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Case report

Human papillomavirus type 18-associated cervical and lung mixed adenoneuroendocrine carcinoma

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ABSTRACT

Human papillomavirus (HPV) is associated with neuroendocrine carcinoma of the cervix and lung. However, these two uncommon cancers rarely occur in a single patient, especially with the same HPV type. We herein present a 65-year-old non-smoker female who developed mixed adenoneuroendocrine carcinoma of the lung with lymph node, brain and adrenal gland metastases 6 years after the diagnosis of stage IA1 cervical mixed adenoneuroendocrine carcinoma. The patient's brain, lung and previous cervix specimens were identically HPV type 18 positive. To our knowledge, this is the first report of a patient with the same HPV type associated mixed adenoneuroendocrine carcinoma in different sites.

1. Introduction

The most common type of human papillomavirus (HPV) reportedly associated with large cell[1,2] and small cell[3,4] neuroendocrine carcinoma of the cervix are type 16 and 18. HPV has rarely been found in small cell lung cancer or neuroendocrine carcinoma of the lung.[5,6] We present a case of a female patient with cervical mixed adenoneuroendocrine carcinoma who underwent radical resection, whereafter lung nodules and multiple metastases later developed after 6 years. The pathologic features of lung and brain lesions were similar to previous cervical carcinoma. Moreover, the HPV type 18 was identified in these three specimens.

2. Case report

A 59-year-old woman was diagnosed with stage IA1 adenocarcinoma of the uterine cervix in 2007. Following initial conization, she underwent radical hysterectomy after which there was no gross residual cancer. The pathologic finding from her conization specimen revealed adenocarcinoma with infiltrative acinar pattern (Fig. 1A). Immunohistochemical study displayed focal cytoplasmic staining for synaptophysin (Fig. 1B), CD56 (Fig. 1C) and thyroid transcription factor-1 (TTF-1) (Fig. 1D), which confirmed the neuroendocrine differentiation. The patient did not receive any adjuvant treatment following the surgery, and annual follow-up examinations with Pap smear showed no evidence of recurrence. Until our recent medical intervention, the patient had remained in her customary health status, with medically-controlled hypertension.

This patient presented to our emergency department with a three-day history of worsening headache six years after she was diagnosed with mixed adenoneuroendocrine carcinoma of the uterine cervix. Upon presentation, she reported rapidly progressive dizziness, vomiting and rightward deviation when walking. Magnetic resonance imaging (MRI) of the brain revealed one left cerebellar mass with mixed components of fluid and loose substance measuring 39 mm in diameter (Fig. 2). A whole-body CT scan for assessment of the extent of metastases revealed multiple nodular lesions in the right lower lobe (RLL) of the lung with right pleural effusion, right hilar lymph node enlargement, another smaller tumor in the left lower lobe and bilateral adrenal gland metastases (Fig. 3). The patient underwent a craniotomy procedure to remove the tumor. The specimen of brain tumor stained by hematoxylin-eosin showed acinar and tubular patterns similar to previous cervical carcinoma (Fig. 4A). The immunohistochemical stains were diffusely positive for synaptophysin (Fig. 4B), CD56 (Fig. 4C) and focally for TTF-1 (Fig. 4D). Ten days later, she underwent

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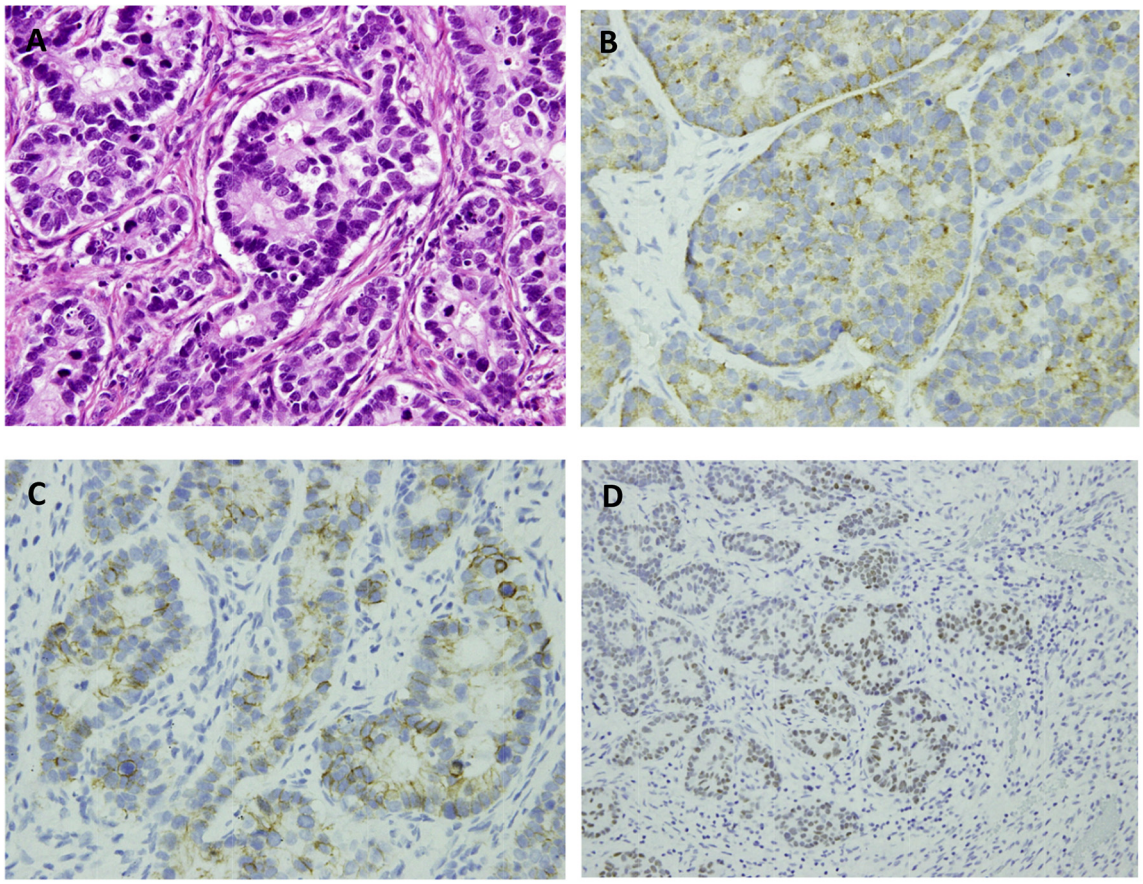

Fig. 1. Specimen removed from the uterine cervix shows mixed adenoneuroendocrine carcinoma. (A) Representative section of the tumor showed adenocarcinoma with infiltrative acinar pattern (H&E, ×200). Tumor cells showing focal cytoplasmic staining for (B) synaptophysin (×200), (C) CD56 (×200) and (D) TTF-1 (×200).

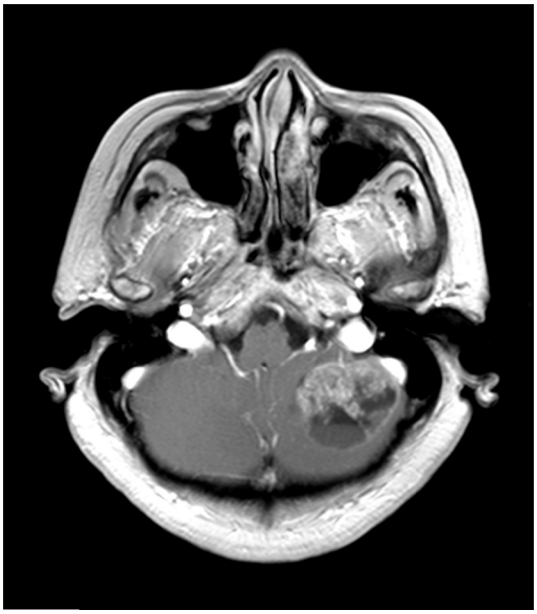

Fig. 2. Brain magnetic resonance imaging showed a nodule with mixed components of fluid and loose substance measuring 39 mm in diameter in the left cerebellum.

percutaneous CT-guided biopsy of her RLL nodules. The resulting biopsy specimen revealed small cell lung cancer with focal adenocarcinoma (Fig. 5A). The noted patterns of immunohistologic staining were CD56 (+), synaptophysin (+) and TTF-1 (+) (Fig. 5B–D). The genetic components for activating mutation of epidermal growth factor receptor were not detected in either brain or lung specimen. HPV DNA in the cervical, brain and lung tumor cells was detected and typed by a genechip (Easychip HPV Blot, King Car, Taiwan). HPV type 18 was identically found in these three specimens.

She underwent whole-brain radiation therapy with 30 gray in 12 fractions. Then the patient was treated with systemic chemotherapy (cisplatin 25 mg/m^2 and etoposide 100 mg/m^2 for three days) monthly for six courses. Subsequently, her chemotherapy was shifted to triweekly CEV regimen (cyclophosphamide 1000 mg/m^2, epirubicin 50 mg/m^2, and vincristine 1.4 mg on day 1) due to the progress of her disease. After 3 cycles of CEV regimen, the treatment plan was adjusted to provide best supportive care due to the patient's poor performance status. Thereafter, this patient died 17 months after she was first diagnosed with mixed adenoneuroendocrine carcinoma of lung.

3. Discussion

Neuroendocrine carcinoma of the cervix represents only about 1–2% of all cervical malignancies.[7,8] Patients with early stage disease treated with multimodality therapy reported a 3-year survival rate of up to 80%.[9,10]This patient had survived for 6 years while maintaining her usual health status after the surgical resection of cervical cancer. However, the patient's brain metastasis as the first manifestation along with disseminated disease upon diagnosis was a noteworthy dilemma in this case.