A Case of Multiple Atypical Adenomatous Hyperplasia of the Lung Detected by Computed Tomography

Hiroaki Nomori¹, Hirotoshi Horio¹, Tsuguo Naruke¹, Keiichi Suemasu¹, Shojiroh Morinaga² and Masayuki Noguchi³

¹Department of Thoracic Surgery, Saiseikai Central Hospital, Tokyo, ²Department of Pathology, Jichi Medical School, Tochigi and ³Department of Pathology, Institute of Basic Medical Sciences, University of Tsukuba, Tsukuba, Japan

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Multiple atypical adenomatous hyperplasia (AAH) of both lungs in a 72-year-old male, detected by computed tomography, is reported. The lesions of the right lung were resected for diagnosis via video-assisted thoracoscopic surgery (VATS). The resected specimen had 22 AAH lesions up to 10 mm in size. For nine of these lesions, the expressions of carcinoembryonic antigen (CEA), c-erbB-2 oncoprotein and p53 gene product were examined by immunohistochemistry and the loss of heterozygosity (LOH) on chromosomes was investigated by polymerase chain reaction analysis. These lesions showed a variety of expressions for CEA, c-erbB-2 and p53 oncoprotein. Three of the nine lesions showed LOH on chromosome 13q, although this was not exhibited in the largest one. These results indicate that each AAH in this case has independent genetic abnormalities and is multicentric.

Key words: atypical adenomatous hyperplasia – lung adenocarcinoma – computed tomography – loss of heterozygosity – carcinoembryonic antigen

INTRODUCTION

In 1999, the World Health Organization classified an atypical adenomatous hyperplasia (AAH) as preinvasive epithelial lesion (1). While AAHs are sometimes found incidentally in resected lung cancer specimens, most of them cannot be detected radiologically. However, recent technological developments, such as helical computed tomography (CT) or thin-section CT, can sometimes allow small lung lesions including AAH to be identified (2). However, there has been few reports of multiple AAH lesions detected by CT (3–5). We present a case of multiple AAH lesions in both lungs, detected by helical CT. We examined the expressions of carcinoembryonic antigen (CEA), c-erbB-2 and p53 oncoprotein by immunohistochemistry and the loss of heterozygosity (LOH) on chromosomes by polymerase chain reaction (PCR) for these lesions.

Case Report

The patient was a 72-year-old male. His smoking history was 20 cigarettes per day from age of 20 to 43 years. In July 1998, a routine chest X-ray film showed a suspicious abnormal shadow in the right lung. A helical chest CT revealed multiple small coin lesions in both lungs, up to 10 mm in size (Fig. 1). There were eight lesions in the right upper lobe and four in the left upper lobe, but none in the middle or lower lobe. Helical CT was used to follow up these lesions in February and July 1999 and they showed no changes in sizes and number. The serum level of CEA was 1.9 ng/ml, the normal range being <5.0 ng/ml. The patient requested a pathological diagnosis for the lesion and lung biopsy was conducted using video-assisted thoracoscopic surgery (VATS).

In July 1999, the largest lesion in the right upper lobe was marked by contrast medium under CT and was resected by lung wedge resection using VATS with intraoperative fluoroscopy. The lesion was deeply located in the lung and the resected specimen was 6.0 × 5.5 × 3.5 cm in size. The volume of the remaining lung in the right upper lobe was sufficient to function. None of the lesions within the specimen was palpable or visible. The specimen was sliced at 5 mm intervals and the sliced tissues were cut into 3 µm thick sections and stained with hematoxylin–eosin.

For reprints and all correspondence: Hiroaki Nomori, Department of Thoracic Surgery, Saiseikai Central Hospital, 1–4–17 Mita, Minato-ku, Tokyo 108-0073, Japan

Abbreviations: AAH, atypical adenomatous hyperplasia; BAC, bronchioalveolar carcinoma; CEA, carcinoembryonic antigen; CT, computed tomography; LOH, loss of heterozygosity; PCR, polymerase chain reaction; VATS, video-assisted thoracoscopic surgery

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LIGHT MICROSCOPY

The histological diagnosis of AAH was made based on the following criteria (6): (1) the lesion is localized with well defined boundaries; (2) atypical cuboidal to low columnar or peg-shaped cells, resembling either type II pneumocytes or Clara cells, have proliferated along the slightly thickened alveolar wall and mild inflammatory infiltration may be present without scar formation; and (3) atypical cells in AAH have variable degrees of nuclear atypia, but it is less prominent than in adenocarcinoma.

Microscopic examination revealed 22 lesions up to 10 × 8 mm in size. All the lesions had relatively well defined boundaries and showed proliferation of atypical cuboidal cells along slightly thickened alveolar septa (Fig. 2). Nuclear atypia was less marked and nuclear sizes were smaller than those seen in general adenocarcinoma. Mitotic figures were not observed. All these lesions were therefore diagnosed as AAHs. There was no significant difference in nuclear atypia among these lesions.

IMMUNOHISTOCHEMISTRY

Immunohistochemical studies were performed for the nine AAH lesions including the largest one, using formalin-fixed paraffin-embedded sections. Monoclonal antibodies against carcinoembryonic antigen (CEA) (Mochida, Kyoto, Japan), p53 oncoprotein (Dako, Denmark) and c-erbB-2 oncoprotein (Novocastra Laboratories, Newcastle, UK) were used as the primary antibody. For immunostaining, the avidin–biotin peroxidase complex method was performed with a Vectastain ABC kit (Vector Laboratories, Burlingame, CA, USA). Whereas the largest lesion showed positive staining for all these antibodies, the other lesions showed different reactions (Table 1). The p53 oncoprotein was positive in the nucleus of AAH cells, c-erbB-2 oncoprotein was in the cytoplasm and CEA was mostly in the cell membrane.

POLYMERASE CHAIN REACTION ANALYSIS

Genomic DNA was extracted from thinly sliced paraffin sections as reported previously (7). Loss of heterozygosity (LOH) on chromosomes 3p (FHIT), 5q (APC), 9p (p16), 13q (Rb), 17p (p53) and 22q (BandM) was examined for the same nine AAH lesions that had undergone immunohistochemical exam-
institutions. The results showed that LOH on chromosome 13q occurred in three of the nine lesions, but not in the others, including the largest one (Fig. 3, Table 1).

The patient is doing well and there is no growth of the remaining lesions in either lung 12 months after surgery.

DISCUSSION

AAH lesions are thought to be possible precursors or even early-stage lesions of well-differentiated adenocarcinoma or bronchioloalveolar carcinoma (BAC) based on the findings of morphometry, DNA ploidy, immunostaining of tumor markers, expression of oncogene and tumor suppressor genes and LOH on chromosomes (7–15). The literature review by Kitamura et al. indicated that AAH lesions showed expressions of 17–60% for CEA, 17% for c-erbB-2 and 5–70% for p53 oncoprotein on immunohistochemical examination and 5–24% LOH on chromosomes 3p, 9p or 17p with PCR analysis (9).

Some of the AAH lesions in this case also showed LOH on chromosome 13q and expressions of CEA, c-erbB-2 and p53 oncoprotein. These results support recent popular opinion that AAH is a clonally proliferative lesion with genetic alterations similar to overt adenocarcinoma of the lung (2,7–14).

Kitamura et al. classified low- and high-grade AAH and early BAC based on nuclear atypia (12). However, morphological distinction between AAH and BAC can sometimes be difficult, especially in small lesions. BAC has a tendency to show intrapulmonary dissemination and we have previously reported seven such cases (16). It is therefore important to differentiate between multiple AAH and BAC with intrapulmonary dissemination. Our PCR examination showed LOH on chromosome 13q in the three smaller lesions but not in the others, including the largest one. While observing the growth potential of the lesions by CT is the best way to distinguish multiple AAH and intrapulmonary dissemination of BAC, our PCR findings suggest that BAC with intrapulmonary dissemination was not present in this case and that these AAH lesions were multicentric tumors.

In summary, we have reported multiple AAHs of the lung detected by CT. Genetic and immunohistochemical examinations suggested that AAHs in this case were of multicentric origin and grew independently.

References


Table 1. Results of immunostaining and polymerase chain reaction analysis for the nine atypical adenomatous hyperplasia lesions

<table>
<thead>
<tr>
<th>No. of AAH</th>
<th>Size (mm)</th>
<th>Immunochemistry</th>
<th>LOH</th>
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<tbody>
<tr>
<td>1</td>
<td>2 × 2</td>
<td>–</td>
<td>+</td>
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<tr>
<td>2</td>
<td>5 × 4</td>
<td>+</td>
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<td>3</td>
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<tr>
<td>8</td>
<td>3 × 2</td>
<td>–</td>
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<tr>
<td>9*</td>
<td>10 × 8</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

AAH, atypical adenomatous hyperplasia; LOH, loss of heterozygosity; CEA, carcinoembryonic antigen. *The largest lesion.