Case Reports

Lung cancer developing in a young patient with Epidermodysplasia verruciformis

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Abstract

Epidermodysplasia verruciformis (EV) is a rare autosomal recessive hereditary disease, characterized by defects in cell-mediated immunity, susceptibility to skin infections by human papillomavirus (HPV) and development of multiple cutaneous sqamouas cell carcinoma. While the oncogenic role of HPV is well recognized, only cutaneous sqamouas cell carcinoma was associated with EV. Herein we report of a patient with EV in whom lung cancer developed at a very young age, raising the possibility that HPV had a causative effect. A 21-year-old man with EV and squamous cell carcinoma of the left lower eyelid was referred to the oncology clinic. One year later, the patient complained of right chest pain. Computer tomography revealed lung mass and a bone lesion. Bone biopsy confirmed the diagnosis of poorly differentiated squamous cell carcinoma of the lung. The cytological features were clearly distinctive from those in the skin. The present case suggests possible association between EV and squamous cell carcinoma of the lung. This observation may contribute to the understanding of the pathogenesis of these conditions.

Key words: Epidermodysplasia verruciformis; Lung cancer; Squamous cell carcinoma

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INTRODUCTION

Epidermodysplasia verruciformis (EV) is an uncommon dermatosis characterized by defects in cell-mediated immunity and susceptibility to skin infections by a group of specific Human papillomavirus infection (HPV) types. These patients characterized by persistent, flat warts and pityriasis versicolor-like macular lesions since their early life. HPV are small DNA viruses infecting keratinocytes in various locations and are associated with neoplastic transformation. The E6 and E7 genes plays dominant role in this process. These genes affect the tumor suppressor genes p53 and Rb by binding to these proteins and enhancing their proteolysis resulting in inhibition of apoptosis of UV damaged cells[1].

The model for HPV role in the development of skin cancer was based on patients with EV. An unknown immunogenetic defect causes to the failure of the patient's immune system to reject EV-HPV harboring keratinocytes resulting in a persistence of HPV infection. The genetic defect is probably influenced by environmental factors, mainly ultraviolet radiation. Two susceptibility loci on chromosome 17p25

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encoding the EVER1 and EVER2 genes have been linked to EV 1. Features of integral membrane proteins located in the endoplasmic reticulum are encoded by these genes. To date, the association between these proteins and the pathogenesis of EV is unclear. Sun exposed areas are the most common sites for malignant transformation resulting in cutaneous sqamous cell carcinoma (SCC). Progressing to carcinoma *in situ* and invasive SCC between the years 30 and 50 are seen in about half of the patients[2]. In over 90% of SCC lesions of EV patients, HPV 5 and HPV 8 types are detected. In these lesions, HPV DNA usually persists extra chromosomally in high copy numbers and is actively transcribed.

HPV has also been associated with the pathogenesis of SCC of the genital tract. However, the role of the HPV in the development of non-small cell lung cancer is unclear[3]. We report a case of a very young patient with EV and cutaneous squamous cell carcinoma who developed non-small cell lung cancer.

CASE PRESENTATION

A 21-year-old man was referred to our oncological clinic for the treatment of squamous cell carcinoma of the left lower eyelid. The patient, of Arab origin, had two sisters and one brother diagnosed with EV which subsequently developed multiple cutaneous squamous cell carcinoma, and were known to the oncology department. Since early childhood he experienced the gradual appearance of warty papules over the back of his hands and later over sun exposed areas, including his face, eyelids, and upper chest. One of the eyelid lesions grew progressively until reaching a diameter of 4 cm and ulcerating. His past medical history was unremarkable and he did excluded cigarette smoking and alcohol intake. No family history of lung cancer or any cancer other than SCC of the skin, was known.

On physical examination this was a young man of good performance status with remarkable warty tumors over his forehead, eyelids and back of the hands, varying in size from 0.5 to 3 cm. On his trunk he had a flat scaly patches resembling pityriasis versicolor. Flat warty papules covered most of his sun exposed skin.

His most prominent eyelid tumor was excised. Well differentiated squamous cell carcinoma of the skin was seen in histopathological examination.

Treatment was completed by irradiation of the eyelid to a dose of 60 Gy using 6 MeV electrons in fractions of 2 Gy.

One year later, the patient complained of right chest pain, without fever, cough or dyspnea. Chest X ray showed bilateral pleural fluid and right lung consolidation. Computer tomography revealed endobronchial mass occluding the left main bronchus. In addition, a blastic lesion was noted in the left rib. Trans bronchial and bone biopsies were performed. Malignant cells, which were positively for cytokeratin-7 and negative for PSA, cytokeratin-5, cytokeratin-6 and TTF was shown in the pathologic examination of the bone lesion. The morphologic picture confirmed the diagnosis of poorly differentiated squamous cell carcinoma of the lung. The cytological features of the tumor cells in the lung specimen were compared to the previous skin tumor. The malignant cells of the lung were clearly distinctive from those in the skin since the appearance of poorly differentiated carcinoma was observed in the lung compared to well differentiate cells in the eyelid.

The patient was therefore diagnosed to have a second primary metastatic lung cancer. He was started with combination chemotherapy using cisplatin and vinerolbine. In spite of this treatment he rapidly deteriorated and died one month later of respiratory failure due to massive lung tumor.

DISCUSSION

A persistent infection by a distinct group of HPV types is the hallmark of EV and progressing to carcinoma *in situ* and invasive SCC[2]. Except to SCC of the skin, malignant thymoma has been described in a patient with a EV-like syndrome[4]. Since the association between EV and immunodeficiency syndromes, is a well established, this case may represent example of an EV-like syndrome in immunodeficiency pa-

tient[4]. To the best of our knowledge, it is the first case of lung cancer in very young patient with EV.

There are several factors in favor of the positive association between EV and the development of lung cancer in our patient. First, the rarity of lung cancer in this age group supports the positive association. Second, the patients did not have any familial history or environmental risk factors for lung cancer. Third, the connection between HPV and bronchial squamous cell carcinoma has been evaluated. Squamo-columnar junctions are located in multiple locations in the respiratory tract. These junctions are considered to be a precondition for the spread of HPV infections in this tract.

Characteristic morphological changes seen in HPV lesions elsewhere were seen also in bronchial squamous cell carcinoma. In addition, HPV DNA has been detected in about one fifth samples analyzed which are about the same rate of HPV DNA detected in other squamous cell cancers that have been identified[4].

Recently, the E6 and E7 transcripts were detected in HPV-positive lung cancers[5]. In addition, meta analyses suggests that HPV16 and HPV18 may be associated with lung tumors, especially in Asia[6]. Since the presence of viral DNA is found only a fraction of tumor cells as well as low copy viral load, the negative test for HPV PCR in the current case does not rule out the role of HPV in the pathogenesis of the current case.

In conclusion, we have reported a very young patient with EV and bronchial squamous cell carcinoma of the lung. The possible association between EV, squamous cell carcinoma of the lung and HPV may contribute to the understanding of the etiology and pathogenesis of these conditions.

Conflicting Interest: The authors certify that they have no affiliation with or financial involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript.

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