CASE REPORT

Hypothalamic-pituitary fungal infection causing panhypopituitarism

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SUMMARY

Madam LPS, a 69 years old lady complained of left eye blurring of vision since January 2017. It was associated with left orbital swelling with chemosis, eye redness, epiphora, several episodes of self-limiting epistaxis and bilateral ophthalmoplegia. Other neurological examinations and cerebellar systems were intact. Magnetic Resonance Imaging (MRI) Brain and Orbit were performed, depicting a sellar mass with suprasellar extension with blood investigations results showed panhypopituitarism. She underwent bilateral orbital decompression. Trans-nasal endoscopic biopsy showed suppurative granulomatous lesion, which cultured Candida Albicans and Candida Galbrata. She was started on antifungal and hormonal replacement therapy for panhypopituitarism. Unfortunately, she did not respond well to treatment as repeated MRI Brain on December 2018 showed increase in size of sellar mass causing obstructive hydrocephalus and increasing size of left orbital lesion. She was counselled for another debulking surgery with a ventriculoperitoneal (VP) shunt. HPE taken were reported as chronic inflammatory process in favour to fungal infection. Pituitary infections may mimic pituitary mass. Some may exhibit symptoms of panhypopituitarism as well. Thus, physical examination, MRI brain imaging as well as HPE of biopsy are important aids to achieve diagnosis. Optimal treatment of fungal pituitary abscess includes transsphenoidal surgery combined with antifungal therapy.

INTRODUCTION

The pituitary gland and the sella region are located just below the centre of the brain in the base of the cranium. This central eminence of the middle cranial fossa is specialized as a saddle-like seat for the pituitary gland – known as sella turcica. At the centre of the cranial cavity; lies the pituitary gland. The hypothalamic-pituitary-adrenal axis (HPA axis) is a form of neuroendocrine unit which consists of the hypothalamus, the pituitary gland, and the adrenal glands.[1] The axis plays a major role in basal homeostasis and in body's response to stress.

Any diseases of the hypothalamus or pituitary gland may result in hypopituitarism due to disruption to the hypothalamus pituitary axis. This will cause diminished secretion of hypothalamic-releasing hormones, thereby reducing secretion of the corresponding pituitary hormones. The clinical manifestations of hypopituitarism depend upon the cause of pituitary disease as well as the type and degree of hormonal insufficiency. A person may be asymptomatic or present with symptoms related to hormone deficiency or a mass lesion, or even nonspecific symptoms such as fatigue.

There is currently no information available on hypothyroidism among Malaysian population. The prevalence of hypopituitarism among adults in Northern Spain is 29 - 45 of 100,000 population. Among the causes of hypopituitarism are pituitary tumour (61 %), nonpituitary tumour (9 %), and a nontumor cause (30 %).[2] Pituitary adenomas are the most common cause of sellar masses from the third decade on(clarify age group), accounting for up to 10 % of all intracranial neoplasms.[3] As such, other factor of hypopituitarism due to non-tumour cause like infection to the sella region is often missed. Hypothalamic-pituitary infections are extremely rare lesions which amount to less than 1% of all pituitary lesions.[4]

Here we would like to discuss a rare case of *Candida glabrata* and *Candida Albican* infection masquerading as a sella tumour in a patient seen in Sarawak General Hospital (SGH), Malaysia.

CASE REPORT

Madam LPS was a 69 years old lady with no know medical illness who complained of left eye blurring of vision since January 2017. The onset was sudden and progressively worsened in the next 2 months. It was associated with left orbital swelling with chemosis, eye redness and epiphoria. She also experienced several episodes of epistaxis (moderate amount of fresh blood, resolved with compression). Further history revealed that she began experiencing lethargy, malaise, loss of appetite and loss of weight (70kg to 50kg) for the past 6 months. There was no recent febrile illness, hearing impairment or signs of increase intracranial pressure. She is a housewife with no recent travelling history, bird rearing, and usage of traditional medications / over the counter drugs. She was from a middle-income family with 7 siblings where 1 of her younger brother was diagnosed with lymphoma.

Upon presentation to the SGH l in April 2017, the initial physical assessment revealed worsening bilateral eye ophthalmoplegia with reduced external ocular movement. Right eye showed quadrantanopia and the left eye had complete tunnelling of the visual field. Visual acuity

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Table I: Madam LPS hormonal profile during presentation on April 2017 and other clinic visits in 2018 and 2019

Laboratory Investigation	April 2017	September 2018	September 2019	Normal Range (unit of measurement)
TSH	1.08	0.005	0.005	0.27- 4.2 mU/L
FT4	1.7	23.45	15.40	12-22 pmol/L
Prolactin	6.1			102- 496 uIU/ml
Cortisol	<14	38.2	1646	171 -536 nmol/L
FSH	0.9			26.0 – 135 IU/L
LH	<0.1			15.9 – 54 IU/L
GH	0.3			0.077 – 5 ug/L

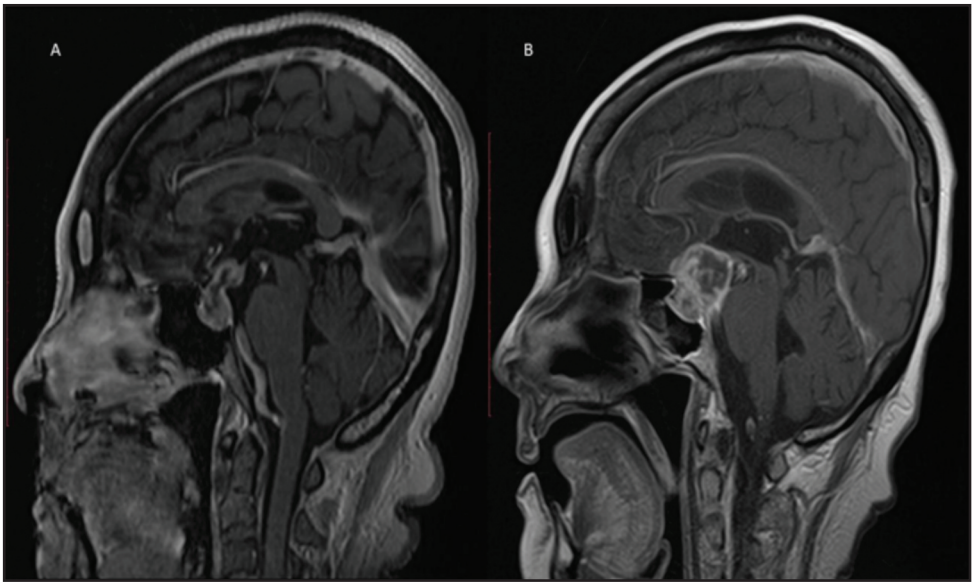

Fig. 1: A) MRI Brain on April 2017 and B) MRI Brain December 2018.

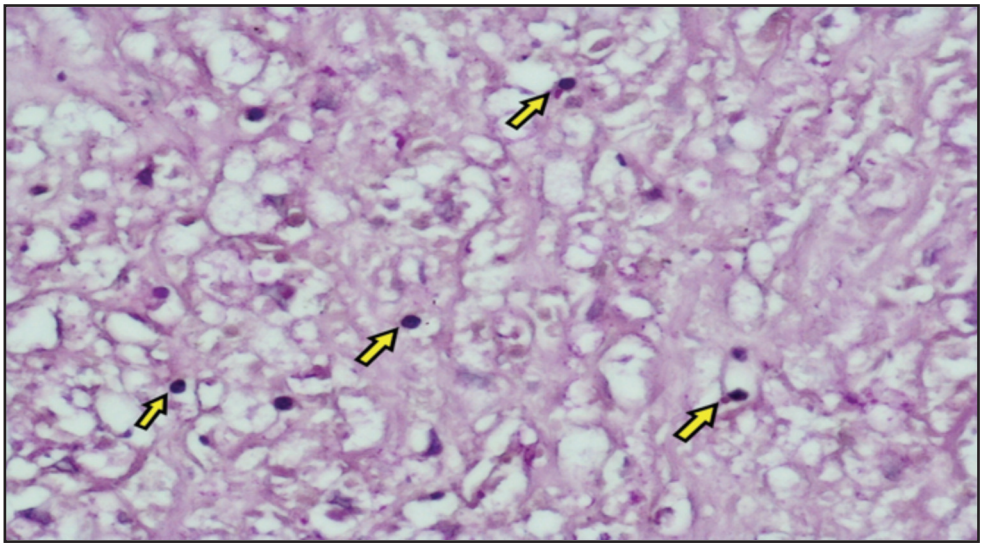

Fig. 2: Periodic acid Schiff stain highlights ovoid yeast cells with no pseudohyphae and characteristic of Candida Galbrata sp at 40x magnification (yellow arrows).

worsened to LE 3/60 and RE 6/45. Other neurological examinations and cerebellar systems were intact. Baseline hormonal profile taken showed panhypopituitarism (Table 1). Biohazards screening for Hepatitis B, Hepatitis C and HIV were negative. Magnetic Resonance Imaging (MRI) Brain and Orbit done was reported as sellar mass with suprasellar extension measuring 1.2x1.3x1.8cm in keeping with pituitary microadenoma or a craniopharyngioma (Figure 1A).

The patient had features that were in keeping with pituitary tumour, she was counselled by the neurosurgical team for a

nasal biopsy to obtain histopathological examination (HPE) samples. Subsequently, she underwent endoscopic nasal biopsy with bilateral orbital decompression in April 2017. Nasal HPE was noted to be suppurative granulomatous inflammation. The nasal fungal culture (C+S) however, grew *Candida albicans* and *Candida galbrata* respectively. Hence, on noticing the positive yield in the fungal culture, she was managed in line for pituitary fungal infection. She was referred to the Infectious Disease team and was started on T. Variconazole 200mg BD for 1-month duration. She was also referred to the endocrinology team for panhypopituitarism. She responded well on maintenance dose of oral Hydrocortisone 10mg/ 5mg/ 5mg, L-thyroxine 50mcg OD and Desmopressin 0.1mg Am/ 0.2m PM. For the treatment of fungal pituitary infection, she was maintained on T. Fluconazole 300mg OD which was planned for 6 months duration. Unfortunately, she developed hepatitis due to oral fluconazole (duration) and her oral anti-fungal medication was stopped.

As she moved into 2018, Madam LPS's condition was regularly monitored in the neurosurgical clinic of SGH. Hormonal profile showed improvement with hormonal replacement and anti- fungal treatment. During her clinic visit in December 2018, she was noted to have on and off fever, lethargy and worsening bilateral lower limb weakness. She was by then continuous bladder drainage (CBD) dependant and had developed sacral sore due to her immobility. A repeated MRI brain on 10/12/18 showed increased in size of sellar mass causing obstructive hydrocephalus and increasing size of left orbital lesion with worsening local involvement (Figure 1B). A ventricular peritoneal shunt (VPS) was inserted by the neurosurgical team to manage the obstructive hydrocephalus and relieved some of Madam LPS symptoms. As her condition was likely due to the resurgence of fungal pituitary infection, Madam LPS was counselled for endoscopic transnasal and transsphenoidal debulking of the lesion with right fascia lata harvest. She agreed for the procedure after being briefed regarding indication and complication of the procedure. At the same time, oral Voriconazole 200mg BD was started as empirical treatment for fungal infection.

After obtaining her consent, the surgery was performed on 24/2/2019. HPE samples were gained and sent for identification and special staining studies. Suprasellar HPE sample were reported as chronic inflammatory process in favour secondary to fungal infection. Special stainings and microscopic examination and stains were performed. Fungal and yeast cell was able to be identified in the microscopic examination (Figure 2). Fungal culture (C+S) however did not yield any growth. She was then allowed home with transfer of care to Hospital Sibu (another tertiary hospital) for regular follow-up to monitor her hormonal profiles and symptoms. Her antifungal (T. Voriconazole 20mg BD) and her hormonal treatment (T. L-Thyroxine 50mcg OD & T. Hydrocortisone 20mg AM, 10mg PM, 10mg ON) were continued and adjusted accordingly by the physician at Hospital Sibu (HS), Sarawak. At HS, she was continued to be monitored by visiting endocrinologist. Hormonal profile taken also showed improvement with hormonal replacements. However, in September 2019, she was admitted to Hospital Sibu for severe sepsis. She succumbed to the illness a few days later.

DISCUSSION

Fungal pituitary abscess is rare as it only amounts to 1% of the pituitary infections.[5] The most common pituitary infections are bacterial in origin namely staphylococci and streptococci. From a review done by Lie et al, most of the fungal pituitary abscess are caused by *Aspergillus* sp. (nine out of ten cases reported).[6] There was one sole case of pituitary abscess which grew Candida sp. In our case, samples taken from Madam LPS's nasal and sellar mass grew *Candida* sp.

The most common presentation of pituitary infections are headache and visual disturbances such as decrease in visual acuity, blurring of vision or loss of vision.[6] Some of the patients may also exhibit symptoms of panhypopituitarism clinically and biochemically. These features may be subtle over months to years and mimic to that in patients with pituitary adenoma. Madam LPS had similar presentation of visual disturbances with panhypopituitarism symptoms such as lethargy, poor oral intake and loss of weight. Her biochemical markers for pituitary function showed adrenal dysfunction which required her to be on hormonal replacement therapy.

Pituitary abscess is most commonly caused by hematogenous seeding of pituitary gland or direct extension of an adjacent infection (meningitis, sphenoid sinusitis, infected cerebrospinal fluid (CSF) fistula).[7] There are several factors involved which may increase the risk of pituitary abscess such as immunocompromised conditions and previous pituitary surgery or irradiation.[8,9] Our patient is an immunocompetent who didn't have any risk factors. Biohazards and diabetes mellitus screening on her were unremarkable. Multiple imaging done on her also showed no concurrent pituitary lesions, like Rathke cleft cysts, pituitary-adenoma or craniopharyngioma which may be a factor that potentiates the risk of infection.

The diagnosis of pituitary infection remains a challenge as relatively few patients present with symptoms of central nervous systems infection. Hence, other modalities of investigations should be utilised to complement the clinical findings. Cultures and swabs from the pituitary lesions via surgical intervention are proven to be beneficial to guide the proper antibiotics treatment. Imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) brain helps to improve the sensitivity with which pituitary lesions are detected and thus, helped to verify the diagnosis of pituitary abscess. Madam LPS's culture grew candida sp. Which lead her to be on antifungal therapy. The repeated fungal culture post transsphenoidal did not yield any growth as she might have been pre-treated earlier on. Nevertheless, the various imaging done on her showed a pituitary mass suggestive on infective in origin. HPE was able to demonstrate presence of fungal/yeast cell by Grocott (methanmine) silver (GMS) stains and Periodic acid Schiff staining as well.

Optimal treatment of fungal pituitary abscess is transsphenoidal surgery combined with antifungal therapy. Surgical option is curative for patients who presented with headache or vision problem as it is directly related to pituitary lesion. Early consultation with infectious disease team is strongly recommended to ensure comprehensive

review and appropriate usage of antifungal therapy. Madam LPS was started on antifungal therapy initially, however her symptoms persisted with increasing size of the pituitary mass leading to removal of it via the transsphenoidal surgery. Post operatively, she was resumed on antifungal Voriconazole as per infectious disease team's suggestions.

CONCLUSION

Fungal pituitary mass is rare and remains a diagnostic challenge. A good clinical history with HPE of tissue obtained will lead us to the correct diagnosis. We need to consider fungal pituitary abscess in the differential diagnosis of pituitary mass as unrecognised pituitary infection will lead to poorer outcome.

REFERENCES

1. Heaney J. Hypothalamic-Pituitary-Adrenal Axis. In: Gellman D.M, Turner J.R. Encyclopedia of Behavioral Medicine. Springer. 2017; 96-98.
2. Regal M, Páramo C, Sierra SM, Garcia-Mayor RV. Prevalence and incidence of hypopituitarism in an adult Caucasian population in northwestern Spain. Clin Endocrinol (Oxf) 2001; 55(6): 735-40.
3. Saeger W, Lüdecke DK, Buchfelder M, et al. Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry. Eur J Endocrinol 2007; 156(2): 203-16.
4. Pekic S, Miljic D, Popovic V. Infections of the Hypothalamic-Pituitary Region. In: Feingold KR, Anawalt B, Boyce A et al. Endotext. 2018.
5. Kaur A, Agrawal A, Mittal M. Presumed pituitary abscess without infectious source treated successfully with antibiotics alone. J Neuroophthalmol 2005; 25(3): 185-8.
6. Liu J, You C, Tang J, Chen L. Fungal pituitary abscess: case report and review of the literature. Neurol India 2013; 61(2): 210-2.
7. Vates GE, Berger MS, Wilson CB. Diagnosis and management of pituitary abscess: A review of twenty–four cases. J Neurosurg 2001; 95(2): 233–41.
8. Iplikcioglu AC, Bek S, Bikmaz K, Ceylan D, Gökduman CA. Aspergillus pituitary abscess. Acta Neurochir (Wien) 2004; 146(5): 521-4.
9. Pekic S, Popovic V. DIAGNOSIS OF ENDOCRINE DISEASE: Expanding the cause of hypopituitarism. Eur J Endocrinol 2017; 176(6): R269-82.