Case Report

Masked Cushing's Disease in an Aged Man Associated with Intraventricular Hemorrhage and Tuberculous Peritonitis

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A 77-year-old man complained of headache, dizziness and tactile hallucination. Based on those clinical signs and the findings of computed tomography scanning and magnetic resonance imaging, he was diagnosed as having pituitary adenoma. Clinical signs and symptoms of Cushing's disease had not been apparent because of the occurrence of the disease at an old age. An increase in serum cortisol and adrenocorticotrophic hormone indicated the presence of Cushing's disease. Physical findings obtained thereafter were also compatible with the disease. While the patient was being prepared for surgery, pituitary apoplexy and intraventricular hemorrhage occurred. Massive ascites appeared as a result of tuberculous peritonitis. In spite of treatment for these complications, his general condition progressively deteriorated and he died 39 days after the intraventricular hemorrhage. This case presents the difficulty in the treatment of masked Cushing's disease in the elderly population.

Key words: Macroadenoma, Pituitary apoplexy, Adenosine deaminase (ADA), Adrenocorticotrophic hormone (ACTH), Cortisol

Many of the signs and symptoms of Cushing's disease result from the action of adrenocorticotrophic hormone (ACTH) and glucocorticoids after it runs a long course. The disease affects middle-aged women and men; it presents full-blown signs and symptoms and usually takes the form of microadenoma. However, when it affects an older person, the signs and symptoms are often masked. This leads to growth of the adenoma resulting in macroadenoma. In this report, we describe an elderly man with masked Cushing's disease due to macroadenoma running a relatively rapid course. He showed rare complications, for example, pituitary apoplexy resulting in intraventricular hemorrhage and tuberculous peritonitis. The diagnosis was established by endocrinological examination and by characteristic pictures in computed tomography (CT) and magnetic resonance imaging (MRI).

METHODS

Total protein, albumin, bilirubin, creatinine, urea nitrogen, fasting blood glucose (FBS), sodium (Na), potassium (K), chloride (Cl), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and aminoacid γ -glutamyltransferase (γ -GTP) in serum were measured by a Hitachi-736 auto-analyzer. 17-Hydroxycorticosteroid (17-OHCS) was measured as Porter-Silber chromogen and 17-ketosteroid (17-KS) was measured by the Zimmerman reaction in Kitazato Biochemical Laboratories (Tokyo, Japan). Serum cortisol was measured with radioimmunoassay kits (Spac-cortisol II) purchased from Dai-ichi Radioisotope Laboratories (Tokyo, Japan). Urinary free cortisol was measured with the same kits after extraction of urine sample with dichloromethane. Serum ACTH was measured by

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two-site immunoradiometric assay (IRMA) with kits (ACTH-IRMA-SRL) purchased from Special Reference Laboratories (Tokyo, Japan). Serum concentration of growth hormone (GH) was measured by IRMA kits purchased from Eiken Immunochemical Laboratories (Tokyo, Japan), thyroid stimulating hormone (TSH) by highly sensitive IRMA, and luteinizing hormone (LH) and follicle stimulating hormone (FSH) with IRMA kits from Dai-ichi Radioisotope Laboratories.

CASE REPORT

A 77-year-old man was admitted to the Division of Neurosurgery of Toranomon Hospital on June 27, 1988, for evaluation of a pituitary tumor. The patient was diagnosed as having hypertension and labyrinthine deafness in 1985, and diabetes mellitus and senile cataract in 1988. All of these were of a mild degree and no medication was necessary. There was a history of pulmonary tuberculosis in his youth. He occasionally complained of headache, dizziness and tactile hallucination since 1985, but neurological and otorhinolaryngological examination revealed no abnormal findings. In April 1988, as his complaints increased, his doctor suspected that his condition was due to a chronic subdural hemorrhage and referred him to neurosurgeons. His CT film showed a round, homogeneous high-density area corresponding to the sella turcica in a plain scan (Fig. 1). It also showed a triangular high-density area in the intrasellar to suprasellar region in a coronal scan (Fig. 2). As the findings suggested a pituitary tumor, the patient was hospitalized for further evaluation.

On physical examination he presented no typical Cushingoid features. His consciousness was clear, but he was aggressive, uncooperative and incomprehensible. The pulse was 96/min, and regular, and the blood pressure was 120/80 mmHg. The head was normal. Although there was a slight tendency toward a "moon" face, neither trunkal obesity nor striae cutis rubra was found. Mobilization of peripheral supportive tissue, subcutaneous bleeding in the extremities, atrophic muscle and skin, and generalized muscle weakness were noted. No edema was observed. Neurologic examination was negative. The lungs were clear, and the heart was normal. Abdominal examination was normal. The chest X-ray film was normal except for considerable

Fig. 1. Brain CT film, taken on admission, showing a round, homogeneous high-density area corresponding to the sella turcica in a plain scan.

Fig. 2. Brain CT film, taken on admission, showing a triangular high-density area in the intrasellar to suprasellar region in a coronal scan.

osteoporosis in the vertebrae in the lateral view. The ocular fundus was normal. Hemianopsia was not present.

The laboratory findings were: white cell count 6,700/mm³ with a differential count of 3% stab form neutrophils, 88% segmented neutrophils, 0% eosinophils, 0% basophils, 1% monocytes and 8% lymphocytes, hemoglobin 10.5 g/dl, platelet count 159,000/mm³, erythrocyte sedimentation rate 16 mm/h, C reactive protein +1, serum protein 49 g/l, albumin 391.3 μ M (2.7 g/dl), total bilirubin 10.3 μ M/l (0.6 mg/dl), creatinine 97.3 μ M/l (1.1 mg/dl), FBS 102 mg/dl, hemoglobin A₁ 9.6%, Na 144 mM/l, K 3.0 mM/l, Cl 98 mM/l, ASA 5.3 IU/l, ALA 4.8 IU/l, LDH 304 IU/l, ALP 29.8 U/l, γ -GTP 41.8 IU/l. The coagulation function was normal. Repeated examinations of urine were normal. The results of endocrinological examination were as follows: urinary 17-OHCS excretion 23.4 mg/day, 17-KS 11.6 mg/day, and urinary free cortisol 36.7 μ M/day (1,330 μ g/day). Plasma ACTH levels ranged from 52 to 61.6 pM/l (234 to 277 pg/ml), and in the presence of serum cortisol, from 0.81 to 0.92 μ M/l (29.5 to 33.2 μ g/dl). Diurnal variation of both cortisol and ACTH disappeared. The corticotropin releasing factor (CRF) loading test (CRF 22 nM = 100 μ g iv) showed no response of ACTH and cortisol. The basal values of all pituitary hormones were low, as shown in Table 1. The simultaneous loading test for three tropic hormones [thyrotropin releasing hormone (TRH) 1.25 μ M (500

μ g), luteinizing hormone releasing hormone (LH-RH) 76.8 nM (100 μ g), and insulin 5 unit iv] also showed no response of TSH, prolactin, LH, FSH, GH, ACTH or cortisol. Serum thyroid hormone levels were normal except for a low value of thyroxine binding globulin (9.4 mg/dl). The MRI film of the head showed an expansive mass lesion in the sella turcica (Fig. 3). As it compressed the hypothalamus upward, the space of the third ventricle was narrowed and the tumor protruded into the sphenoidal sinus.

Based on the above findings, we diagnosed his illness as Cushing's disease with macroadenoma and scheduled him for transsphenoidal surgery. However, he became delirious and abdominal distention became obvious progressively; "frog abdomen" was demonstrated as a result of massive ascites. His general condition deteriorated rapidly. He was transferred to the Division of Endocrinology on November 1, 1988. The chest X-ray film showed pleural effusion on the right. As the ascites progressively increased, abdominal paracentesis was performed several times. The features of the fluid were those of a transudate with high levels of adenosine deaminase (ADA), between 67.4 IU/l and 59.1 IU/l, exceeding the normal range. A tentative diagnosis of tuberculous peritonitis was made and an ascitic fluid sample was cultured for tubercle

Table 1. Endocrinological findings

Diurnal variation of ACTH and cortisol		8°	11°	15°	23°		
ACTH (pM/l)		61.6	54.9	56.0	52.0		
Cortisol (μM/l)		0.92	0.81	0.92	0.88		
CRF 21.4 nM iv	0′	15′	30′	45′	60′	90′	120′
ACTH (pM/l)	61.8	68.0	69.3	85.1	82.0	76.7	74.9
Cortisol (μM/l)	1.04	1.10	1.08	1.19	1.12	1.18	1.17
TRH 0.8 μM, LH-RH 76.8 nM, insulin 5 U iv		0′	30′	60′	90′	120′	
TSH (mU/l)		0.31	1.08	1.10	0.96	0.93	
PRL (nM/l)		1.2	2.7	2.4	1.9	1.7	
LH (IU/l)		5.3	27.2	27.6	22.8	23.9	
FSH (IU/l)		4.8	13.6	13.8	14.8	15.8	
GH (pM/l)		13.6	77.3	50.0	36.4	22.7

Fig. 3. Brain MRI film, taken on admission, showing an expansive mass lesion in the sella turcica.

Fig. 4. Brain CT film reveals staining in the pituitary in a plain scan probably due to apoplexy and intraventricular hemorrhage.

bacilli. Based on these findings he received anti-tuberculous drugs but these were temporarily withheld because of paralytic ileus and gastrointestinal bleeding. On November 20, his consciousness suddenly fell into III-300 (III-3 method). On neurological examination no remarkable changes were noted. The plain CT film revealed staining in the pituitary due probably to apoplexy and intraventricular hemorrhage (Fig. 4). Transiently he suffered from diabetes insipidus, polyuria and a decrease in urine specific gravity and urine osmolality. Soon a decreased level of ADH in the blood was noted.

The levels of ACTH and cortisol remained high. Thereafter, pulmonary edema, and impaired function of the liver and kidney appeared as the cardiac myopathy with arrhythmia progressed. Left spontaneous pneumothorax and pneumonia appeared as complications. Impaction of mucous sputum in the respiratory tract led to respiratory arrest. Despite rapidly instituted treatment he died on December 28. Numerous colonies of mycobacterium appeared in the cultures of ascitic fluid at 4 wk.

DISCUSSION

Cushing's disease usually occurs in middle age adults. The natural course of the disease is slowly progressive for over 10 yr and presents typical signs and symptoms. The disease is due to pituitary microadenoma in the majority of cases. But the present patient did not show signs or symptoms of Cushing's disease until macroadenoma was incidentally detected by the CT scan which was originally intended for his psychological symptoms. The course of his disease progressed rapidly as a result of the macroadenoma, and the symptoms included pituitary apoplexy and intraventricular hemorrhage. Glucocorticoid excess was probably responsible for the tuberculous peritonitis. This patient also showed an atypical response to CRF. Although the CRF-loading test shows an exaggerated response in 80% of the cases of Cushing's disease with microadenoma (1), no response was observed in this case.

The frequency of pituitary apoplexy varies from 1.5% to 27.7% according to the literature (2-6). In Japan, the incidence has been reported to be 9.1% (7) is in agreement with the report of Lopez (3).

Pituitary apoplexy can arise from a tumor of any size (7). The trigger varies, but the cause in most cases remains unknown (8–13). Wakai et al (7) stated that pituitary apoplexy is related to neither gender, hormonal function of the adenoma nor histological type, but it is related to age. Elderly people more frequently have pituitary apoplexy. However, regarding gender, Lopez (3) and Wright et al (14) reported that pituitary apoplexy occurs more frequently in males than females. The relationship of hormonal function of adenomas to pituitary apoplexy remains controversial. A higher incidence of pituitary apoplexy in patients with GH-producing tumors (13) and in ACTH-secreting tumors has been reported (15). A report contrary to the latter has also been published (7). It is not rare for pituitary apoplexy to result in spontaneous subarachnoid hemorrhage. In the present case intraventricular hemorrhage was observed. Direct rupture of the surface vessel of the tumor into the ventricle is the most likely explanation. As aneurysms of the cerebral arteries frequently coexist with Cushing's disease (7.4%) (16), the possible rupture of an occult aneurysm can not be ruled out in this patient. In an elderly patient, it is possible that symptoms of Cushing's disease are masked and remain occult, leading to a delay in the diagnosis of Cushing's disease. In a society in which the population of aged people is increasing, the so called "masked Cushing's disease" must be suspected for persons with a slight mental abnormality and signs and symptoms of pituitary adenoma.

Rapidly progressive massive ascites due to tuberculous peritonitis was observed in this patient. Although it is not rare to observe miliary tuberculosis in Cushing's disease, association of tuberculous peritonitis with Cushing's disease was so rare that no case report was found within the range in our literature search. As previously stated, tuberculous peritonitis could be detected by measuring ADA in the ascitic fluid. It has been reported that if the ADA level of the pleural fluid is greater than 50 U/l, tuberculous pleuritis is strongly suggested. The diagnostic significance of ADA in ascitic fluid has not been clearly established for tuberculous peritonitis. Measurement of ascitic ADA may offer an important clue to the diagnosis of tuberculous peritonitis as demonstrated in the present case.

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