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Squamous Cell Carcinoma of the Lung Following Adult-onset Recurrent Respiratory Papillomatosis

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Malignant transformations of recurrent respiratory papillomatosis (RRP) are rare, and are usually associated with prior radiation therapy or a history of smoking. In this report, we describe an uncommon case of a 54-year-old woman with no history of either irradiation or active smoking, who developed squamous cell carcinoma of the lung from adult-onset recurrent respiratory papillomatosis (AO-RRP) with lung involvement in the 10-year follow-up period. Serial chest radiographs and computed tomography scans showed widely scattered parenchymal lesions, both solid and cavitary, central and peripheral. The lung lesions grew slowly and some became confluent. To the best of our knowledge, squamous cell carcinoma of the lung is a rare complication of RRP without a history of irradiation or smoking.

Key words: recurrent respiratory papillomas, adult-onset recurrent respiratory papillomatosis, human papilloma virus, squamous cell carcinoma

INTRODUCTION

Recurrent respiratory papillomas (RRPs), caused by the human papilloma virus (HPV) family[1], are benign epithelial neoplasms consisting of a central fibrous connective tissue core covered by squamous epithelium. They can cause serious clinical problems because of their potential for airway obstruction, frequent recurrence, a tendency to spread throughout the respiratory tract, and malignant transformation[2].

Two forms of RRP are recognized: a juvenile and an adult form[3]. The typical group of patients with adult-onset recurrent respiratory papillomatosis (AO-RRP) are white, married, middle class, and heterosexual[3]. There are two proposed mechanisms for contracting HPV as AO-RRP: infection by oral contact with infected genitals or acquired at birth from an HPV-infected mother[4].

It is not common, but it is possible, for RRP to stay in the larynx and also to spread into the trachea, bronchus, and lung parenchyma[5]. According to statistics reported by Derkay, 6% of patients with AO-RRP may require tracheotomy[3]. Several reports have demonstrated malignant transformations of RRP. The major cofactors are cigarette smoking, irradiation, and chemotherapy[6].

We present a 10-year follow-up study of a 64-year-old woman diagnosed with AO-RRP. Worsening of her lower airway disease and lung involvement, with multiple cavitary lesions, was observed at follow-up. A CT-guided transthoracic needle biopsy of a lung lesion was performed in December 2005. The pathological findings confirmed the diagnosis of squamous cell carcinoma.

CASE REPORT

In 1994, a 54-year-old woman was first evaluated for a foreign body sensation in the throat. She had a history of hypertension and type 2 diabetes mellitus. She had no history of radiation therapy or active smoking. A laryngeal nodule was resected by endoscopic forceps in June 1994. The specimen obtained from surgery did not present with features typical of squamous papilloma. Two years later, in 1996, she was admitted to our hospital and presented with symptoms of hoarseness and progressive dyspnea over the preceding six months. A physical examination revealed decreased breath sounds and sparse rhonchi over the right upper lung field. Laboratory data, including a complete blood count, tumor markers (α-fetoprotein [AFP],

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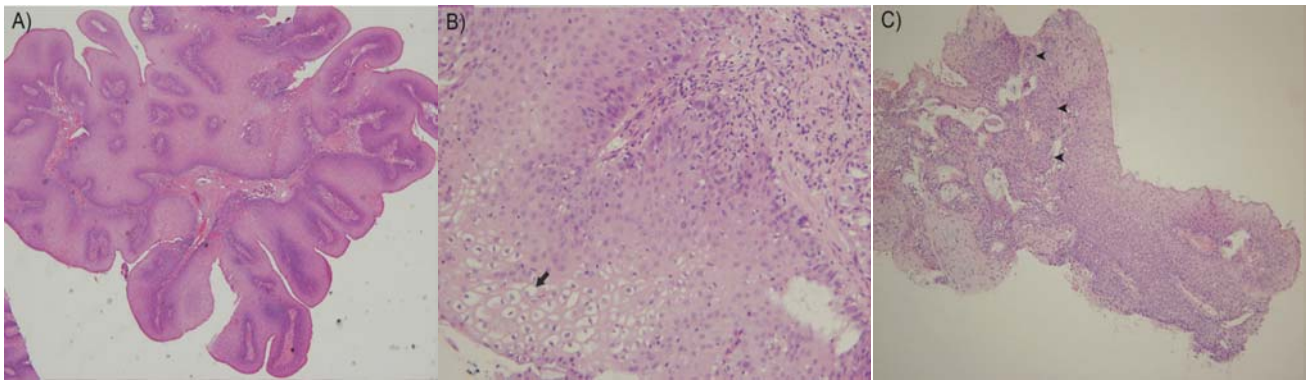

Fig. 1 (A) Microscopic appearance of the papilloma showed papillary growth tumor with nonkeratinized stratified squamous epithelium (H&E, 100X). Microscopic appearance of (B) one transthoracic needle biopsy specimen showed koilocytotic change of the squamous epithelium (arrow) (H&E, 200X), (C) the other showed squamous cell carcinoma characterized by sheets of tumor cells invaded the stroma (arrowheads) (H&E, 100X).

carcinoembryonic antigen [CEA], cancer antigen 125 [CA125]), urinalysis, and serology, were within normal limits, but her glucose level was 182 mg/dL. The squamous-cell-carcinoma-related antigen (SCC-Ag) test was not performed during this period. A chest radiograph showed abnormal opacity over the right hilum. A CT scan demonstrated narrowing of the anterior segmental bronchus of the right upper lobe. A laryngoscopic examination discovered one subglottic and one supraglottic papilloma. The patient underwent excision of the tumors by direct microlaryngoscopy and ablation with a carbon dioxide (CO_2) laser. The pathological findings supported the diagnosis of squamous papillomas (Fig. 1A).

One month after the surgical excision, a chest radiograph showed right upper lobe collapse and a CT scan demonstrated a wedge-shaped consolidation in the anterior aspect of the right upper lobe. Fiberoptic bronchoscopy showed an endobronchial tumor completely obstructing the orifice of the right B3b bronchus. Squamous cell carcinoma in situ was diagnosed by biopsy of the tumor. A right upper lobectomy was then performed. In the lobectomy specimen, a squamous papilloma with carcinoma in situ was discovered in the bronchus. The lung parenchyma and lymph nodes were free of tumors. Six months later, the patient had a tracheotomy for airway obstruction and the tracheotomy was closed after the symptoms were relieved.

Between 1997 and 2000, endoscopic removal of papillomas was performed several times, using a CO_2 laser and cupped forceps. In July 2000, a CT scan of the chest revealed solid, cystic, or cavitary nodules in the bilateral lung fields. We performed laboratory tests for a possible bacterial, mycobacterial, or fungal etiology, without any significant findings. Two months later, a wedge resection of the right lower lobe was performed at another hospital. Intrapulmonary squamous papillomatosis was reported. A sputum specimen was negative for HPV DNA and typing by polymerase chain reaction (PCR). Bone scintigraphy and abdominal ultrasonography showed no sign of metastases.

In July 2003, the patient again suffered a foreign body sensation in the throat, cough, and chest pain, and returned to our hospital. The tumor marker SCC-Ag had reached an abnormally high level (39.58 ng/mL) for the first time. The rest of the laboratory data, including tests for CEA, CA125, and CA153, were all within normal limits. Serial follow-up chest X-rays demonstrated a patchy opacity in the right lower lung field and multiple solid or cavitary lesions in the bilateral lung fields (Fig. 2A). In November 2003, a follow-up chest CT scan showed solid, cystic, or cavitary lesions in the bilateral lung fields (Fig. 2B). In January 2005, a follow-up chest CT was performed. The lesions were still present and had progressively changed shape (Fig. 2C). In December 2005, the patient underwent a CT-guided transthoracic needle biopsy of the lung lesion in the right lower lobe. Malignant transformation of pulmonary papillomatosis was diagnosed from the pathological morphology (Fig. 1B, C). Human papillomavirus was detected by nested PCR. DNA was extracted from the paraffin-embedded specimens. The nested PCR methodology included the MY09/MY11 oligoprimers as the outer pair and the GP5/GP6 oligoprimers as the inner pair. A DNA fragment of the appropriate size (185 bp) was amplified from the patient's sample, and in the positive control. No

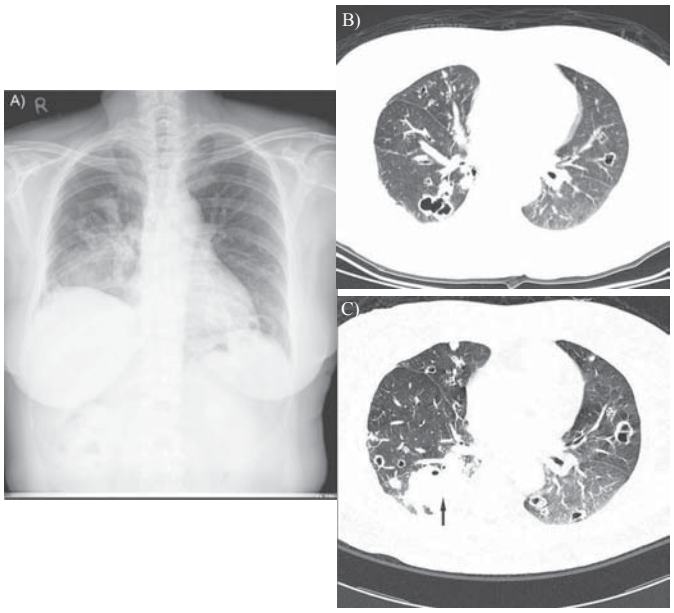

Fig. 2 (A) In November 2004, the chest x-ray film demonstrated a patchy opacity in the right lower lung field and multiple solid or cavitary lesions in the bilateral lung fields. (B) In November 2003, the chest CT scan of lung demonstrated extensive parenchymal involvement, both solid and cavitary, central and peripheral. (C) In January 2005, the follow-up chest CT scan of lung demonstrated that the lesions were existed and progressively changed the shape. In December 2005, the patient underwent a CT-guided transthoracic needle biopsy of the lung lesion in right lower lobe (arrow).

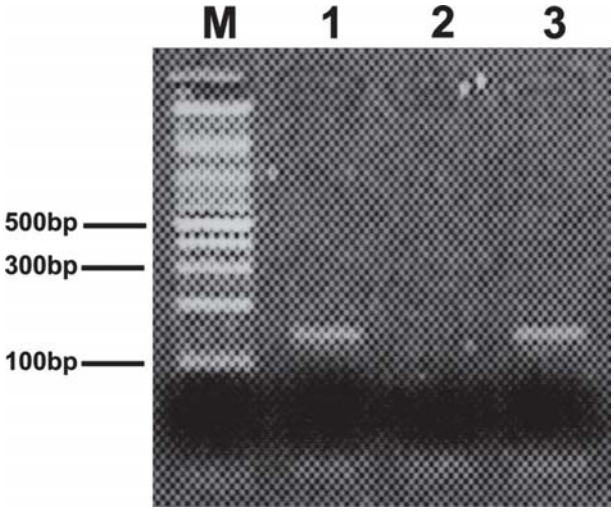

Fig. 3 Polymerase chain reaction amplification of DNA extracted from patient (lane 1). Lane 2 corresponds to the negative control, and lane 3 to positive control. M: molecular weight markers.

specific product was amplified from the negative control (Fig. 3). The purified DNA fragment amplified by PCR was subjected to direct nucleotide sequencing. HPV type identification was carried out by aligning the HPV sequence with those from the GenBank database using BLAST software. These results indicated that HPV-11 was detectable in the tumor of this patient.

The patient received follow-up regularly at our outpatient department. In March 2006, the patient developed severe pneumonia and died a month later from sepsis and adult respiratory distress syndrome.

DISCUSSION

Recurrent respiratory papillomatosis is the most common benign neoplasm of the larynx, and HPV is well established as the cause of RRP. HPV 6, 11, and more rarely 16 have been identified in RRP[1].

The manifestations and clinical courses of RRP differ based on the age of onset. AO-RRP is less aggressive and less common than its juvenile counterpart[7]. New-onset dysphonia in adults is the most consistent initial symptom of AO-RRP. The most frequent sites of extralaryngeal spread in RRP, in order of frequency, are the oral cavity, trachea, and bronchi[3]. The spread of papillomas to the tracheobronchial tree and pulmonary parenchyma is associated with a higher incidence of complications. Pneumatoceles, lung abscesses, and tracheal stenosis have all been described[8].

Radiographically, the characteristic manifestation of papillomatosis in the lung is the round nodule, which may appear either solid or cystic, with thick or thin walls. Most of the nodules are small and homogeneous when first detected, but develop air-containing cavities as they grow to several centimeters in diameter. At times, these lesions are large thin-walled cystic structures when discovered. Air-fluid levels can appear in the cavities when superinfection occurs. Rarely, fluid or pus may completely fill a cavity, causing a cystic lesion to become solid in appearance on chest radiography. The lung lesions grow slowly and may become confluent[5].

The radiographic differential diagnosis of these cavities includes metastatic tumor, fungal disease, tuberculosis, septic embolism and infarction, rheumatoid nodules, and Wegener's granulomatosis. However, the association of the cavities with laryngeal and tracheal lesions or upper airway obstruction, as occurs in papillomatosis, is more specific. This combination of findings could occur with metastatic laryngeal carcinoma, tuberculosis, or occasion-

ally with fungal infections. Moreover, the slow progression of pulmonary cavities is considered a likely characteristic of papillomatosis. More rapid progression would be expected to occur with metastatic tumors or infectious processes.

The treatment for respiratory papillomatosis is difficult because the lesions are frequently recurrent. To date, although several medical and surgical treatments have been applied to RRP, no single therapeutic modality has been shown to be consistently effective in eradicating it.

The rate of occurrence of carcinoma from RRP is 7.8%[6]. The most typical pattern of RRP malignant transformation is aggressive disease progression with pulmonary spread and a subsequent diagnosis of lung carcinoma in the third or fourth decade of life. Although the malignant transformation of pulmonary papillomatosis is rare without a history of irradiation or smoking[9], the finding of HPV 11 has been shown to be associated with such transformation. At present, there is no effective cure for this malignant transformation[10].

When encountering AO-RRP, as in our patient, it is important for the clinician to be cautious in the finding of HPV 11 for the aggressive pulmonary spread and such malignancy. Therefore, close clinical, radiological, laboratory, and histopathological follow-up of certain patients with RRP is required.

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