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An unusual case of hypopituitarism associated with non-small cell lung cancer

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Summary. *Background:* Non-small cell lung cancer (NSCLC) is the most common cause of cancer-related death which can present with various clinical situations. Hypopituitarism when encountered with NSCLC may be due to diverse etiologies including pituitary metastasis, hypophysitis, pituitary infarction or a consequence of therapeutical interventions such as surgery or radiotherapy. *Result:* We present an unusual case of hypopituitarism in a NSCLC patient associated with a benign disorder, a sinus mucocele and thereby review the pathogenesis of hypopituitarism accompanying malignant diseases. *Conclusion:* Our case represents an example of association of a benign disorder with malignancy causing severe deterioration of life quality. Although rare, pituitary metastasis is the initial possible diagnosis in the setting of non-small cell lung cancer.

Key words: hypopituitarism, metastasis, non-small cell lung cancer, pituitary, sinus mucocele

Introduction

Hypopituitarism is defined as the deficient secretion of pituitary hormones due to the diseases of hypophysis and hypothalamus or other structures in the neighbourhood through various mechanisms. Non-small cell lung cancer is the most common cause of cancer-related death which has the potential to develop metastasis during its evolution and emerge with diverse clinical presentations according to the site of metastasis (1). Symptoms such as fatigue, emesis and vomiting may be encountered anytime during the course of disease and may be the sole presentation of hypopituitarism. Pituitary adenomas, infarction, surgery or radiotherapy might cause hypopituitarism. Although rare, pituitary metastasis is one of the causes of pituitary hormone deficiency in the setting of malignancy. The most common presenting symptoms in patients with pituitary metastases are diabetes insipidus (DI) and oculomotor nerve palsies (2). Although visual loss and anterior pituitary insufficiency is a common finding for pituitary adenoma these symptoms are less frequently encountered with pituitary metastasis. Here we report an unusual case of hypopituitarism resulting from a sphenoid sinus mucocele in a patient with locally advanced non-small cell lung cancer and review the etiology of hypopituitarism associated with malignant diseaases.

Case report

A 63-year old men was admitted to our hospital in May 2013 with complaints of cough and fatigue. His chest computed tomography scan revealed a peripheric 3.5x4 cm mass at left upper lobe and multiple mediastinal lymph nodes with 2 cm largest diameter. Since broncoscopic evaluation and broncoalveolar lav-

age did not reveal malignancy, mediastinoscopy was performed. Mediastinoscopic biopsy of the lymph node revealed adenocarcinoma metastasis. The patient was informed about the possible treatment modalities including chemotherapy and radiotherapy, but he refused to receive any type of oncological treatment. Six months after the diagnosis of locally advanced non-small cell lung cancer, the patient was admitted to the emergency department with severe headache, emesis and vomiting. On admission he was conscious and oriented with arterial blood pressure 90/60 mm Hg and heart rate 76 beats/minute. He had no visual field impairment. There was no sign of focal neurological deficit and the other system examinations were normal. His complete blood count and biochemistry tests were normal except for mild hyponatremia (Na: 131 meq/L) and hyperkalemia (5.4 meq/L). Cranial magnetic resonance imaging (MRI) showed subcortical ischemic gliotic foci predominating at bilateral frontal lobes. In order to exclude adrenocortical insufficiency that might have caused hyponatremia and hyperkalemia cortisol levels were evaluated. Basal cortisol levels were suppressed (2.5 µg/dL). Thyroid function tests also pointed to secondary hypothyroidism due to hypopituitarism (free T3: 1.5 pg/mL, normal range: 1.7-3.7 pg/mL, free T4: 0.7 ng/dL; normal range: 0.7-1.48 ng/dL, TSH: 0.17 mIU/mL; normal range: 0.3-4 mIU/mL). Other anterior pituitary hormones were also supressed (FSH: 0.1 mIU/mL, LH: 0.1 mIU/mL, ACTH: <5 pg/mL). Free testosterone levels were low (15 pg/mL; normal range: 20-50 pg/mL) and prolactin was within normal limits (22 ng/mL; normal range: 10-25 ng/mL). Subsequent MRI of sella demonstrated a lesion originating from sphenoid sinüs which caused an erosion at clivus and expansion in sella turcica with extension to bilateral cavernous sinuses (Fig. 1). The lesion was hyperintense on T2-weighted images and showed contrast enchancement after gadolinium infusion. Pituitary gland exhibited heterogeneous contrast enchancement pattern without obvius sign of glandular metastasis. Radiologically the lesion originating from sphenoid sinus was evaluated as a sinus mucocele and it was supposed to cause hypopituitarism through expansion of sella turcica and pressure exertion on pituitary cells. The patient was administered thyroid hormone and steroid replacement treatment with L-thyroxine 50 mcg and prednisolon 5 mg daily, respectively, until subsequent evaluation. The patient's complaints regarding emesis and fatigue improved after hormone replacement therapy. Endoscopic spheniodotomy and drainage of the sinus mucocele was offered. However he declined further interventional and oncological treatment and was lost to follow up. The patient died of respiratory complications as a result of the lung disease involvement in January, 2014.

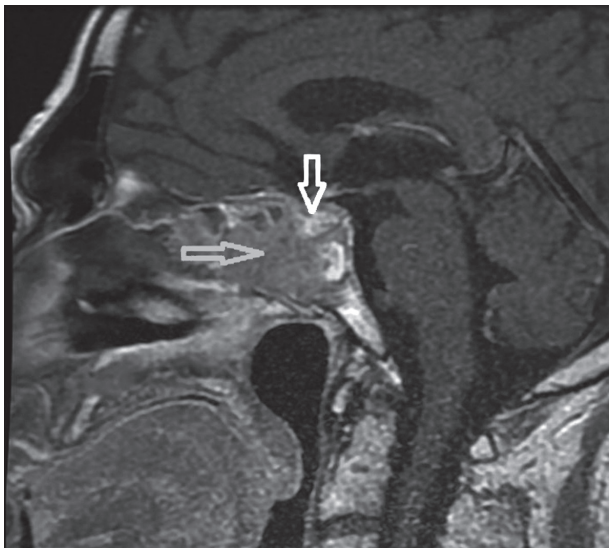

Figure 1. Sphenoid sinus mucocele expanding sella turcica. (white arrow: pituitary gland, grey arrow: sinus mucocele)

Discussion

Hypopituitarism is a disorder which refers to decreased secretion of pituitary hormones due to the diseases of pituitary gland or hypothalamus. Besides pituitary infarction, hemorrhage, radiation or surgery, mass lesions originating from hypophysis or from nearby structures can cause temporary or permanent damage by exerting pressure on pituitary cells (3). Type and degree of hormonal insufficiency determines the clinical manifestations and severity of the disorder. In our case, hypopituitarism was supposed to be the result of destruction of sella by a sinus mucocele originating from sphenoid sinus which was an unexpected finding in the setting of a malignant disease. The patient's complaints

and biochemical findings pointed to the insufficiency of all anterior pituitary hormones. He had no polyuria and polydipsia nor visual field impairment suggesting the preservation of posterior pituitary gland and optic chiasm.

Pituitary metastasis is a rare cause of hypopituitarism which was first presented as an autopsy finding in a melanoma patient by Cushing in 1857 (4). The frequency of metastasis to pituitary gland has been reported as 1% to 6% in some studies with the highest rates belonging to breast and lung cancer, respectively (5). Pituitary metastasis of neoplastic diseases predominantly present with clinical manifestations of posterior pituitary hormone deficiencies. In a series of 190 cases of symptomatic pituitary metastasis, DI was reported in 45.2% of patients, optic nerve impairment in 27.9% and anterior pituitary insufficiency in 23.6% (6). Stalk compression is usually manifested by prolactin elevation with levels less than 200 ng/mL excluding the diagnosis of prolactin secreting adenoma (7). In the current case prolactin levels were within normal range suggesting the absence of stalk compression. Earlier studies also underscore the prevelance of DI in pituitary metastasis which is attributed to the trend of metastasis to the posterior lobe and infundibulum (8-10). The predilection for posterior lobe is mainly caused by the nourishment of anterior lobe by the portal vessel system rather than a direct arterial blood supply (11). Another contributing factor is supposed to be the larger contact area of posterior lobe with adjacent dura (4). Thus, detection of anterior pituitary hormone deficiency in a patient with malignancy should suggest other possible causes of hypopituitarism besides pituitary metastasis.

The differential diagnosis of hypopituitarism comprises infiltrative disease of hypophysis in the absence of a history of trauma, stroke, pituitary apoplexy or an evident metastasis. Lymphocytic hypophysitis is the most common form of hypophysitis. The cause is usually unknown. Initially lymphocytic infiltration and enlargement of the pituitary is followed by destruction of the pituitary cells (12). Typical radiologic features of this entity is a mass mimicking adenoma or diffuse and homogeneous contrast enhancement of the anterior pituitary (13). In our case there was no mass like lesion in the pituitary gland or homogenenous contrast enhancement pattern pointing to the diagnosis of hypophysitis.

Sinus mucoceles are cyst-like lesions lined with respiratory epithelium that most commonly produce bone destruction within the paranasal sinuses. Approximately two-thirds of all sinus mucoceles involve the frontal sinuses, and the majority of the remainder involve the ethmoidal sinus. Sphenoidal sinus mucoceles occur rarely and have an incidence of 1% of all paranasal sinus mucoceles (14). There is no accepted consensus as to why sinus mucoceles are formed, but theories include chronic sinus ostial occlusion, mucous gland degeneration and inflammatory polyps. Radiation to the head and neck appears to be a predisposing factor. Headache and ocular symptoms such as visual defects, diplopia and ptosis are the commonest presentation. To our knowledge this is the second case of hypopituitarism associated with sphenoid sinus mucocele in the literature (15). The patient in the previous case had presented with symptoms of headache, anterior pituitary hormone deficiency and diplopia, and the symptoms were relieved after endoscopic drainage.

Conclusions

Our case represents an example of association of a benign disorder with malignancy causing severe deterioration of life quality. Although rare, pituitary metastasis is the initial possible diagnosis in the setting of non-small cell lung cancer. However, the absence of DI and visual impairment, which is the most frequent presentation for pituitary metastasis, might suggest other disorders that provokes pituitary hormone deficiencies. Reversal of complaints with simple manipulations underscores the value of evaluation of all nonspesific symptoms comprehensively even in the advanced disease setting.

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