most cases of pituitary metastasis presenting with central diabetes insipidus as the primary clinical presentation have led to an early diagnosis of pituitary metastasis. The perplexity arises when symptoms are masked and when patients present with symptoms of hyponatremia. Often, these preliminary signs to the presence of pituitary metastasis are often overlooked as these pathognomic symptoms are rare.

Advancement in imaging modalities with interest in neuroimaging has led to precision diagnosis pituitary metastasis. Amongst the literature review and cases presented, initial imaging by CT scan required more comprehensive images requiring MRI. The clinical outcome limited by late presentation in combination with advanced systemic disease should not be a limitation for precision imaging. Oncology offers targeted stereotactic radiosurgery as an effective palliative approach for most patients with pituitary metastasis. (18)

Conclusion

Central diabetes insipidus unmasked by corticosteroids is a less recognized, potentially lethal but fully reversible complication of pituitary metastasis. Symptoms or signs of central diabetes insipidus should be sought in all patient with advanced malignancies presenting with polyuria and hypernatremia. Prompt restoration of pituitary hormones is warranted in affected patients to allow timely restoration of hormonal balance and preventing endocrine emergencies.
Table 1. Brief summary of cases discussed from clinical patients and literature review identifying clinical presentations, investigations, diagnosis and clinical outcome.

| No | age | Sex | Diagnosis                                                                                                                                   | Serum osmo mmol/L | Urine osmo mmol/L | Na mmol/L | Clinical outcome                                           | Imaging                                                                                                                                   | Notes                                                                                                                                 |
|----|-----|-----|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------|------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| CR1 | 67  | F   | Diagnosis: lung adenocarcinoma with extensive metastases to liver and bone                                                                  | 309               | 115               | 156        | Opted for palliative care succumbing 3 months after admission | MRI showed a lobulated lesion in the right side of the posterior pituitary measuring 0.7 x 1.0 x 0.4cm and a well-defined lesion measuring 0.7 x 0.8 x 0.6cm at the superior aspect of the pituitary infundibulum. |                                                                                                                                       |
| CR 2 | 56  | F   | Diagnosis: nasopharyngeal carcinoma stage IV with pituitary metastasis                                                                           |                   |                   |            | Patient opted for palliative care and succumbed within 1 month. | CT brain revealed increasing size of primary tumour with intracranial extension involving cavernous sinus, pituitary fossa and left temporal and pontine infiltration. |                                                                                                                                       |
| CR 3 | 55  | M   | Diagnosis: nasopharyngeal carcinoma stage IV with pituitary metastasis                                                                           | 294               | 161               | 148        | For palliative chemotherapy with paclitaxel/Carboplatin    | CECT Residual tumour at left inferior orbital fissure, leptopect canal with local infiltration into the cavernous sinus, pituitary sella and right sphenoid sinus |                                                                                                                                       |
Polyuric > 150cc urine output per hour

171 F

Diagnosis: Primary lung malignancy with cerebral and pituitary metastasis diagnosed partial CDI initially obscured by concomitant central hypocortisolism and possible bronchogenic carcinoma-associated SIADH, only becoming overt after steroid replacement.

Clinical Presentation: lethargy, poor oral intake, functional decline and progressive confusion on a background of visual blurring for a number of months.

Low t4 8 pmol/L 8–21
TSH 1.21mIU/L 0.34–5/60
Am Cortisol 147 nmol/L 240–618
LH < 1IU/L 11–59
FSH 17–11

Urine output > 2.7L/day

355 392 163
No biopsy due to advanced malignancy – palliative care with hypopit replacement transferred to an inpatient hospice on nasal DDAVP and oral dexamethasone

MRI-well defined suprasellar mass measuring 26 mm x 26 mm x 19 mm, and multiple intracerebral hypodensities with perilesional oedema consistent with metastases

Indication for steroid 1.
For allergies cover for CT scan
2. dexa for perilesional oedema

March 2015

180 F

hepatocellular carcinoma with pituitary metastasis

January 2012, the patient died of hypovolemic shock.

MRI of the brain revealed a tumor measuring 13 mm × 13 mm in the sella turcica, which had spread across the suprasellar region

Postmortem examination of the pituitary tumor revealed tumoral hepatocytes in a thick trabecular pattern, the typical appearance of well differentiated HCC

2015
| ADH      | 0.27 pg/mL | 0.3–4.2 pg/mL |
|----------|------------|---------------|
| LH       | <0.10 mIU/mL | 7.5–56.2 mIU/mL |
| FSH      | 0.27 mIU/mL | 9.2–124.7 mIU/mL |

Clinical presentation: sudden-onset anorexia accompanied by hypotension and bradycardia. Ix revealed panhypopit. Diabetes insipidus (DI) developed five days into the replacement therapy.

| 69 M | Clinical presentation: with vomiting, low blood pressure and hypoglycaemia. Ix revealed panhypopit. Diabetes insipidus (DI) developed five days into the replacement therapy |
|------|--------------------------------------------------------------------------------------------------|
|      | Serum cortisol 12.6 (100-250 ng/mL) Free T4 6.8 pg/mL (8-18 pg/mL) TSH 0.005 mIU/mL (0.5-4 IU/mL), Testosterone 0.025 (2.5-10 ng/mL), FSH 0.5 IU/mL (1-8.4 IU/mL), LH 0.1 IU/l (10.5 IU/l) Low urine osmolarity. |

Bronchoscopy and biopsy demonstrated a pulmonary adenocarcinoma. Hence we concluded to a lung cancer with multiple pituitary and adrenal gland metastases. MRI demonstrated an inhomogeneous pituitary hypertrophy, with convexity of the sellar diaphragm, a nodular thickening of the pituitary stalk, and a loss of high intensity signal from the posterior pituitary.

| 77 M | Clinical presentation: 1-day history of confusion, insomnia and reduced appetite. No focal neurological deficit, visual field defect or ophthalmoplegia. Laboratory testing showed hypopituitarism-started replacement |
|------|----------------------------------------------------------------------------------------------------------------------------------|
|      | Free thyroxine 4.8 pmol/l TSH 0.99 miu/l LH <0.5 FSH <0.5 Prolactin 95 miu/l Testosterone <0.3 Cortisol 44 nmol/l |

Palliative care initiated-patient succumbed shortly after diagnosis.

(CT) brain scan was performed, revealing an enhancing (1.5 × 1.7 cm) suprasellar mass with also oedema of the overlying optic tract. Complicated by cranial DI and SIADH –
Five days after discharge, the patient re-presented to hospital with cranial DI. Urine output > 4L/day. Primary lung cancer with metastasis to the pituitary was made, complicated by cranial DI.

**Jan 2016**

**Clinical presentation:** sudden headache. History of distal radical gastrectomy for stage IIa adenocarcinoma - presenting with panhypopituitarism.

**Diagnosis:** Advanced metastatic adenocarcinoma, serum cortisol levels (58 nmol/l). Developed DI post-hydrocortisone – with urine output > 1.2L/4 hour.

Transsphenoidal tumor excision was performed and intraoperatively, the lesion had a fibrous pseudo-capsule with a soft core of avascular necrotic tissue. Refused investigations for possible gastric carcinoma recurrence and adjuvant oncologic therapy. He succumbed three weeks after surgery.

**MRI** showed a single 1.2 cm isointense pituitary lesion with loss of the usual posterior lobe hyperintensity on T1-weighted sequence. Contrast imaging revealed a heterogeneously enhancing pituitary tumor suggestive of intrasellar hemorrhage with a thickened stalk of 3 mm.

**May 2015**

**Clinical Presentation:** fatigue, 50-pound weight loss, anorexia, constipation and nonspecific abdominal pain for 4 months. Pituitary function evaluation revealed panhypopituitarism.

**Diagnosis:** RCC of a horseshoe kidney with symptomatic isolated pituitary gland metastasis.

Hormone 1-year prior Presentation Normal range: TSH (mIU/L) 1.72 – 0.07 L 0.4-4.5 Free T4 (ng/dl) 0.6 L 0.8-1.8 FSH (mIU/ml) 1.5 L 1.6-8 LH (mIU/ml) 0.2 L 1.5-9.3 AM cortisol (µg/dl) 3.3 L 4-22 Prolactin (ng/ml) 78.8 H 2.0-18 Testosterone (ng/dl) 290 (1 pm) Not done 250-1,100

Treatment with steroids unmasked central DI.

Right heminephrectomy confirmed RCC. Soon after he complained of progressively worsening headache and visual disturbance. Histopathology from urgent trans-sphenoidal hypophysectomy revealed RCC. The patient began post-surgical radiotherapy, but eventually he declined further treatments. In the end, he was placed on hospice where he passed away.

CT head showed 2.6 cm × 1.8 cm × 2.5 cm sellar mass likely with bilateral cavernous sinus extension.

(MRI) was contraindicated due to retained bullet fragments in his left upper chest.

Repeat CT head found the sellar mass was 3.6 cm × 2.2 cm × 2.5 cm and included a 1.0 cm suprasellar extension that abutted the optic chiasm.
Clinical Presentation: Hypotensive with sepsis secondary to influenza A/H1N1-pneumonia requiring high ionotropic support. Initiated on corticosteroids in ICU. Developed central DI 24 hours after steroid initiation

Diagnosis: Recurrent breast cancer with diffuse bone and mediastinal metastases.

Further exploration of pituitary axis testing confirmed panhypopituitarism with a low FSH level in a postmenopausal patient and low serum levels of TSH, free T4, growth hormone, and IGF-1. Also, posterior lobe pituitary insufficiency was confirmed with levels of vasopressin and copeptin

Pituitary MRI showed signal increase suggesting hemorrhage in sagittal T1-weighted and coronal T2-weighted MRI, but coronal T1-weighted MRI with contrast showed inhomogeneous enhancement of pituitary with metastasis.

Clinical Presentation: one month of weight loss and decreased appetite. She had no headaches, increased thirst or visual symptoms.

Diagnosis: Occult breast malignancy with extensive metastases.

Her biochemistries showed panhypopituitarism: ACTH 5.3 (010.2 pmol/L), cortisol 79 nmol/L, Free Thyroxine 6 (8-21 pmol/L), Thyroid Stimulating Hormone 0.81 (0.34-5.60 mIU/L), Insulin-like GF 1 42 (81-225 ug/L), Prolactin 274 (73-478 mIU/L), FSH 3 (17-114 IU/L), Luteinizing Hormone < 1 (11-59 IU/L)

Urine Na : 37

She was commenced on chemotherapy and brain radiation therapy. Unfortunately, four weeks later, she passed away from cecal perforation and peritonitis.

CT of the body and brain showed a mass in the cecum, suprasellar, and extensive intramuscular, bone, lung, lymph nodes and cerebellar deposits.

MRI of the pituitary fossa showed a 1.3 x 0.9 cm suprasellar mass inseparable from the pituitary stalk. The pituitary gland was normal.

Clinical presentation: loss of consciousness and gait disturbance. His serum sodium level was 117mEq/L. MRI revealed pituitary metastasis with anterior hormone deficiencies. Patient was initiated on steroids and polyuria ensued.

Patient underwent subtotal resection of the tumor via a transphenoidal approach. HPE revealed metastasis

Magnetic resonance imaging revealed a suprasellar tumor that showed inhomogeneous enhancement and was
Diagnosis: Pituitary metastasis in a patient with male breast cancer that resulted in pituitary dysfunction from estrogen receptor-positive breast cancer.

The patient underwent conventional post-operative radiotherapy combined with hormone replacement therapy and has remained free of symptoms for 16 months.

July 2014
References

1. Branch CL, Jr, Laws ER., Jr Metastatic tumors of the sella turcica masquerading as primary pituitary tumors. J Clin Endocrinol Metab. 1987;65:469–474. [PubMed]

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

3. Ref Komninos J, Vlassopoulos V, Protopapa D, Korfias S, Kontogeorgos G, Sakas DE, Thalassinos NC. Tumors metastatic to the pituitary gland: case report and literature review. J Clin Endocrinol Metab. 2004;89:574–80. doi: 10.1210/jc.2003-030395. [PubMed] [Cross Ref]

4. Delarue J, Chomette G, Pinseau Y, Brocheriou C, Auréli M (1964) Pituitary metastases. Frequency. Histopathologic study. Arch Anat Pathol (Paris) 12:179–182

5. Twelve cases of pituitary metastasis:A case series and review of the literature Mendel Castle-Kirszbbaum Tony Goldschlager Benjamin Ho Yi Yuen Wang James King3 Springer Science+Business Media, LLC, part of Springer Nature 2018

6. Neurosarcoidosis-associated central diabetes insipidus masked by adrenal insufficiency Lemuel Non1, Daniel Brittol, Catherine Anastasopoulos2 BMJ Case Rep. 2015; 2015; bcr2014206390. Published online 2015 Jan 22. doi: 10.1136/bcr-2014-206390 PMCID: PMC4307084 PMID: 25612752

7. Ishikawa SE, Fukagawa A, Higashiyama M et al (2001) Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. J Clin Endocrinol Metab 86:1665–1671. https://doi.org/10.1210/jc.2003-030395

8. XX Chin, TPL Quek, MKS Leow , Central diabetes insipidus unmasked by corticosteroid therapy for cerebral metastases: beware the case with pituitary involvement and hypopituitarism. JOURNAL OF THE ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH VOLUME 47 ISSUE 3 SEPTEMBER 2017 247 – 9 | doi: 10.4997/JRCPE.2017.307 Endocrine Society’s 97th Annual Meeting and Expo, March 5–8, 2015 - San Diego

9. Pituitary metastasis of hepatocellular carcinoma presenting with panhypopituitarism: a case report Tomoko Tanaka, Katsuji Hiramatsu, Takuto Nosaka, Yasushi Saito, Tatsushi Naito, Kazuto Takahashi, Kazuya Ojufi, Hidetaka Matsuda, Masahiro Ohkane, Tomoyuki Nemoto, Hiroaki Kato, Youkazu Nakamoto BMC Cancer. 2015; 15: 863. Published online 2015 Nov 6. doi: 10.1186/s12885-015-1831-7

10. An acute adrenal insufficiency revealing pituitary metastases of lung cancer in an elderly patient Hela Marmouch,1,& Sondes Arfa,1 Saoussen Cheikh Mohamed2, and Ines Khochtali Pan Afr Med J 2016; 23: 34. Published online 2016 Feb 8. doi: 10.11604/pamj.2016.23.34.8905

11. Competing interests in a lung cancer with metastasis to the pituitary gland: syndrome of inappropriate ADH secretion versus diabetes insipidus. Oxf Med Case Reports. 2016 Jan; 2016(6): 125–129. Published online 2016 Jun 1. doi: 10.1093/omcr/omw044 PMCID: PMC4887828 PMID: 27274855 Gaurav Singh Gulsin,1,* Madeleine Louisa Bryson Jacobs,2 Shailesh Gohil,3 Adam Thomas,4 and Miles Levy3

12. Symptomatic Metastasis to the Pituitary Gland: A Report of Three Cases and Review of the Literature. J Neurol Disord 3:236. doi: 10.4172/2329-6895.1000236 Yung C, Timothy SKC, Peter KHP, et al. (2015)

13. Isolated pituitary metastasis from renal cell carcinoma in a horseshoe kidney Kay K Win, Niita Blecher, William Tester, Sergy Ginzburg, Lauren Pomo Journal of Solid tumor DOI: https://doi.org/10.5430/jst.v8n1p37 2018

14. Acute-Onset Panhypopituitarism Nearly Missed by Initial Cosyntropin Testing. Claudine A.Blum,1 DanielSchneeberger,1 MatthiasLang,1 JankoRakic,1,2 MarcPhilippeMichot,1 andBeatMüller1 1 Medical University Clinic ,Kantonsspital Aarau,Aarau,Switzerland 2 Department of Pneumology,MedicalClinic,KantonsspitalBaden,Baden,Switzerland Published 3 October 2017 Case Reports in Critical Care Volume 2017, Article ID 7931438, 4 pages https://doi.org/10.1155/2017/7931438

15. PITUITARY METASTASIS SECONDARY TO OCCULT BREAST MALIGNANCY: A CASE REPORT Kalpana Vijakumar, MBBS, Su Ping Brenda Lim, MBBS, MRCP, Wai Han Hoi, MBBS, MRCP Tan Tock Seng Hospital ABSTRACTS – Pituitary Disorders/Neuroendocrinology Jan 2016

16. A case of pituitary metastasis in a patient with male breast cancer developing anterior lobe dysfunction successfully treated by using hormone replacement therapy Fukunaga A1, Yazaki T, Shimizu K, Ochiai M. Department of Neurosurgery, Kyosai Tachikawa Hospital. No Shinkei Geka. 2014 Jul;42(7):629-33. PMID: 25006103

17. Benjamin. L.: Ein Krebs Fall. Virchows Arch. Path. Anat. 12 (857) 566-569

18. Stereotactic radiosurgery for pituitary metastases. Surg Neurol. 2009 Sep;72(3):248-55; discussion 255-6. doi: 10.1016/j.surneu.2008.06.003. Epub 2008 Sep 11 Kano H1, Niranjan A, Konziozka D, Flickinger JC, Lunsford L.D.