Pulmonary Atypical Adenomatous Hyperplasia And Bronchioloalveolar Carcinoma

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OBJECTIVE To study the relationship between atypical adenomatous hyperplasia (AAH) and bronchioloalveolar carcinoma (BAC).

METHODS Morphometric, immunohistochemical and ultrastructural analyses were performed in 4 patients with low grade AAH, 5 with high grade AAH and 7 with BAC.

RESULTS The mean nuclear areas of high grade AAH and BAC were greater than those of low grade AAH (P<0.05); p53 protein expression was negative in 4 cases of low grade AAH, while the positive rates in high grade AAH and BAC were 40% (2/5) and 57% (4/7), respectively.

CONCLUSION The development of BAC is stepwise. AAH appears to be a lesion closely related with BAC, probably as its genuine precursor.

KEYWORDS: lung, atypical adenomatous hyperplasia, bronchioloalveolar lung carcinoma, p53 protein, electron microscopy.

Lung cancer is the most common malignancy in humans. Among the various histologic types of lung cancer, adenocarcinoma is one of the main types. A recent study indicated that adenocarcinoma had displaced squamous carcinoma as the most common pulmonary carcinoma. Bronchioloalveolar carcinoma (BAC) is a specific form of lung adenocarcinoma, different from the ordinary adenocarcinomas in three subtypes: mucoepithelial, bronchioloepithelial and inflammatory-sclerosing. Histologically, BAC is defined by tumor cell growth along pre-existing alveolar structures. BAC exhibits unique histogenesis and morphologic features distinguishing it from bronchogenic adenocarcinoma. For early detection, therapy and prevention of BAC, it is essential to study its histogenesis and pathogenesis. Kitamura et al. reported that the development of BAC appears to be stepwise. Atypical adenomatous hyperplasia (AAH) is morphologically similar to BAC. AAH cells share many biologic properties with BAC cells, including certain genetic abnormalities. It has been suggested that AAH is a putative precursor or even early-stage lesion of BAC. So far, however, direct evidence that AAH cells develop into BAC cells is lacking. Cytomorphologic and biologic characteristics of AAH and BAC cells were studied through hospital files based on recent references in the literature to evaluate the relationship between AAH and BAC and the possibility of AAH as a precursor of BAC.

MATERIALS AND METHODS
Specimen classification criteria

In this study, all the lung specimens were selected from Tianjin Chest...
Hospital between 1990 and 1999. They were diagnosed and classified into 7 BAC lesions, 4 low-grade AAH lesions, and 5 high-grade AAH lesions.

The low and high grade atypical AAH lesions were identified using the criteria of Kitamura et al. In AAH showing low-grade atypia, the density of cells was low, and the cells were arranged in a single layer, either intermittently or continuously, on the alveolar septum. The nuclei were small showing minimal variations in size, shape, and chromaticity (Fig. 1). In AAH showing high-grade atypia, the density of cells was high, and the nuclei were larger, exhibiting greater variations in size, shape, and chromaticity (Fig. 2).

RESULTS
Pathology
On gross examination, the AAH lesions were usually recognized as small ones on the cut surface of the lung. In 9 specimens, the lesions were only several millimeters in maximal diameter, white or gray-white, with a distinct margin. Within the lesion, alveolar structure could be recognized.

On histologic examination, cuboid or low-columnar cells resembling Clara cell or type II alveolar cells were seen along the alveolar septa. Due to fibrosis or lymphocytic infiltration, the alveolar septa were slightly thickened, but no interstitial scar formation was observed. The AAH cells showed various degrees of cellular atypical hyperplasia, such as nuclear hyperchromasia, enlargement, irregularity, pleomorphism, prominent nucleoli, hypercellularity, and disarray in cell arrangement, however, the degree of atypia was generally mild to moderate. Binucleated and multinucleated cells were occasionally seen. As in BAC cells, inclusions were frequently observed in AAH cells.

Morphometry
Using the software package for micro-imaging analysis, the nuclear areas of AAH and BAC cells were measured. The mean nuclear areas in high-grade AAH and BAC were markedly larger than those in low-grade AAH, with significant differences ($P<0.05$) (Table 1).

![Table 1. Morphometric measurements of AAH cells and BAC cells](image)

$*P<0.05$

Immunohistochemistry and Ultrastructure
Immunohistochemistry staining of AAH cells and BAC cells was performed using the mouse monoclonal p53 antibody. The results showed that p53-protein accumulation was not identified (0%) in any of the 4 low-grade AAHs, in 2 (40%) of the 5 high-grade AAHs, and in 4 (57%) of the 7 BACs (Table 2, Fig. 3).