

Hypothalamus-Pituitary Infundibular Mass Lesion Manifesting with Hypopituitarism and Diabetes Insipidus — — A Case Report

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Abstract

A 50-year-old Taiwanese man with cirrhosis of the liver had a 5 year history of sexual dysfunction and was noted to have apparent signs of hypogonadism including absence of pubic and axillary hair and feminine facial features. Hypotension, hyponatremia, and eosinophilia were also found. Initial endocrinologic studies revealed undetectable serum levels of FSH, LH, testosterone, and DHEA-S but elevated prolactin level. Morning cortisol and free thyroxine serum levels were both below normal limits. Hypopituitarism was confirmed subsequently with GnRH stimulation test and insulin hypoglycemic test. Patient was given thyroxine and corticosteroid replacement and testosterone injections as treatment for panhypopituitarism. However, an abrupt increase in urine output developed soon after the administration of glucocorticoid. Neurogenic diabetes insipidus (DI) was then diagnosed via water deprivation and stimulation with desmopressin. The cause of the endocrinologic abnormalities was attributed to a 8×3×9 mm mass lesion within the pituitary infundibulum as the MRI revealed.

Patient opted for a period of conservative therapy with hormone replacement. However, follow-up MRI of the pituitary a year later showed enlargement of the infundibular mass to 2×1×1 cm, with involvement of the hypothalamus as well as the posterior pituitary. The nature of the mass lesion is still unknown. Differential diagnoses include granulomatous, infiltrative, infectious, vascular, and primary or metastatic tumoral diseases.

Coexistence of hypopituitarism and diabetes insipidus signifies possible involvement of hypothalamic-pituitary region. Isolated anterior pituitary diseases rarely cause DI. Pituitary stalk abnormalities may have malignant and non-malignant, and localized as well as systemic causes. All must be considered in the differential diagnosis. (J Intern Med Taiwan 2002;13: 300-307)

Key Words : Pituitary infundibular lesion, Hypopituitarism, Diabetes insipidus

Introduction

Although hypopituitarism and central diabetes insipidus have been well-studied as separate entities, cases manifesting both conditions are uncommon and usually signify involvement of the

hypothalamus-pituitary region rather than the pituitary gland itself 1. Here we describe a case of pituitary stalk lesion presenting with unequivocal hypopituitarism who later developed diabetes insipidus as well. Even though the nature of the lesion is yet to be determined, this case was nonetheless replete with findings that allowed us to reach a convincing endocrinologic diagnosis.

Case Report

A 50-year-old Taiwanese man with recently diagnosed cirrhosis of the liver initially presented with anorexia and malaise of two weeks' duration. Because apparent stigmata of hypogonadism were noted incidentally by his gastroenterologist, he was referred to us for an endocrinologic workup. The patient was a married man who had fathered four healthy living children. For the past 4 years he had resided in Vietnam as a businessman. His history of sexual dysfunction began about 5 years ago, when he first noticed diminished libido and impotence. At about the same time he also began to lose pubic and axillary hair. However, due to a lack of concern, he did not seek help. His other complaints included weight loss of 6 kg over the past year, an intermittent reddish skin rash over his upper body, and a chronic dry cough. He denied polyuria and polydipsia. He had neither headaches nor visual impairment. He did not have any prior head trauma and had not been diagnosed with any systemic illness other than cirrhosis of the liver.

On presentation patient appeared to have normal body habitus and proportion. Height was 161 cm and weight was 55 kg. Blood pressure was low normal in general but was down to 80/48 mmHg on one occasion. Heart rate and body temperature were within normal limits. Patient's face appeared feminized, with fine wrinkling and lack of facial hair (Fig. 1). Visual acuity and visual fields appeared intact, and neurologic examination was grossly normal. Skin was notable for erythematous, annular lesions resembling tinea corporis that involved the neck and upper arms. External genitalia were unambiguously male, although pubic as well as axillary hair was absent.

Serum biochemistry was remarkable for hyponatremia (123 meq/L), hypokalemia (3.0 meq/L), hypoalbuminemia (2.1 g/dL), and elevated liver function indices (AST 120 U/L, ALT 34 U/L, alkaline phosphatase 1070 U/L, and γ -GT 344 U/L). Fasting plasma glucose was 71 mg/dL.

Hematologic findings included normochromic, normocytic anemia (Hb 10.6 g/dL) and eosinophilia (WBC 6,800 / μ L, 15% eosinophils). Patient tested negative for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody.

Preliminary endocrinologic findings were supportive of hypopituitarism (Table 1). Serum FSH and LH were both below detectable limits. Serum testosterone and DHEA-S levels were likewise undetectable. Morning (8 a.m.) serum cortisol was low (0.4 μ g/dL), while the corresponding ACTH level was normal (22.3 pg/mL). Similarly, free thyroxine level was low (0.4 ng/dL) whereas TSH level was normal (1.363 mU/L). Serum prolactin, however, was slightly elevated (24.8 ng/mL). For confirmation of panhypopituitarism, a series of hormonal stimulatory tests were conducted (Tables 2 and 3). Growth hormone deficiency was established via an insulin hypoglycemic test, which at the same time confirmed adrenal insufficiency with a low cortisol response. Similarly, FSH and LH levels responded poorly to LHRH stimulation. Although TSH secretion responded

positively to TRH stimulation, its level continued to rise even at 60 min after TRH administration. In other words, the TSH peak response was delayed. Serum prolactin was slightly elevated even at baseline. However, its response to TRH stimulation was less than expected (stimulated level normally doubles baseline value).

Eventually a pituitary/sellar MRI was obtained, and the cause of hypopituitarism was attributed to a 8×3×9 mm homogeneous, low intensity mass lesion within the pituitary infundibulum. The mass was midline without causing deviation of the pituitary stalk. The pituitary itself was normal in configuration and size. No other mass-like lesions or abnormalities were noted in the hypothalamus and surrounding structures. (Fig. 2)

Patient was consequently begun on hormone replacement. He was given oral cortisone acetate 25 mg in the morning and 12.5 mg in the evening. Levothyroxine was given at a daily dose of 0.05 mg. He also received monthly injections of depot testosterone 250 mg.

Within days after the administration of cortisone, patient developed an abrupt increase in urine output (up to 10 L per day). Diabetes insipidus was subsequently confirmed by a water deprivation test (Fig. 3), and its central origin was established by the prompt response of urine osmolality to the administration of DDAVP. In addition, serial serum ADH levels were all below detectable limit during the test, further confirming the neurogenic origin of DI. Oral desmopressin 0.05 mg daily was therefore added to the treatment regimen.

In an effort to determine the nature of the pituitary infundibular mass, a series of laboratory and imaging tests were conducted. In particular, patient was screened for metastatic disease. However, none of the imaging studies, including chest x-ray, abdominal ultrasonography, chest and abdominal CT

scans, and upper GI endoscopy, reveal evidence of any primary tumor mass. Biopsy of the liver confirmed cirrhotic change without harboring malignant cells. Although a Gallium-67 scan showed questionable uptake in the hilar regions of the lungs, it did not correlate with a normal chest CT scan. Finally, tumor markers including CEA, alpha-fetoprotein, and Ca-199 were all negative. Non-cancerous conditions with possible involvement of the pituitary-hypothalamus were also considered. Granulomatous diseases including tuberculosis, sarcoidosis, and histiocytosis lacked support from clinical findings, laboratory results and imaging studies. A biopsy of the annular skin lesions was performed because of suspicion of cutaneous sarcoidosis. It however revealed only mild inflammatory infiltration without granuloma formation. Hemochromatosis was ruled out by normal iron reserve indices.

It thus appeared that the pituitary infundibular mass was more likely a primary, localized lesion. However, because patient was averse to the suggestion of surgical intervention, we did not pursue a pathologic diagnosis at the time. He was thus conservatively managed with hormone replacement as an outpatient.

One year later a follow-up pituitary MRI was obtained (Fig. 4). The infundibular mass lesion had grown in size to about 2×1×1 cm. It appeared to involve the tuber cinereum of the hypothalamus,

the posterior pituitary, and the optic chiasm (visual field testing did not reveal a definite defect). Patient was strongly urged to undergo surgery. However, as he is still deliberating up to the present, the diagnosis of this mass lesion remains inconclusive.

Discussion

Our patient initially presented with hypopituitarism, with diabetes insipidus becoming apparent later on. Although isolated hypopituitarism and central diabetes insipidus are widely encountered, cases manifesting both conditions concurrently are much rarer despite the anatomic proximity of the anterior and posterior pituitary. Such presentation often suggests involvement of the hypothalamus-pituitary region. Diseases originating in the pituitary itself do not usually cause diabetes insipidus. Pituitary tumors for example, will compromise antidiuretic hormone secretion only if they grow large enough to invade the median eminence and hypothalamus 1. In our particular case, the lesion originated within the pituitary stalk and later expanded into the hypothalamus as well. Stalk abnormalities are known to cause hypothalamic-pituitary dysfunction, presumably due to involvement at the hypothalamic level with or without blocking the hypophyseal portal circulation 2.

The development of diabetes insipidus in our patient therefore did not come as a surprise to us after the MRI located the lesion to the pituitary stalk. Occasionally, the neurohypophysis is able to reorganize itself and preserve secretory function if the stalk is not severed too high above a certain level 3. The

presence of DI in our patient, then, signified a more extensive disruption of the stalk that was sufficient to compromise the secretion of ADH. The observation that his DI appeared only after glucocorticoid replacement was also consistent with the fact that cortisol is required for effective free water clearance from the collecting ducts of the kidney, and therefore adrenal insufficiency is able to mask DI 4.

The endocrinologic tests by themselves also provided indication that the lesion might not be confined to the anterior pituitary. It is well known that TSH level may be normal in hypothyroidism due to hypothalamic-pituitary disease 5, as was observed in our case. Upon TRH stimulation, the patient's TSH level increased, although its peak was delayed. Such pattern favored a hypothalamic rather than a pituitary origin of hypothyroidism 6. Furthermore, the baseline prolactin level was elevated in this patient, suggesting that the hypothalamic inhibition of prolactin secretion might have been interrupted. It therefore lent further support to a supra-pituitary lesion. The positive though subnormal response of prolactin to TRH stimulation was also supportive of a supra-pituitary lesion.

The stimulatory tests otherwise gave unequivocal evidence of growth hormone and gonadotropin deficiency. Although adrenal insufficiency was also established, the serum ACTH level was not suppressed. This was nonetheless compatible with secondary adrenal insufficiency, in which a normal corticotropin concentration is frequently observed despite low cortisol levels 7.

Pituitary stalk enlargement is an uncommon radiologic finding 8. It has been associated with a

variety of conditions including granulomatous, infiltrative, infectious, vascular, and tumoral diseases 9. For our case, the search for an underlying disease with a possible connection to the stalk lesion was unfruitful. Sarcoidosis was initially considered because it is known to have a predilection for the pituitary-hypothalamic system, and diabetes insipidus has been reported in 5-10% of cases of neurosarcoidosis 10. Our patient 掇 chronic cough, eosinophilia, and skin lesions morphologically suspicious for cutaneous sarcoidosis initially appear to be compatible findings for sarcoidosis. However, a skin biopsy revealed no granuloma formation and our patient also lacked the pulmonary, ocular, and other characteristic features of sarcoidosis.

Langerhans cell histiocytosis has been reported to infiltrate the hypothalamo-pituitary axis in 5-50% of autopsied LCH patients. It frequently causes DI as well as anterior pituitary dysfunction 11. However, the disease affects mainly children and is thought to occur very rarely in adults. Moreover, our patient lacked the skin, lung, bone and hematologic involvement that is characteristic of this disease.

Evidence was equally lacking for other infiltrative and inflammatory disorders known to involve the hypothalamus-pituitary region. Tuberculosis was unlikely without pulmonary and other systemic manifestations. Hemochromatosis was ruled out by patient 掇 normal iron reserve. Lymphocytic hypophysitis more commonly occurs in women during pregnancy or postpartum period 12 and, in the absence of such clinical correlation, would have required biopsy for proof in our patient.

Multifocal fibrosclerosis, a very rare cause of concurrent hypopituitarism and central DI, would have shown signs of fibrous disorders occurring at different anatomical sites 13.

Lymphocytic infundibuloneurohypophysitis was first described by Imura et al in 1993. The diagnosis was based on the finding of inflammatory cells in the biopsy specimens of 2 patients in their series who had DI and thickening of the pituitary stalk or enlargement of the neurohypophysis 14. More recently, Sheen et al also reported 3 cases of pituitary stalk enlargement complicated with DI. Although none had histopathologic proof, the authors nonetheless attributed the cause to lymphocytic infundibuloneurohypophysitis on the ground of compatible MRI findings and lack of evidence for other causes 15. The cases described by Imura et al had self-limited disease and the abnormalities disappeared during follow-up 14. Although the stalk abnormalities persisted in Sheen 掇 cases, they did not appear to progress 15. For our patient, it would be tempting to likewise assign the diagnosis of infundibuloneurohypophysitis. However, unlike Imura 掇 and Sheen 掇 cases, our patient 掇 DI was preceded by a more prominent hypopituitarism. Moreover, the progressive enlargement of his stalk lesion would induce us to favor a less benign condition. Metastasis to the pituitary stalk was in fact one of our first considerations. However, a search for a primary tumor elsewhere via imaging studies was unfruitful. Lymphoma and other hematologic malignancies were also unlikely as the imaging studies revealed no abnormalities of lymphoid tissues and the peripheral blood smear was significant only for eosinophilia and mild anemia. It therefore appeared to us that the patient 掇 stalk lesion might possibly be a primary CNS tumor. The list of differential diagnoses would include astrocytoma, meningioma, craniopharyngioma,

dysgerminoma, chordoma, hamartoma, neurofibroma, medulloblastoma, and other benign tumors such as choristoma and myoblastoma 2. Craniopharyngioma was not very likely in this patient as it more often occurs in younger age groups and radiographically appears as a calcified mass in over 80% of cases 16. Germinoma was also unlikely, since the patient's alpha-fetoprotein level was not elevated.

Due to the patient's reluctance to undergo surgical procedures, we agreed to a period of medical management and surveillance during the first year, as we could not rule out the possibility of the stalk lesion being a self-limited, benign condition. Indeed, in addition to Imura's cases of infundibuloneurohypophysitis, there have been other reports of idiopathic stalk enlargement that regressed spontaneously or after a trial of corticosteroid or anti-tuberculous treatment 17. However, as this patient's lesion has actually grown in size, surgical intervention is now warranted.

In conclusion, we reported a case of pituitary infundibular mass lesion with manifestations of hypopituitarism and diabetes insipidus. Although the nature of this lesion cannot be ascertained at present without obtaining a surgical specimen for pathologic diagnosis, we feel this is nonetheless a case of interest to clinicians. In particular, it demonstrated how the various endocrinologic derangements observed in this patient can be referable to a single anatomic lesion. Moreover, the endocrinologic studies illustrated how the location of the lesion might be speculated on the basis of the observed hormonal pattern. Finally, this case presented a diagnostic challenge whereby various systemic as well as localized, and malignant as well as non-malignant conditions must be considered in its differential diagnosis.

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下視丘-腦垂體莖腫瘤併發垂體機能不足
及尿崩症——病例報告

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摘 要

病患為五十歲男性肝硬化病人患有性功能喪失五年。理學檢查發現生殖腺功能低下之徵狀包括陰毛、腋毛缺乏及面貌女性化。亦發現有低血壓、低血鈉及嗜伊紅血球偏高。初步內分泌學檢驗顯示血液 FSH, LH, testosterone 及 DHEA-S 均測不到而 prolactin 上升。早晨 cortisol 及甲狀腺素血液濃度皆偏低。腦垂體機能不足隨後以 GnRH 刺激試驗及胰島素低血糖試驗證實。病患於是給予甲狀腺素、皮質醇及睪固酮補充治療。然而在給予皮質醇後病人尿量大量增加。因而以限水測試及 desmopressin 反應診斷為中樞尿崩症。磁振攝影顯示一 8x3x9 mm 腫瘤位於腦垂體莖，為病患之內分泌機能異常病因。病患選擇以荷爾蒙補充保守治療。然而一年後追蹤磁振攝影顯示垂體莖腫瘤明顯擴大為 2x1x1 cm 並侵入下視丘及後腦垂體。垂體莖腫瘤尚未有病理診斷。鑑別診斷包含肉芽腫疾病、滲入性疾病、感染、血管病變、及原發或轉移性腫瘤。腦垂體機能不足同時合併尿崩症較可能源自下視丘-腦垂體部位之病灶。局限於前腦垂體之病灶甚少併發尿崩症。垂體莖病灶之起因涵蓋惡性及良性、局部及系統性疾病；鑑別診斷均須考量。

Table 1. Initial hormonal profile (normal ranges)

FSH	< 0.3	U/L	(1.4-18.1)
LH	< 0.5	U/L	(1.5-9.3)
Prolactin	24.8	ng/mL	(1.61-18.77)
Testosterone	0.00	ng/mL	(2.86-15.0)
DHEA-S	0.0	µg/dL	(80-560)
Cortisol (8 a.m.)	0.4	µg/dL	(5-20)
ACTH	22.3	pg/mL	(9-46)
TSH	1.363	mU/L	(0.35-5.5)
Free T4	0.4	ng/dL	(0.8-2.0)
T3	0.9	ng/mL	(0.8-2.0)

Table 2. Combined Insulin Tolerance and TRH Test

Time (min)	0	20	30	60	90
Glucose (mg/dL)	71		39	31	68
GH (ng/mL)	0.14		0.40	0.51	0.52
Cortisol (µg/dL)	2.4		1.7	3.7	4.0
TSH (mU/L)	2.422	11.721	14.036	16.570	
Prolactin (ng/mL)	32.4	43.2	48.2	44.7	

*Regular insulin 8 U and TRH 200 µg given intravenously at 0 min.

*Patient primed with depot testosterone 250 mg 20 days before test.

Table 3. LHRH Stimulation Test

Time (min)	0	15	30	45	60
FSH (U/L)	< 0.3	< 0.3	0.4	0.5	< 0.3
LH (U/L)	< 0.5	< 0.5	< 0.5	< 0.5	< 0.5

*Gonadorelin 100 µg given intravenously at 0 min.

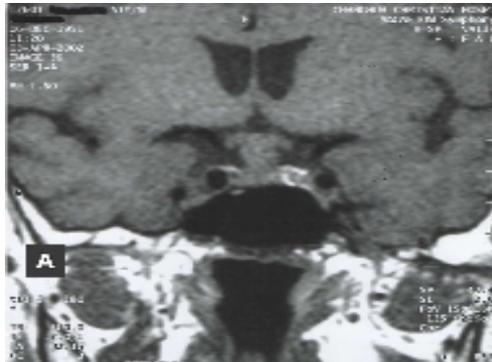


Figure 1. Patient's outward appearance on initial visit.

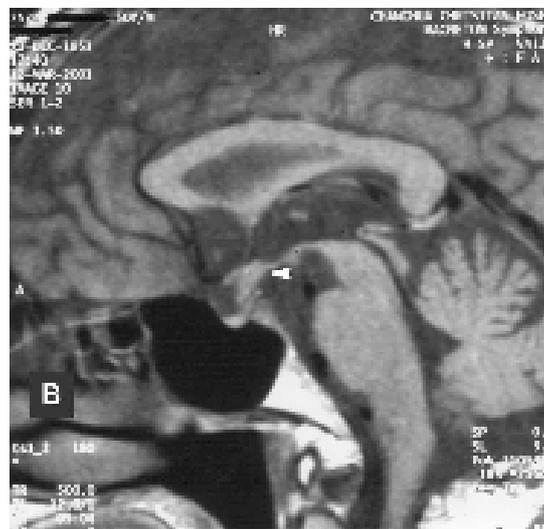
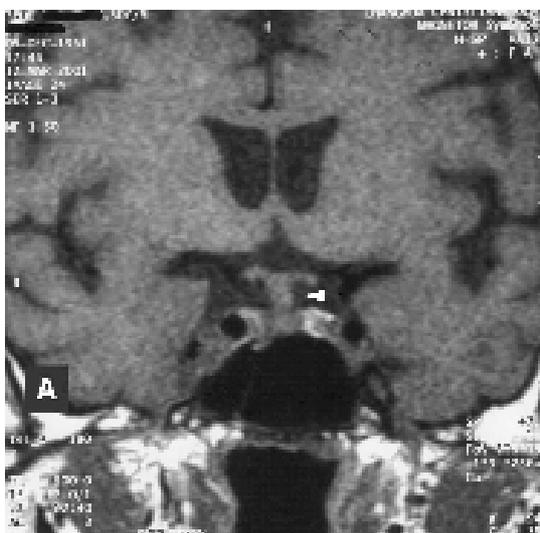


Figure 2. Initial MRI of the pituitary. Note mass lesion resulting in enlargement of the pituitary stalk (arrows).

Figure 3. Water deprivation test:

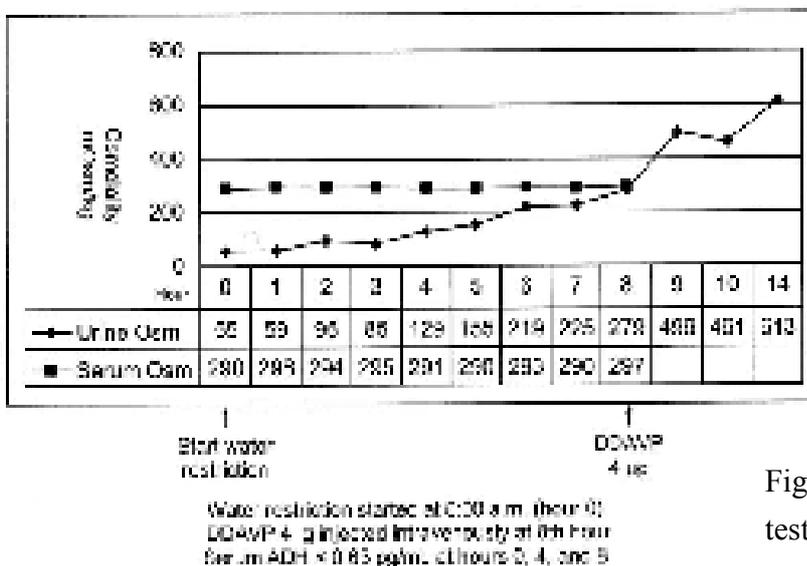


Figure 3. Water deprivation test

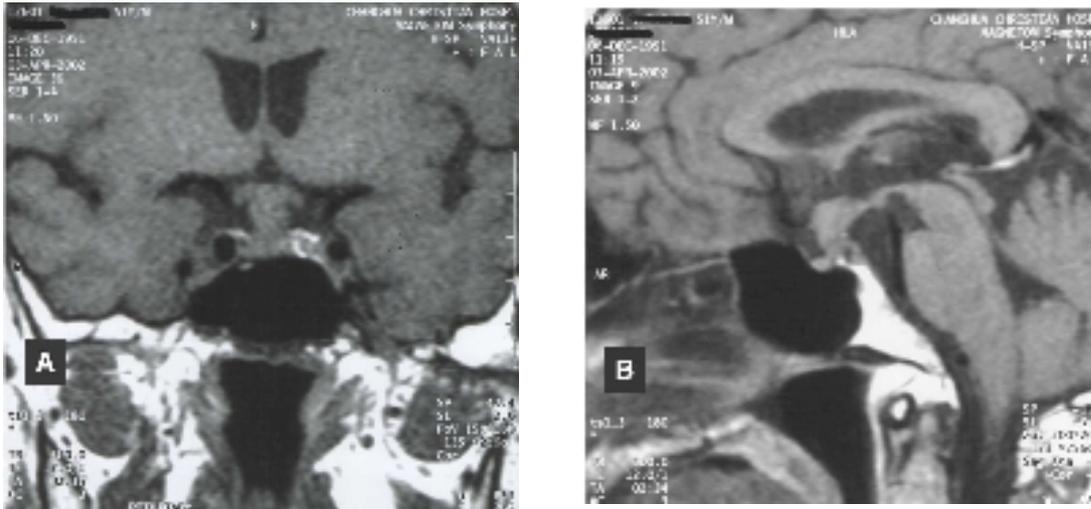


Figure 4. MRI of the pituitary one year later. The stalk lesion has appreciably enlarged. It involved the tuber cinereum of the hypothalamus as well as the posterior pituitary.