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Mood Disorder due to Nonfunctioning Pituitary Adenoma with a Major Depressive-like Episode in a Postmenopausal Woman

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Pituitary adenomas (PA) account for up to 15% of primary intracranial neoplasms and are usually benign tumors occurring in the sella turcica of the brain. PA can be neurologically silent initially and present with only affective disorders such as a major depressive or bipolar disorder. Among the different types of PA, emotional disorders are relatively uncommon in nonfunctioning PA, possibly because they have less influence on endogenous hormone levels. Here, we report a postmenopausal woman who initially presented with a major depressive episode and was subsequently found to have a nonfunctioning pituitary adenoma. Some features of the presentation, such as atypical headaches, an irregular sleep-wake pattern, transient diplopia and inappropriately low levels of gonadotropins, suggested that her major depressive episode was caused by a nonfunctioning pituitary adenoma. Finally, a clinical diagnosis of mood disorder due to nonfunctioning pituitary adenoma with major depressive-like episode was made. Our case suggests that patients in a psychiatric setting may present with a general medical condition, and the finding in this case may have implications for a better understanding of the pathophysiological role of depression associated with medical illness. This case highlights the importance of neuroimaging studies and the need to raise awareness of transient diplopia presented in a postmenopausal woman with her first major depressive episode.

Key words: pituitary adenoma, depressive disorder, diplopia, estrogen, mirtazapine

INTRODUCTION

Pituitary adenomas (PA) account for up to 15% of primary intracranial neoplasms and are usually benign tumors occurring in the sella turcica of the brain[1]. PA can be neurologically initially silent and present with only affective disorders such as a major depressive disorder[2] or a bipolar disorder[3]. Endocrine disturbances related to PA are considered to contribute to affective disorders, a view that is supported by studies demonstrating alterations in components of hypothalamic-pituitary-end organ axes[4]. Adynamia, which means weakness and fatigability, is a physiological disturbance associated with depressed mood that can be caused by hypogonadism, hypothyroidism or hypocortisolism in patients with PA accompanied by hypopituitarism[5]. Depression is also implicated in the excess production of adrenocorticotropic hormone (ACTH)[6], growth hormone (GH)[7] and prolactin-producing PA[8]. Because PA may be a secondary cause of depressive disorder, it must always be considered in patients presenting with features atypical of primary idiopathic depressive disorders. Nonfunctioning PA represents about a quarter of pituitary tumors occurring in middle or old age[9] and has not generally been associated with emotional disorders, perhaps because these tumors have little influence on endogenous hormone levels[10]. We report a postmenopausal woman who initially presented with a major depressive disorder and was subsequently found to have a nonfunctioning pituitary adenoma.

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CASE REPORT

Our patient, a 60-year-old postmenopausal woman, was relatively healthy and without a major medical or surgical history. She experienced the transition from perimenopause into menopause when she was 58 years old. The subject reported normal development milestones and had no previous history of psychiatric disorder, alcohol or illicit substance abuse. Her difficulties in sleep onset, waking at the desired time and cluster-like atypical headaches began

in June 2005. These problems had a gradual impact on her daily activities. She has taken zolpidem (10 mg) at bedtime to help falling asleep since 2005, but her sleep quality was never satisfactory. In November 2005, her first major depressive episode began, without any adverse life event or psychosocial stressor. She experienced typical melancholic depressive symptoms, including sadness, loss of pleasure, fatigue, low self-esteem, negative thinking, poor appetite, body weight loss of 4 kg in one month, inability to concentrate, frequent forgetfulness, anhedonia, decreased libido, insomnia, social withdrawal and gradual impairment of her normal ability to function. She believed that her thinking processes slowed and she was not as quick to grasp new ideas as before, because she previously had an excellent memory and never needed a reminder book of any kind, before these symptoms. She stated that she did not have the motivation to adequately take care of her home, do her normal household chores, or have the enthusiasm to interact with her husband or other family members. These depressive symptoms continued, and by March 2006, she had developed intense suicidal and paranoid ideas. Immediately after her depressive symptoms began to worsen, she suddenly noted binocular horizontal diplopia with restrictions in elevation and adduction. This occurred on March 22, 2006, and lasted continuously for three days. On March 25, 2006, diplopia was replaced by mild blurred vision. Negative findings were reported in consecutive visual acuity tests, visual field examination and funduscopy performed by ophthalmological specialists in two clinics and one medical center, respectively. She was admitted to our psychiatric inpatient unit on April 12, 2006, because of her severe depressive symptoms and high suicidal risk.

Physical examinations and laboratory tests on admission included complete blood counts with differential counts, a panel of metabolic tests, a liver function test, and urinalysis. All were unremarkable. A Mini-Mental State Examination showed normal cognitive function. On admission, her score on the Hamilton Rating Scale for Depression (HAM-D, 21 items) was 29. She was treated with the antidepressant of mirtazapine (30 mg/day) and two hypnotics, including estazolam (2 mg/day) and zolpidem (10 mg/day) from the start of her hospitalization. Visual acuity was 6/10 in each eye and visual fields were full. She insisted that she would become totally blind even if the results of ophthalmological examination were all negative. In view of her subjective perception of blurred vision in both eyes, magnetic resonance imaging (MRI) of the brain was arranged. An intrasellar pituitary adenoma measuring 1.3 cm was found, with compression and rightward displacement of the adenohypophysis (Fig. 1). Endocrinological tests were performed to determine the nature of pituitary adenoma. Thyroid function, including T3, free T4 and thyroid stimulating hormone, were normal. The follicle-stimulating hormone (FSH) level was 11.17 mIU/ml (reference range for postmenopausal patients, 40-160 mIU/ml). The luteinizing hormone (LH) level was 3.8 mIU/ml (reference range for postmenopausal patients, 6-30 mIU/ml). The estradiol level was less than 0.1 pg/ml (reference range for postmenopausal patients, 13-93 pg/ml). FSH and LH were inappropriately low in the presence of a very low estradiol level. Levels of prolactin, human growth hormone, ACTH, and cortisol were all within normal ranges.

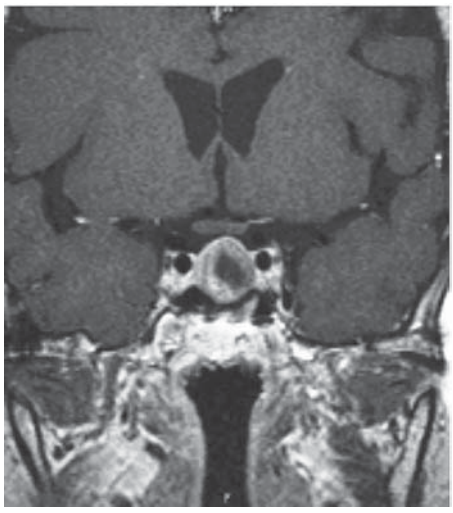

Fig. 1 Magnetic resonance imaging (MRI) of the brain showed an intrasellar pituitary adenoma measuring 1.3 cm, with compression and rightward displacement of the adenohypophysis (arrow).

The patient continued to receive the antidepressant therapy for her depressive disorder. Despite some initial side effects, including dry mouth and sedation, the subject was able to tolerate the antidepressant treatment with a gradual improvement in her mood. The conservative treatment strategy for her nonfunctioning pituitary adenoma was a follow-up scan at six months, then one yearly for two years, and subsequently one scan every 2-5 years if the tumor remained asymptomatic or stopped growing. She was discharged on April 20, 2006, and her HAM-D score was 21 on discharge. Her depressive symptoms resolved dramatically on May 19, 2006, and her HAM-D score was 4. This was a complete remission of her major depressive episode. She has remained euthymic and is able to shop, care for her family, and attend to the details of her household chores.

DISCUSSION

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria[11], the diagnosis of major depressive disorder cannot be made when mood symptoms are due to the direct physiological effects of a substance (e. g., a drug of abuse, a medication, or other treatment) or a general medical condition such as hyperthyroidism. If there is evidence from the history, physical examination, or laboratory findings that the mood disturbance is the direct physiological consequence of a general medical condition, the diagnosis of mood disorder due to a general medical condition should be made. In addition, if the mood symptoms meet the full criteria of a major depressive episode, the specific type of "with major depressive-like episode" should be added. Our subject initially presented with the symptoms that met the DSM-IV-TR criteria for a primary major depressive disorder, but five months later was found to have a nonfunctioning pituitary adenoma with compression of the adenohypophysis. We made our final clinical diagnosis of mood disorder due to the tumor with a major depressive-like episode for the following reasons.

We believe that a temporal connection existed between nonfunctioning pituitary adenoma and major depressive episode, and this suggested a causal relationship between the two disorders. A number of clinical features, including atypical headaches, the irregular sleep-wake pattern and insomnia, appeared before the depressive symptoms, indicating that the pituitary adenoma occurred before the depression. This presentation agreed with the previous reports that associated cluster-like atypical headaches[12] and the dysregulation of circadian rhythms[13] with pituitary adenoma. Second, the appearance of visual dysfunction that was related to the pituitary adenoma apparently signaled the exacerbating severity of her depression. The subject developed transient, binocular horizontal diplopia, one of the clinical features of cranial nerve III dysfunction, immediately after her depressive symptoms worsened. She has not reported diplopia after the remission of her depression. A reciprocal relationship appears to exist between the two disorders in our subject. The third reason why we believe there is a causal relationship lies in the hormone data. The subject was in early postmenopause for two years, and her endogenous estrogen level declined gradually as pituitary FSH and LH levels increased. She had inappropriately low levels of FSH and LH in the presence of an extremely low estradiol level. Although normal aging can be associated with progressive decline of gonadotropin secretion in healthy postmenopausal women, some patients with nonfunctioning pituitary adenoma show levels of gonadotropin far lower than healthy controls aged 50-80 years. This suggests a high sensitivity and specificity of gonadotropin measurements for the diagnosis of a nonfunctioning pituitary adenoma[9]. The decreased levels of gonadotropin accompanied by suppression of the positive feedback response to low estrogen level in our subject may be directly related to the nonfunctioning pituitary adenoma that subsequently caused the accelerating decline of endogenous estrogen in this postmenopausal woman. Estrogen was been implicated in the pathophysiology of major depressive disorders through the influence on neurotransmitter-mediated systems[14] and the inhibition of monoamine oxidase activity[15]. Mounting evidence indicates that sudden estrogen withdrawal, fluctuating levels, and sustained deficit may induce depressive disorders in estrogen-sensitive women[16]. Our subject's illness suggested that the influence of nonfunctioning pituitary adenoma on the gonadotropin levels may indirectly affect the modulating effect of estrogen on the neurotransmitter system involved in mood disorders and precipitate the development of a major depressive episode. Fourth, in contrast to primary major depressive disorders, the mood symptoms in patients with a mood disorder due to a general medical condition do not improve until the general medical condition is removed or controlled. Although the development of the major depressive episode in our subject may be implicated in accelerating decline of endogenous estrogen level caused by the nonfunctioning pituitary adenoma, the subject was successfully treated with the antidepressant mirtazapine without removing the tumor or estrogen therapy. This clinical evidence may appear to be contrary to the diagnosis of a mood disorder due to a nonfunctioning pituitary adenoma. However, a few possible mechanisms may explain the outcome of the treatment. The efficacy of mirtazapine is well-documented for the treatment of sleep problems, circadian rhythm disturbance and depression[17], and therefore would help to alleviate the symptoms associated with the nonfunctioning pituitary adenoma in our subject. Mirtazapine belongs to the serotoninergic antidepressants, which appear to be potent in reducing inflammatory edema. Therefore, this drug perhaps would lessen the effect of any local inflammation due to the nonfunctioning pituitary adenoma. Mirtazapine was chosen instead of estrogen therapy because estrogen is considered ineffective for depression in postmenopausal women[18]. Although a major depressive disorder and a nonfunctioning pituitary adenoma may coexist independently, the probability that the major depressive episode in our subject was

due to the nonfunctioning pituitary adenoma seems to be high from these observations.

Transient binocular horizontal diplopia consistent with cranial nerve III dysfunction was observed in our subject. Diplopia is a relatively uncommon manifestation of pituitary tumors, with the prevalence ranging from 1% to 14%. It usually occurs consequent to isolated third, sixth or more rarely fourth nerve palsies. Cranial nerve III is the most frequently affected ocular motor nerve, and the possible mechanisms to explain the preference of third nerve involvement included pressure transmitted to the cavernous sinus by the growing tumor and compression of the third nerve between the tumor and the interclinoid ligament[19]. Brief episodes of diplopia related to third-nerve dysfunction may occur with third-nerve compression, ischemia[20], or alterations of intracranial pressure[21]. Spontaneously, transient and recurrent diplopia related to third-nerved palsies may also occur in the otherwise normal individuals, but the attacks are seldom bilateral or last more than four hours[22]. The diplopia in our subject that lasted for three days was therefore highly suggestive of an intracranial lesion. We believe that the presence of transient diplopia is an important clinical feature that should not be neglected.

Our patient was a postmenopausal woman experiencing her first major depressive episode. In addition to the pathophysiological approach to treating her depression, she also received interdisciplinary screening tests for psychosocial factors related to depression. The expression by menopausal women of the "empty nest syndrome" (when children leave home) was extensively used to characterize the psychosocial origin of depressive symptoms manifesting during the menopausal transition[23]. Given the effect of psychosocial factors on the risk of developing depressive symptoms in some postmenopausal women, the clinical pathway involving both psychosocial screening and pathophysiological approach appears warranted in every postmenopausal woman experiencing her first major depressive episode.

In conclusion, we describe a patient whose nonfunctioning pituitary adenoma was detected at her first presentation to mental health services for severe depressive symptoms and high suicidal risk. The finding in this case may have implications for a better understanding of the pathophysiological role of depression associated with medical illness. This case highlights the need to raise the awareness of transient diplopia in a postmenopausal woman with a major depressive episode, and the need to consider the possibility of a nonfunctioning pituitary adenoma. We also emphasize the need for neuroimaging studies when a pituitary adenoma is suspected in a postmenopausal woman experiencing her first major depressive episode.

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