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A case of melanocytic cervical adenosquamous carcinoma complicated with Cushing's syndrome

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Summary

Background: To date, cervical carcinoma complicated with Cushing's syndrome were all diagnosed as small cell carcinoma histologically, but not adenosquamous carcinoma. Here the authors present the diagnosis, management, and prognosis of a case of melanocytic cervical adenosquamous carcinoma complicated with Cushing's syndrome. *Case*: A 28-year-old woman was admitted with the chief complaint of post-coital bleeding for one month. Gynecological examination revealed a nodular yellowish-pigmented vegetation (6×5 cm) on the cervix. Laboratory findings proved the diagnosis of Cushing's syndrome. Histopathological diagnosis showed the adenosquamous carcinoma with melanoma differentiation. Immunohistochemical stainings for melanoma A and anti- adrenocorticotropic hormone (ACTH) were positive in the majority of the tumor cells, which indicated that this melanocytic cervical carcinoma lesion was the source of ectopic ACTH production resulting in Cushing's syndrome. *Conclusion*: This is a unique case of a rare type of cervical carcinoma.

Key words: Melanocytic carcinoma; Cervical adenosquamous carcinoma; Cushing's syndrome.

Introduction

Cushing's syndrome refers to a series of symptoms and signs which result from excessive glucocorticoids. Majority of endogenous Cushing's syndrome (75-80%) is caused by excessive secretion of adrenocorticotropic hormone (ACTH) from pituitary adenomas, the remaining 20-25 percent is contributed by adrenal neoplasia (10-15%) or ectopic ACTH secretion (10%) [1,2]. Generally, about half of non-pituitary (i.e. ectopic) sources of ACTH are from small cell carcinoma of the lung; the remaining are from various neuroendocrine tumors such as bronchial and thymic carcinoids [3, 4], and rarely from uterine cervix. So far, only five cases of cervical carcinoma were complicated with Cushing's syndrome. Histologically all of the patients were diagnosed as small cell carcinoma, with high incidence of vascular invasion, lymph node involvement, hematogenous metastasis, and poor prognosis [5]. To date, melanocytic cervical adenosquamous carcinoma complicated with Cushing's syndrome has not been presented in the literature.

Case Report

In August, 2009, a 28-year-old woman was admitted to the Department of Gynecology, the First Affiliated Hospital of China Medical University, with the chief complaint of post coital bleeding for one month. On admission, her body temperature was 36.5°C, blood pressure was 120/90 mmHg, body height was 166 cm, and body weight was 62 kg. Physical signs showed a moon face, and truncal obesity. Laboratory examination showed high levels of serum cortisol (> 1,380 nmol/l) and plasma ACTH (793 pg/ml) without diurnal variation. Thyroid function was almost normal with free thyroxine (FT_4) 10.23 pmol/L, total thyroxine (TT_4) 2.71 pmol /L, and thyroid stimulating hormone (TSH) 0.0728 mIu /L. Testosterone (TSTO) was 13.42 nmol/l, serum potassium (K^+) was 2.28 mmol/l, and serum bicarbonate (HCO_3^-) was 36.8 mmol/l. Magnetic resonance imaging (MRI) of the pituitary gland and computed tomography imaging (CT) of the adrenal gland revealed no abnormalities. Therefore, the diagnosis of ectopic ACTH syndrome was confirmed by these laboratory findings.

Gynecological examination revealed a nodular yellowish-pigmented vegetation (6×5 cm) on the cervix, with normal vulva and vagina, and growth was found in the cervix. The uterus was normal in size, mobile without other adnexal mass. Histopathological diagnosis of the lesion showed the adenosquamous carcinoma with melanoma differentiation (Figure 1). Immunohistochemical stainings for melanoma A and anti-ACTH were positive in the majority of the tumor cells (Figure 2), which indicated that this melanocytic cervical carcinoma lesion was the source of ectopic ACTH production resulting in Cushing's syndrome. The tumor was in Stage IIa according to the International Federation of Gynecology and Obsterics (FIGO) classification.

On July 22nd, 2008, the patient received intravenous PVB chemotherapy (cisplatin 50 mg/m^2, vincristine 1.5 mg/m^2, and bleomycin 20 mg/m^2) for three days per cycle, and the process was uneventful. After three weeks she was admitted to hospital again. Her Cushingoid features had been progressing severely. Physical signs showed a moon face, facial plethora, supraclavicular and cervical fat pads, central adiposity, violaceous striae, thin skin, and proximal muscle weakness. Gynecological examination revealed a dark-yellow, papillary mass (5 ×5 cm) on the posterior lip of the cervix, which was smaller in size than before. Vagina

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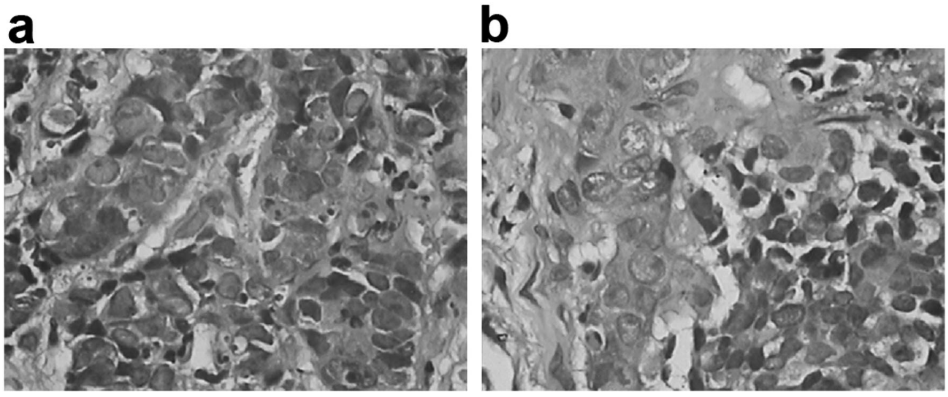

Figure 1. — a) Representative HE staining of adenocarcinoma [×400]. b) HE staining showing typical squamous cells [×400].

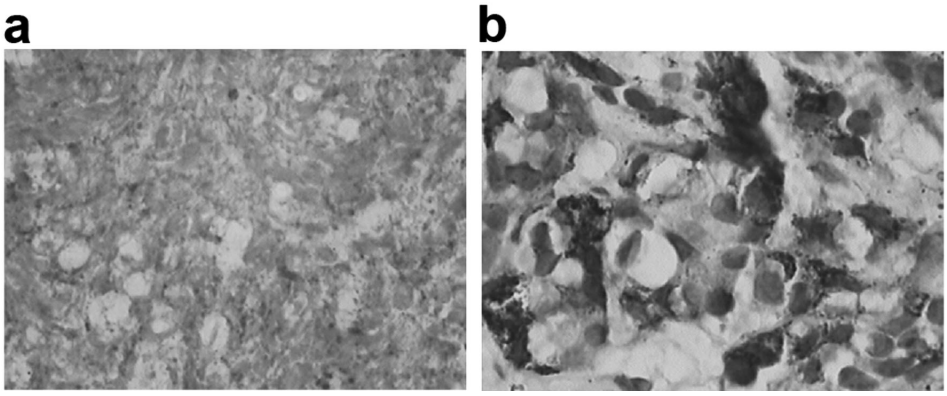

Figure 2. — a) Immunohistochemical staining for melanin [×400]. b) Immunohistochemical staining for ACTH [×400].

and parametrial tissue were not involved. Laboratory findings showed high levels of serum cortisol (> 1,380 nmol/l) and plasma ACTH (> 1,250 pg/ml) without diurnal variation. TSTO was 9.8 nmol/l, serum K^+ was 1.91 mmol/l, arterial blood pH value was 7.5, partial pressure of carbon dioxide (PCO_2) was 44.4 mm Hg, partial pressure of oxygen (PO_2) was 59 mm Hg, HCO_3^- was 33.8 mmol/l, and base excess (BE) was 10.7 mmol/L. Multiple parenchymal nodules in the liver were found by CT scan, indicating cervical carcinoma metastasis to the liver. Since cervical adenosquamous carcinoma was not sensitive to both chemotherapy and radiotherapy, the effect of previous chemotherapy was not satisfactory and biological treatment was recommended to the patient, but she declined. She received the same CVB chemotherapy as the previous one. However, 12 days later, the patient died and she only survived for 46 days after diagnosis.

Discussion

The present report showed the diagnosis, management, and prognosis of a unique case of a rare type of cervical carcinoma, the melanocytic cervical adenosquamous carcinoma complicated with Cushing's syndrome. So far, only five cases of cervical carcinoma were complicated with Cushing's syndrome and were all diagnosed as small cell carcinoma histologically. To the best of the present authors' knowledge, this is the first report demonstrating the melanocytic cervical adenosquamous carcinoma complicated with Cushing's syndrome.

Ectopic adrenocorticotropic secretion (EAS), including a variety of tumors, from undetectable benign lesion of pituitary to widespread metastatic carcinoma, is responsible for 12-17% of Cushing's syndrome. Besides the most common cause, the small cell carcinoma of lung, the other causes of EAS include bronchial carcinoids, thymic tumors, islet cell carcinomas of the pancreas, medullary thyroid carcinomas, and phaeochromocytomas [6]. Furthermore, it has been reported that a case of melanocytic neuroendocrine thymic carcinoma represented Cushing's syndrome [7], so did five cases of small cell neuroendocrine cervical carcinoma [5]. To date, melanocytic cervical adenosquamous carcinoma complicated with Cushing's syndrome has not been presented in the literature.

It was reported that 10-20% of patients with Cushing's syndrome present typical clinical manifestations; the patient in this report showed a moon face, facial plethora, supraclavicular and cervical fat pads, central adiposity, violaceous striae, thin skin, and proximal muscle weakness, which were consistent with the signs of Cushing's syndrome. Furthermore, other findings, such as increased androgen level, hypokalemic metabolic alkalosis, and the disappearance of

blood cortisol diurnal variation without pituitary tumors also confirmed the diagnosis of ectopic ACTH syndrome.

The cell type of ectopic ACTH secreted tumors is mainly APUD cells, which originate from embryonic ectodermal neural crest, but 15% of ectopic ACTH secretion tumors cells are non-APUD cells, such as adenocarcinoma, squamous cell carcinoma. It was generally believed that hepatic carcinoma or melanocytoma could not secret ACTH since they are developed from endoderm, however, a case of melanocytic neuroendocrine carcinoma of the thymus complicated with Cushing's syndrome has been reported [7].

It is widely known that normal human melanocytes produce and secrete α-melanocyte stimulating hormone (MSH) and ACTH, with the common precursor proopiomelanocortin (POMC). POMC is a kind of prohormone which could originate a variety of bio-active peptides, such as ACTH, α, β, γ-MSH, β-lipotropin, and β-endorphin. POMC is not only expressed in the pituitary, but also in various organs and non-pituitary tumors, including melanoma. It was suggested that POMC is highly expressed in melanoma cells, and its expression is correlated with tumor progression [8]. The high expression of POMC might be derived from increased expression of corticotropin-releasing hormone (CRH), which works as a melanoma growth factor [9]. The POMC gene is located on chromosome 2p23, and biologically active mRNA is about 1200 bp. The expression of POMC gene is tissue-specific. Under physiological conditions, only the POMC expressed in the pituitary and hypothalamus could encode biologically active POMC protein due to the control of specific promoter. In other tissues, although POMC mRNA could be expressed, it is not biologically active, because it is only 800 bp in length due to the lack of signal peptide sequence. However, if pituitary or hypothalamus-specific POMC promoter was activated in other tissues, protein with POMC activity will be secreted and results in ectopic ACTH syndrome. In this case, during first admission, there were no tumors in other organs or tissues except cervix, and melanoma cells were detected in cervical lesions of this patient. Considering the relevance of melanoma cells and ACTH, the present authors concluded that the ectopic ACTH syndrome of this patient may be derived from melanoma cells of cervix.

During first admission, considered the young age and the large size of the lesion, neoadjuvant chemotherapy was given. For the second time, multiple intrahepatic metastasis occurred and the general state of the patients was very poor, therefore surgery treatment could not be done. The present authors advised the patient to take biological treatment because some kinds of melanomas might be sensitive to it, but the patient declined. The clinical condition of the patient deteriorated rapidly with only 46 days of survival after diagnosis, due to the low degree of differentiation of the cervical adenosquamous carcinoma, the hematogenous metastasis accompanied by melanoma, and ectopic ACTH syndrome. To the best of their knowledge, this rare case has not been reported yet. Therefore, the pathogenesis, early diagnosis, and more effective treatment to extend the survival time need to be investigated further.

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References

[1] Newell-Price J., Trainer P., Besser M., Grossman A.: "The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states". *Endocr. Rev.*, 1998, *19*, 647.

[2] Lindsay J.R., Nieman L.K.: "Differential diagnosis and imaging in Cushing's syndrome". *Endocrinol. Metab. Clin. North Am*., 2005, *34*, 403.

[3] Ilias I., Torpy D.J., Pacak K., Mullen N., Wesley R.A., Nieman L.K.: "Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health". *J. Clin. Endocrinol. Metab.*, 2005, *90*, 4955.

[4] Azzopardi J.G., Williams E.D.: "Pathology of 'nonendocrine' tumors associated with Cushing's syndrome". *Cancer*, 1968, *22*, 274.

[5] Kuzuya K., Nakanishi T.: "Endocrine tumor of the uterine cervix". *Nihon. Rinsho.*, 2004, *62*, 903.

[6] Isidori A.M., Lenzi A.: "Ectopic ACTH syndrome". Arq. Bras. *Endocrinol. Metabol.*, 2007, *51*, 1217.

[7] Lagrange W., Dahm H.H., Karstens J., Feichtinger J., Mittermayer C.: "Melanocytic neuroendocrine carcinoma of the thymus". *Cancer*, 1987, *59*, 484.

[8] Funasaka Y., Sato H., Chakraborty A.K., Ohashi A., Chrousos G.P., Ichihashi M.: "Expression of proopiomelanocortin, corticotropin-releasing hormone (CRH), and CRH receptor in melanoma cells, nevus cells, and normal human melanocytes". *J. Investig. Dermatol. Symp. Proc.*, 1999, *4*, 105.

[9] Sato H., Nagashima Y., Chrousos G.P., Ichihashi M., Funasak Y.: "The expression of corticotropin-releasing hormone in melanoma". *Pigment. Cell. Res.*, 2002, *15*, 98.

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