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Case Report

Isolated Pituitary Tuberculoma

Katsuya Saito,[1] Masahiro Toda,[1] Satoka Shido,[1] Toshiki Tomita,[2] Kaoru Ogawa,[2] and Kazunari Yoshida[1]

Pituitary tuberculomas are extremely rare, even in the developing countries where tuberculosis is endemic. We report a rare case of isolated pituitary tuberculoma mimicking a pituitary adenoma or a Rathke's cleft cyst in Japan, a developed country. The patient was a 69-year-old woman presented with visual disturbance. Head magnetic resonance imaging (MRI) with contrast enhancement revealed an isolated intrasellar mass showing central hypointensity with an irregularly enhancing rim. She was operated on via an endoscopic transsphenoidal approach. Histopathological findings and an interferon-gamma release assay were highly suspicious of an isolated tuberculous granuloma. After proper infection control management, she was treated with four-drug antituberculous therapy (ATT). Follow-up MRI showed no recurrence 3 years after the discontinuation of ATT. An isolated pituitary tuberculoma has rarely been reported, especially in developed countries. In conclusion, neurosurgeons should consider an isolated pituitary tuberculoma as one of the differential diagnoses for pituitary tumors, because special management for infection control is required for tuberculosis. An interferon-gamma release assay is helpful for the difficult diagnosis of an isolated pituitary tuberculoma with inactive tuberculosis.

Keywords: intracranial tuberculosis, pituitary tumor, pituitary tuberculoma, antituberculous therapy, interferon-gamma release assay

Introduction

Central nervous system (CNS) tuberculomas have been often reported from the developing countries where tuberculosis is endemic.[1–10] However, the development of drugs and improvement of socioeconomic conditions have reduced the frequency of intracranial tuberculomas, which constitute only 0.5–4% of all intracranial space-occupying lesions.[1–4,10,11] Intracranial tuberculomas are commonly located in the cerebellum and cerebral cortex,[12] and pituitary tuberculomas are extremely rare.[1,2,4–7,10,11] Indeed, almost all previous reports of pituitary tuberculomas are from developing countries.[1–7,9,10] However, with the increasing incidence of immuno-compromised adults with acquired immune deficiency syndrome (AIDS), diabetes mellitus, or malignancy, or who are undergoing immune-suppressive treatment, there is likely to be a concurrent global increase of pituitary tuberculomas in developed countries.[12,13] Here, we report quite a rare case of pituitary tuberculoma mimicking a pituitary adenoma or a Rathke's cleft cyst in Japan.

Departments of [1]Neurosurgery and [2]Otorhinolaryngology, Head and Neck Surgery, Keio University School of Medicine, Tokyo

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Case Report

A 69-year-old woman presented with visual disturbance. On visual field examination she had several scotomas in the bitemporal field. Head magnetic resonance imaging (MRI) revealed an intrasellar mass. Her basal serum pituitary hormone levels were almost normal, while her hormone stimulation tests (gonadotrophin-releasing hormone stimulation, thyrotrophin-releasing hormone stimulation, and insulin tolerance test) showed the impaired reaction of growth hormone and gonadotrophin (Table 1). When she was an elementary school student, she tested positive for tuberculin skin testing. She also had a family history of tuberculosis, with her father's hospitalization for lung tuberculosis. Her general systemic examination was unremarkable, and her chest X-ray was normal. She was not immune-compromised. MRI revealed an 18-mm sellar mass with the compression to optic nerve (Fig. 1). The intrasellar mass showed hypointense on T_1-weighted image (T_1WI), predominantly hyperintense with a hypointense rim on T_2-weighted image (T_2WI) and central hypointense with an irregularly enhancing rim on contrast-enhanced T_1WI (Fig. 1A–E). Thickening of the pituitary stalk was

Table 1 The result of preoperative hormone stimulation test (gonadotrophin-releasing hormone stimulation, thyrotrophin-releasing hormone stimulation, and insulin tolerance test)

	0 M	15 M	30 M	60 M	90 M	120 M
Glu	105	64	29	126	84	98
GH	0.2	0.2	0.4	1.3	0.9	0.6
LH	3.5	6.0	9.2	11.5	12.6	13.0
FSH	14.0	15.6	17.9	19.2	21.1	25.2
ACTH	25	30	93	176	53	36
Cortisol	16.3	15.0	19.8	26.3	22.2	19.2
TSH	1.49	4.91	7.09	5.89	4.48	3.50
fT3	2.3	2.2	2.3	2.3	2.7	3.3
fT4	1.1	1.1	1.1	1.1	1.2	1.3
PRL	19.6	71.0	66.5	46.6	34.5	32.0

Normal range of basal hormone levels; GH 0.13–9.88 ng/mL, LH 6.7–38.0 mIU/mL, FSH 26.2–113.3 mIU/mL, ACTH 7.2–63.3 pg/mL, Cortisol 4.0–23.3 ug/mL, TSH 0.3–3.7 μU/dL, fT3 2.5–4.5 pg/dL, fT4 0.9–1.9 ng/dL, PRL 6.12–30.54 ng/mL. M: minute, GH: growth hormone, LH: luteinizing hormone, FSH: follicle stimulating hormone, ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, fT3: free T3, fT4: free T4, PRL: prolactin.

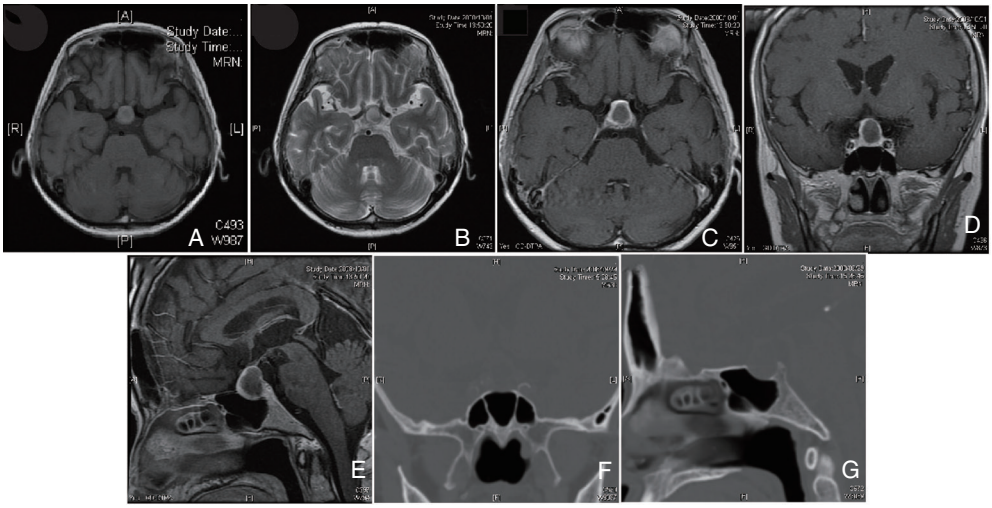

Fig. 1 Preoperative MRI and CT findings. Preoperative plain MRI showing iso-intensity on T_1-weighted image (A) and high-intensity on T_2-weighted image (B). An axial section (C), a coronal section (D), and a sagittal section (E) of contrast-enhanced MRI showing rim-enhancement of the tumor. A coronal section (F) and a sagittal section (G) of preoperative bone CT showing intact paranasal sinuses and clivus. MRI: magnetic resonance imaging, CT: computed tomography.

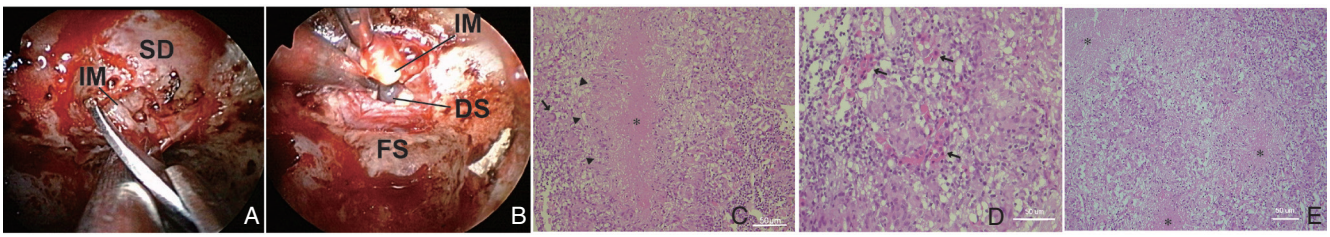

Fig. 2 Intraoperative photographs (A–B) and histological findings of the surgical specimen (C–E). A–B: An intrasellar mass showing the margin of grayish and fibrous solid component (A) and a central core of yellowish-white pus (B). C–E: Hematoxylin-eosin staining of the surgical specimen showing epithelioid cell granulomas with necrosis. The central necrosis (C, asterisk) with multiple epithelioid cells (C, arrow head) is surrounded by a multinucleated giant cell (C, arrow) and lymphocytes. The pituitary parenchyma (D, arrow) is observed along with granulomas. Several areas of necrosis are present (E, asterisks). Scale bar, 50 μm. IM: intrasellar mass, SD: sellar dura, DS: diaphragma sella, FS: floor of sella turcica.

not observed. A computed tomography (CT) scan demonstrated intact paranasal sinuses and intact clinoid processes (Fig. 1F, G). The patient was operated on via an endoscopic transsphenoidal approach. The intrasellar tumor mass appeared pale grayish and fibrous in the marginal component, and yellow-whitish and soft in the central component. (Fig. 2A, B) An intraoperative diagnosis by frozen sections was suggestive of a tuberculous granuloma. The patient was not extubated until smear specimens prepared from a sputum sample were confirmed to be negative. Postoperatively, transient diabetes insipidus was observed.

Tubercle bacillus was not detected by smears, culture tests, and polymerase chain reaction (PCR) tests for the surgical specimen, sputum, and gastric fluid and urine samples. Whole-body CT scanning did not reveal any inflammatory lesions including tuberculosis. Histopathology of the surgical specimen revealed the replacement of normal pituitary tissue by an active inflammatory infiltrate with multiple epithelioid cell granulomas, multinucleated giant cells, and lymphocytes with several areas of necrosis (Fig. 2C–E). Ziehl–Neelsen staining (acid-fast bacilli staining) was negative. QuantiFERON® TB-Gold (Cellestis Limited, Carnegie, Victoria, Australia) an interferon-gamma release assay used in tuberculosis diagnosis, showed a positive response (ESAT-6 antigen: 0.44 IU/mL, CFP-10 antigen: 0.49 IU/mL). Serologic tests for syphilis, Treponema pallidum hemagglutination test, and cytoplasmic anti-neutrophil cytoplasmic antibodies testing were negative, while plasmatic levels of angiotensin converting enzyme (9.9 IU/L) were normal. Because the sellar lesion was highly suspicious of a tuberculoma, the patient was started on antituberculous therapy (ATT) consisting of pyrazinamide, ethambutol, rifampicin, and isoniazid for 2 months, followed by rifampicin and isoniazid for 4 months. Postoperative MRI at 3 and 6 months did not show any enhancing sellar granuloma lesion. Although 3 years have passed after the discontinuation of ATT, follow-up MRI showed no recurrence (Fig. 3A–B).

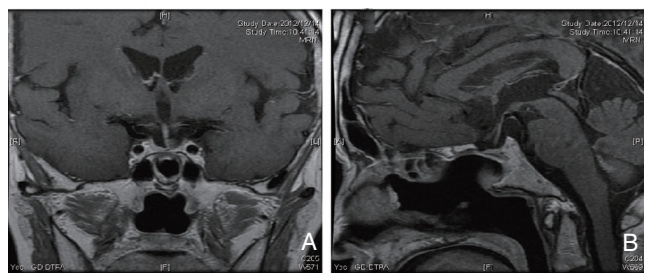

Fig. 3 Postoperative follow-up MRI. A coronal section (A) and a sagittal section (B) of the 3-year postoperative MRI, showing no recurrence of the intrasellar mass. MRI: magnetic resonance imaging.

Discussion

CNS tuberculosis occurs in approximately 1% of all patients with active tuberculosis.[12] Although the mechanisms are still unclear, it is thought to arise secondarily from the hematogenous spread or direct contamination from paranasal sinuses, which results in the formation of small subpial and subependymal foci in the brain.[10,12] In some patients, foci rupture and release bacteria into the subarachnoid space causing meningitis. In others, foci enlarge to form tuberculomas without meningitis. Clinical symptoms of CNS tuberculomas are dependent on the anatomical location, or are often asymptomatic.[12]

Pituitary tuberculomas have been usually reported to occur predominantly in adult women aged between 40 years and 60 years.[4–6,10,11] Most patients were previously healthy with no evidence of immunosuppression. Only 25–30% of cases with sellar tuberculomas have past or concurrent history of extrasellar tuberculosis.[4] Thus, the isolated pituitary tuberculomas mostly mimicked pituitary adenomas in previous reports,[4–6,10,11] and it was impossible to diagnose without surgical specimens. Similar to previous reports,[4–6,10,11] there were no extrasellar tuberculous lesions including extracranial tuberculosis in this case. Preoperatively, a Rathke's cleft cyst, a cystic pituitary adenoma, a craniophagyngioma, a metastatic tumor, or inflammatory disease was suspected from MRI findings. Although previous papers reported a thickening of pituitary stalk and involvement with paranasal sinus or clivus as relatively common MRI findings of sellar tuberculomas,[1,4,6,7,10] these findings were not confirmed in our case. Thus, the intraoperative pathological diagnosis indicating the tuberculous lesion surprised us. In the retrospective assessment of MRI findings, this case was compatible with previous reports showing that a central hypointense mass with an enhancing rim on a contrast-enhanced image was suggestive of a caseating granulomatous lesion.[1,2,13]

In the operation room, the patient should not be extubated until a smear specimen prepared from sputum samples is confirmed to be negative. This is essential for proper infection control management of suspected tuberculosis. We could not detect tubercle bacillus directly by smears, culture tests, and PCR tests. However, the absence of tubercle bacillus does not exclude the possibility of tuberculous disease, because organisms frequently cannot be detected in tissue sections when the lesions are predominantly proliferative.[7] In the published literature,[1,4,6,10,11,13] failed direct detection of tubercle bacillus was not rare, especially in isolated pituitary tuberculomas. In many reports, sellar tuberculomas were finally diagnosed by only indirect pathological findings such as necrotizing granulomas.[1,4,6,10,11,13] The differential diagnosis of pituitary granulomatous diseases include sarcoidosis, syphilis, paranasal fungal infections, lymphocytic and granulomatous hypophysitis, and Wegener's granulomatosis.[1,4,6,7,10,11] A histologically important feature of granulomas is whether or not they contain necrosis.[1,14] The identification of necrosis in granulomas is important because granulomas with necrosis tend to have infectious causes, typically tuberculosis. In addition, our case did not present any systemic symptoms and abnormal findings associated with such other granulomatous diseases. An interferon-gamma release assay was also useful for diagnosing the latent tuberculosis infection of this patient. This assay is an enzyme-linked immunosorbent assay (ELISA)-based, whole-blood test detecting interferon-gamma from lymphocytes in response to *Mycobacterium tuberculosis* specific antigens, and is not affected by Bacille Calmette-Guérin vaccination status.[12] Patients are considered positive for *M. tuberculosis* infection if the interferon-gamma response to tuberculosis antigens is above the cut-off value. In this case, the past history of a strongly positive tuberculin skin test, a family history of tuberculosis, and a positive response of an interferon-gamma release assay strongly indicated the granulomatous pituitary lesion was because of the tuberculosis infection.

Pituitary tuberculomas have good outcomes in most cases when patients were adequately treated with ATT.[1,4–7,10,11] Thus, the main purpose of surgery is to obtain a specimen for histological diagnosis to exclude other granulomatous and infectious lesions in addition to common sellar lesions, such as pituitary adenomas and Rathke's cleft cysts. Surgical decompression may also be considered. Thwaites et al.[12] reported that tuberculous cerebral abscess and vertebral body tuberculosis with symptomatic compression to the nervous tissue may necessitate early surgical intervention. After pituitary tuberculomas are suspected by intraoperative diagnoses of frozen sections, surgical decompression might also be considered for pituitary tuberculomas with symptomatic compression to the optic nerve. The transsphenoidal approach is recommended as a surgical approach, because it can permit both tissue diagnosis and tumor decompression without cerebrospinal fluid contamination.[1,4–7,11] Regarding chemotherapeutic regimens, a systematic review and meta-analysis concluded that 6 months of treatment were probably sufficient for all forms of CNS tuberculosis,[12,15] although most authorities recommend 12 months of treatment.[12] In this case, follow-up MRI at 3 years has shown no recurrence of tuberculomas.

Conclusion

We report a rare case of isolated pituitary tuberculoma mimicking a pituitary adenoma or a Rathke's cleft cyst in Japan. Even in developed countries, neurosurgeons should recognize isolated pituitary tuberculomas as a differential diagnosis for pituitary tumors, because special management for infection control is required for tuberculosis. In addition, isolated pituitary tuberculomas are difficult to diagnose histopathologically because of the failed direct detection of tubercle bacillus, and, therefore an interferon-gamma release assay is helpful to diagnose tuberculoma with inactive tuberculosis.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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Corresponding author:
Katsuya Saito, MD, Department of Neurosurgery, Keio University School of Medicine, 35 Shinano-machi, Shinjnku-ku, Tokyo 160-8582, Japan.
✉ csrbb415@yahoo.co.jp