



Case report

Pituitary tuberculoma: A consideration in the differential diagnosis in a patient manifesting with pituitary apoplexy-like syndrome



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ABSTRACT

Pituitary tuberculoma is extremely rare, even in endemic regions of tuberculosis and much less frequently as a presentation of pituitary apoplexy. We describe a 25-year-old female presented with sudden onset of headache and vision loss of left eye which mimicking symptoms of pituitary apoplexy. MRI of the pituitary gland showed a rim-enhancing lesion at the intrasellar region extending into the suprasellar area, but absence of posterior bright spot with enhancement of the pituitary stalk. Pituitary hormonal evaluation revealed panhypopituitarism and diabetes insipidus. An urgent transphenoidal surgery of the pituitary gland was undertaken for which the histopathology showed necrotizing granulomatous inflammation with infarcted adjacent pituitary tissue. Despite negative fungal and AFB staining, pituitary tuberculoma was presumptively diagnosed based on imaging, pathology and the high incidence of tuberculosis in the country. After the course of anti-tuberculosis therapy, the clinical findings were dramatically improved, supporting the diagnosis. Pituitary tuberculoma is extremely rare in particular with an apoplexy-like presentation but should be one of the differential diagnosis list of intrasellar lesions in the patient presenting with sudden onset of headache and visual loss. The presence of diabetes insipidus and thickened with enhancement of pituitary stalk on MRI were very helpful in diagnosing pituitary tuberculosis.

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Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Despite the advance of therapeutic treatment, tuberculosis still remains one of the world's biggest problems. In 2014, 9.6 million people were estimated to be new cases of active tuberculosis worldwide [1]. The lungs are the most common sites for *M. tuberculosis* infection, presenting either asymptomatic latent infection or active pulmonary tuberculosis. Extrapulmonary sites of infection, representing about 20% of immunocompetent patients, can occur in any organ with or without overt

pulmonary involvement [2]. Extrapulmonary tuberculosis is often difficult to diagnose and necessitated a high index of suspicion.

Central nervous system (CNS) tuberculosis accounts for only 1% of tuberculosis cases worldwide, mostly in areas where the prevalence of tuberculosis are high. Hematogenous spreading which later developed the tuberculous foci in the brain, meninges, or adjacent bone is the main pathogenesis of CNS tuberculosis. The forms of CNS and most other forms of extrapulmonary tuberculosis, such as tuberculous meningitis, tuberculous encephalitis, tuberculoma or tuberculous brain abscess, depend on the location of tuberculous foci and host immune factors [3].

Pituitary tuberculoma is extremely rare, with the first case reported by Coleman et al. in 1940. Up to 2015, only 81 cases of pituitary tuberculoma had been documented in the previous literatures commonly presenting with gradual onset of headache and visual disturbances with or without systemic symptoms [4]. Pituitary apoplexy is a rare condition that occurs only 2–7% in pituitary adenoma and characterized by acute infarction and/or

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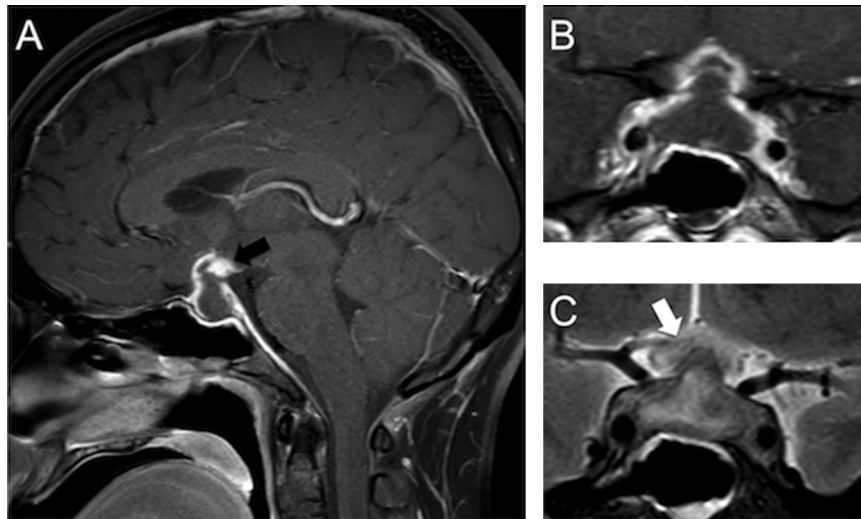


Fig. 1. (A) Sagittal and (B) coronal postcontrast T1-weighted images shows rim enhancing hypointense T1 lesion in the sellar and suprasellar region with thickened enhancement of the pituitary stalk (black arrow) and additional meningeal enhancement along sellar floor and clival area. (C) Coronal T2-weighted image demonstrates compression of the optic chiasm (white arrow) by this lesion with hyperintense T2 change, representing optic neuropathy.

hemorrhage of the pituitary gland [5]. Moreover, pituitary tuberculoma manifesting as apoplexy is extremely rare [6–8]. Without history of fever or multi-organ tuberculosis, the diagnosis of pituitary tuberculoma in a patient with apoplexy-like presentation is even harder to establish. We herein report pituitary apoplexy-like presentation of pituitary tuberculoma in a young female without associated systemic tuberculosis and demonstrate the clues in the differential diagnosis.

Case report

A 25-year-old Laotian female, who lived in Thailand for ten years, presented with low-grade fever, sudden onset of headache, and rapidly progressive visual loss in both eyes for 5 days. There was no previous history of headache, chronic cough, weight loss, prolonged fever or history of exposure to tuberculosis. She gave birth to her second child 2 years before without any complications and successfully breastfed for 9 months, indicating intact hypothalamic-pituitary-gonadal axis previously.

On examination, the patient was alert and cooperative, but acutely ill looking. Vital signs were: body temperature 37.8 °C, blood pressure 100/60 mmHg, pulse rate 60 beats/min and respiratory rate 16 breaths/min. Best corrected visual acuity was hand movements of the left eye and 20/40 of the right eye. Right temporal hemianopia was detected by Goldmann perimeter. Other cranial nerves and neurological examinations were normal. A magnetic resonance imaging (MRI) of brain showed rim-enhancing lesion, hypointense on T1-weighted image, mixed hypo- and hyperintense on T2-weighted image, occupying the sellar region with suprasellar extension, measuring about 1.4 × 2.5 × 2.2 cm (Fig. 1). Meningeal enhancement and thickened enhancement of pituitary stalk was seen with absence of posterior bright spot. The lesion compressed optic chiasm causing hyperintense signal in T2-weighted image of both optic nerves and optic chiasm. Chest x-ray was unremarkable. Anti-HIV and VDRL testing were negative.

Anterior pituitary hormone evaluation revealed panhypopituitarism; thyroid stimulating hormone 0.081 uIU/mL (0.35–4.94), serum free T4 0.71 ng/dL (0.70–1.48), early morning cortisol <1 mcg/dL, prolactin <0.6 ng/mL (5.18–26.53), insulin like growth factor-1 81 ng/mL (117–329). Hyponatremia with serum sodium of 124 mmol/L was found. With regular menstrual cycles by using oral contraceptive pill, luteinizing hormone (LH) and follicle-

stimulating hormone (FSH) were not evaluated. Then the patient was initially treated adrenal insufficiency with intravenous hydrocortisone. Polyuria from central diabetes insipidus was unmasked after hydrocortisone therapy.

Due to acute visual loss, the patient underwent urgent endoscopic transphenoidal pituitary surgery. Thickening of dura mater was noted intraoperatively. A firm un-suckable mass at sellar and suprasellar region, appeared like caseous necrotic tissue, was found separately from normal adjacent pituitary gland. Decompression of optic chiasm and excisional biopsy of mass were performed. Histopathology showed necrotizing granulomatous inflammation with adjacent infarcted normal pituitary tissue (Fig. 2). Gomori Methenamine Silver stain and acid fast bacilli stain were negative. In addition, polymerase chain reaction (PCR) of *Mycobacterium* spp. was negative.

The combination of histological findings, enhanced pituitary stalk in post-contrast MRI and the fact that patient living in endemic area highly suggested the diagnosis of pituitary tuberculoma. Treatment was initiated with a 2-month combination of isoniazid, rifampin, pyrazinamide and ethambutol, followed by 7 months of isoniazid and rifampin. *Mycobacterium* and fungus

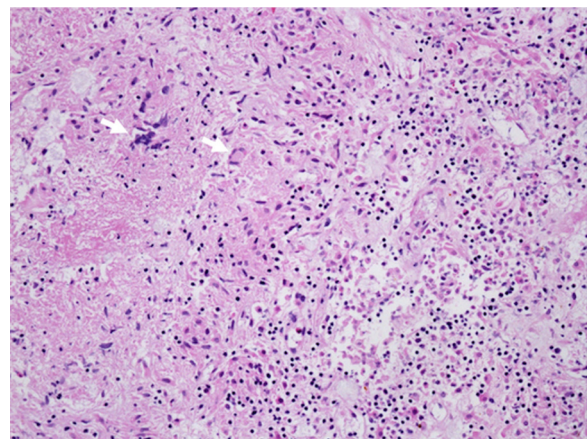


Fig. 2. Tissue biopsy from intrasellar region revealed necrotizing granulomatous inflammation (left) with multinucleated giant cells (white arrows) and infarction of the pituitary parenchyma (right) (H&E, 200×).

Table 1
Previous case reports of pituitary tuberculoma presented with apoplexy-like symptoms.

Reference, year	Sex, age	Manifestations and hormonal profile	Extracranial tuberculosis	Pituitary imaging	Route of surgery and intraoperative findings	Pathological and microbiological results	Duration of treatment	Follow-up
[6], 2001	M, 27	Three episodes of intense headache for 5 months, altered sensorium and blurring of vision for 1 month which gradually recovered; Hormonal profile: normal	N/A	Initial CT scan: sellar and suprasellar mass 1.6 × 1.8 cm with hemorrhage, MRI 6 weeks later: sellar mass 0.6 cm, thickened hypophyseal stalk	Transphenoidal surgery and biopsy of capsule; Findings: greyish, very firm, not suckable, the mass showed area of necrosis but no evidence of hemorrhage	Ill-defined granulomas; negative for AFB	18 months (INH, RIF, ETH for 3 months then INH, RIF for 15 months)	At 9 months <ul style="list-style-type: none"> • Hormonal profiles: normal • MRI: lesion markedly reduced in size, thickened hypophyseal stalk
[7], 2005	F, 27	Sudden onset of headache, ptosis of left eye, left facial numbness in V1-V2 dermatomes, drowsy; Hormonal profile: mildly elevated prolactin	No	MRI: sellar-suprasellar mass, hyperintense on T2, heterogeneous enhancement of the mass and pituitary stalk after gadolinium	Transphenoidal surgery and partial excision of mass; Findings: greyish, firm, fibrous densely adherent to surrounding structures	Ill-defined granulomas; negative for AFB and mycobacterium culture	Antituberculous regimen N/A	<ul style="list-style-type: none"> • Ptosis and numbness improved completely within 3 weeks • Hormonal profiles: normal • MRI at 6 months: complete resolution
[8], 2014	F, 17	Sudden onset of headache, vomiting followed by bilateral visual loss and altered sensorium for 10 days, intermittent low grade fever for 2 weeks; Hormonal profile: subclinical hypothyroidism	No	MRI: sellar and suprasellar mass, enhanced after gadolinium, communicating hydrocephalus, leptomeningeal enhancement	Not done	PCR for MTB positive from CSF	9 months (INH, RIF, PZA, STR for 3 months, INH, RIF for 6 months) with short course of dexamethasone for 6 weeks	<ul style="list-style-type: none"> • Gradual improvement in sensorium and vision in the first week • Asymptomatic after 3 months

M, male; F, female; N/A, not available; CT, computerized tomography; MRI, magnetic resonance imaging; AFB, acid fast bacilli; PCR, polymerase chain reaction; MTB, Mycobacterium tuberculosis; CSF, cerebrospinal fluid; INH, isoniazid; RIF, rifampin; PZA, pyrazinamide; ETH, ethambutol; STR, streptomycin.

culture were later reported negative. Hormonal replacement including prednisolone and levothyroxine were given. Short-term therapy of oral desmopressin was given for 3 weeks which was later stopped during follow up. Her headache rapidly resolved. She regained her 20/20 vision of both eyes within 1 week with only a small visual field defect in left periphery before discharge from hospital. Unfortunately, her secondary adrenal insufficiency and hypothyroidism are still persistent at 9-month follow-up.

Discussion

Our patient presented with pituitary apoplexy-like symptoms and rim-enhancing sellar-suprasellar lesion with enhanced pituitary stalk on the pituitary MRI favored non-adenoma etiologies. The preoperative differential diagnosis included inflammatory and granulomatous lesions of pituitary gland, including lymphocytic hypophysitis, pituitary abscess, tuberculosis, fungal infection, sarcoidosis, Wegener's granulomatosis and Langerhans' cell histiocytosis. For the differential diagnosis, lymphocytic hypophysitis typically affected women during peripartum period with symmetrical enlargement of pituitary gland and homogeneous contrast enhancement from MRI. Pituitary abscess often presented with an indolent course, with or without fever, rarely with acute onset. MRI of the pituitary gland showed intrasellar cystic lesion and peripheral enhancement after contrast, which resembled our cases. Fungal infection, such as aspergillosis, usually observed in immunocompromised patients, frequently extended from paranasal sinus infection [9]. Our patient did not have multisystem involvement as sarcoidosis or other systemic granulomatous diseases. Confirmed by intraoperative and histological finding of caseous necrotic mass, the most likely diagnosis was pituitary tuberculoma. Not surprisingly, the acid fast bacilli stain was negative and no evidence of extracranial tuberculosis from physical examination and chest x-ray, as reported in most of the past literatures, and the response to antituberculous therapy supports the diagnosis of a pituitary tuberculoma.

To best of our knowledge, there were 81 case reports of pituitary tuberculoma until now and only 3 cases presented with apoplexy-like symptoms (Table 1) [6–8]. In the summary of 81 cases (Table 1 and Supplemental material), mean age was 34.1 ± 13.6 years (range, 8–68 years) and majority of them were female (72.8%) without underlying diseases. The most common symptoms were headache (85.2%) followed by visual disturbances (48.1%). Only 12 of 81 patients (14.8%) had a history of low-grade fever, thus it is not very helpful for diagnosis. Endocrine disturbances were the first presenting symptoms including galactorrhoea (23.7% of female), amenorrhoea (37.3% of female) and polyuria from central diabetes insipidus (8.6%). The presence of central diabetes insipidus was one of the key features in distinguishing pituitary tuberculoma from pituitary adenoma. Initial anterior pituitary hypofunction was noted in 51.9% and hyperprolactinemia in 27.6% of patients.

Twenty-four of 81 patients (29.6%) had evidence of tuberculosis in other organs, either precedingly or concomitantly, such as pulmonary tuberculosis (11/24), lymphadenitis (8/24), spine (1/24), prostate gland (1/24), sinusitis (1/24) and skin abscess (2/24). Prior history of extracranial tuberculosis as long as 22 years before the episode of pituitary tuberculoma had been reported [10]. Evidence of extracranial tuberculosis is very helpful for the diagnosis of pituitary tuberculoma, and avoids unnecessary transphenoidal pituitary surgery. However, if the rapid visual deterioration is found with significant pressure

effect on the optic apparatus on MRI, urgent endoscopic transphenoidal surgery must be done.

The pituitary apoplexy-like symptoms could be resulted from caseous necrosis within the tuberculoma itself [6,8] or may be partly explained by infarction of normal pituitary gland seen in histopathology. Tuberculous vasculitis may be the cause of ischemic or hemorrhagic necrosis in tuberculoma, pituitary gland or adjacent tissue [7].

This patient's imaging showed hypo- to isointense signal on T1-weighted image and hyperintense signal on T2-weighted image. These signal characteristics are nonspecific and resemble those of a pituitary adenoma. However, peripheral contrast enhancement of sellar lesion after gadolinium is unusual for pituitary adenoma. Contrast MRI typically demonstrated thickening and enhancement of pituitary stalk in many cases of pituitary tuberculoma. From previous literatures of 79 cases, 20 from 42 cases with available MRI (47.6%) demonstrated thickened with enhancement of pituitary stalk, probably one of the most important clues to the diagnosis. Recently, magnetic resonance spectroscopy (MRS) has emerged as a noninvasive modality to detect specific chemicals in tissues of interest. MRS of a tuberculoma demonstrated elevated lipid peaks at 0.9, 1.3, 2.0 and 2.8 ppm, and a phosphoserine peak at 3.7 ppm. The lipid resonance, at 0.9 and 1.3 ppm occur due to the presence of methylene and terminal methyl groups on fatty acids found in caseous necrosis of tuberculoma [11,12]. Nevertheless, these MRS findings can be found in lymphoma and toxoplasmosis.

The transphenoidal approach was the preferred route of surgery, mainly used for diagnosis confirmation and decompression of adjacent structures without contaminating of organisms into intracranial structures as compared to transcranial approach [4]. A radical surgery, which carried the risk of cerebrospinal fluid leakage, was not necessary since medication treatment was effective postoperatively. Typical intraoperative findings are firm to hard, non-suckable greyish lesion with thickening of dura. Pituitary tuberculoma may be managed conservatively, without surgery, if the diagnosis was confirmed by other tests, such as cerebrospinal fluid PCR for tuberculosis in cases with co-existing tuberculous meningitis.

Fifty-two cases from literatures with available pathological reports were reviewed. Thirty-one cases (59.6%) had granuloma without caseous necrosis while 20 cases had typical granuloma with caseous necrosis. Pus was aspirated in one patient, and no tissue was collected. While microbial identification is straightforward in pulmonary tuberculosis, pituitary tuberculoma is rarely bacteriologically confirmed. Only 2 cases reported positive for acid fast bacilli from pathological tissue [13,14] and 2 cases showed mycobacterial growth on the Löwenstein-Jensen medium [14,15]. In other 2 cases, PCR for *M. tuberculosis* DNA was positive, but negative for acid fast bacilli stains [16]. Only one case was tested positive for both acid fast bacilli stain and mycobacterial growth on culture media [14]. Moreover, QuantiFERON TB-Gold interferon gamma release assay was tested positive in one case report [17]. Presumptive diagnosis is mostly required pathology finding of granulomatous lesion because of commonly negative microbial identification.

Combination of bactericidal drugs, such as isoniazid, rifampin, pyrazinamide, streptomycin, that penetrate effectively the blood brain barrier should be prescribed. Various regimens treated for 9–24 months had been used, depend on the clinical and imaging responses. A significant reduction in size after treatment have been reported as early as 2 months [18], usually with complete resolution of sellar mass at the end of the regimen. However, persistent of enhanced pituitary stalk after gadolinium administration without symptoms or evidence of sellar mass had been reported in some cases [19,20]. The improvement of

endocrinological status was reported in some patients but data were inconsistent regarding courses of endocrine dysfunction in detail.

Conclusions

We reported an additional case of pituitary tuberculosis with pituitary infarction that should be in the differential diagnosis of intrasellar lesions presented with sudden onset of headache and visual loss. The presence of diabetes insipidus and thickened with enhancement of pituitary stalk on MRI were very helpful in diagnosing pituitary tuberculosis.

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Disclosure

None of the authors have any potential conflicts of interest associated with this research.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.idcr.2016.07.012>.

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