

Alveolar atypical hyperplasia in association with primary pulmonary adenocarcinoma: a clinicopathological study of 10 cases

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Abstract

Background A distinctive cytologically atypical lesion has been found in patients with primary adenocarcinoma of the lung. The aim of this study was to characterise the lesion and assess its role in tumour pathogenesis.

Methods Lung parenchyma from 175 consecutive resection specimens for primary pulmonary adenocarcinoma were examined. Foci of atypical hyperplasia were identified. Cell proliferation state and expression of S100 and carcinoembryonic antigens were evaluated by immunohistochemistry. Clinical data on cigarette smoking and occupational exposure to carcinogens were abstracted from inpatient case notes.

Results Ten cases (5.7%) with these distinctive cytologically atypical lesions were identified. The lesions showed immunohistochemical evidence of increased cell proliferation and focal carcinoembryonic antigen expression. The associated adenocarcinomas were of peripheral (parenchymal) type. There was an association with cigarette smoking and two of the 10 patients had synchronous carcinomas elsewhere in the lung.

Conclusion The clinical and pathological associations of these lesions suggest that they may be important in the histogenesis of primary pulmonary adenocarcinoma.

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Adenocarcinomas constitute 20-30% of primary malignancies in the lung in most major series. There has been a suggestion in some reports from the United States that this proportion may be increasing.^{1,2} Adenocarcinoma is of particular interest in that it is the commonest form of lung cancer in non-smokers and it is also more common in women.^{1,2} The pathogenesis of this tumour is not as clearly defined as that of the more common squamous carcinoma, in which a histological progression from squamous metaplasia of bronchi through dysplasia and carcinoma in situ to invasive malignancy can often be shown.³ Pulmonary scars have been proposed as precursors of adenocarcinoma but there is much conflicting evidence in this regard.^{4,5} We present data on a distinctive histological lesion

that we have found in 10 patients who had pulmonary resection for primary adenocarcinoma. The morphological and immunohistological characteristics of the lesion suggest that it may be important in the histogenesis of parenchymal adenocarcinoma of the lung.

Materials and methods

In the Department of Pathology at the University of Edinburgh specimens from pneumonectomy and lobectomy for lung cancer are examined with a standard protocol that involves inflation in formalin and subsequent serial sagittal sectioning of fixed specimens. This procedure allows for preservation of gross morphological detail in the pulmonary parenchyma. Routine blocks are taken from the bronchi, hilar nodes, and tumour as appropriate. It is also our practice to sample macroscopically "normal" pulmonary parenchyma, at least one tissue block being taken from each lobe of lung if possible. We review all cases.

Representative samples of non-tumorous lung tissue received over a five year period (1986-90) were examined for epithelial abnormalities. Between one and five blocks (mean 1.5) were available from each case. Epithelial changes seen in areas of obstructive pneumonitis or other obvious inflammatory disease were discounted as reactive changes in alveolar lining cells are well recognised in this context. When an area of epithelial abnormality was seen in non-inflamed lung the gross specimen, if available, was reviewed and further tissue blocks were taken. Abnormal epithelial lesions were evaluated immunohistochemically with monoclonal antibodies to PC10 (a fixation resistance epitope on the proliferating cell number antigen),⁶ S100, and carcinoembryonic antigen by a standard technique with a horseradish peroxidase conjugated avidin biotin detection system.

Clinical details were obtained for all patients by review of hospital records with particular reference to smoking and occupational history.

Results

In the period 1986-90, 760 specimens from resections for lung cancer were examined. A diagnosis of adenocarcinoma was made in 175 cases (23%). In 10 cases (5.7%) of primary adenocarcinoma characteristic well circumscribed areas of epithelial and stromal

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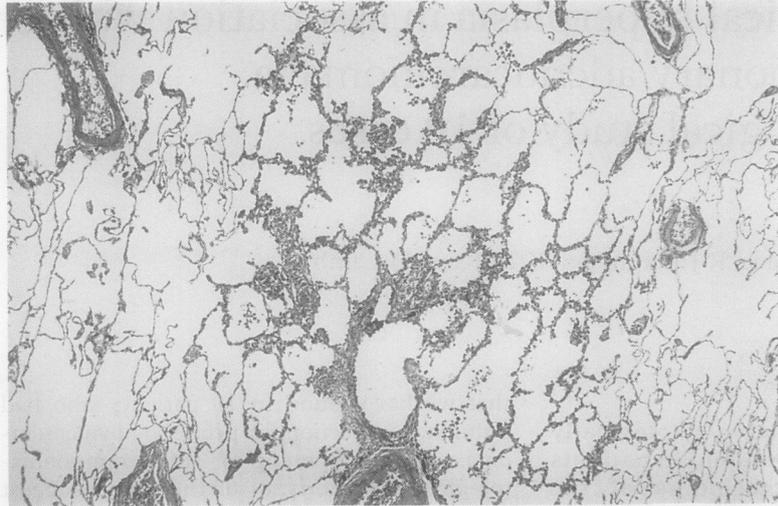


Figure 1 Low power photomicrograph of non-pneumonic lung parenchyma showing centrally a poorly defined but definite broadening of the interstitium (haematoxylin and eosin $\times 250$).

abnormality were identified on a background of non-inflamed lung parenchyma (fig 1). Morphologically the lesions were all similar and consisted of a mild expansion of the pulmonary interstitium—which in some cases showed a variable infiltrate of lymphocytes—lined by strikingly atypical epithelial cells with cytological similarity to type 2 pneumocytes (fig 2). These cells were usually easily distinguished from the malignant cells of the associated carcinoma. Between one and six such lesions were identified in each case and in two cases lesions were seen in a lobe other than that in which the main tumour mass was located. Immunohistochemical study showed that many of the abnormal epithelial cells, unlike the surrounding parenchyma, expressed carcinoembryonic antigen, although not as strongly as the adenocarcinomas. There was an increased rate of cell proliferation, as assessed by PC10 expression, in the abnormal epithelial lesions when compared with the adjacent unaffected lung parenchyma. The pulmonary adenocarcinomas, by contrast, showed extremely high PC10 expression indicating

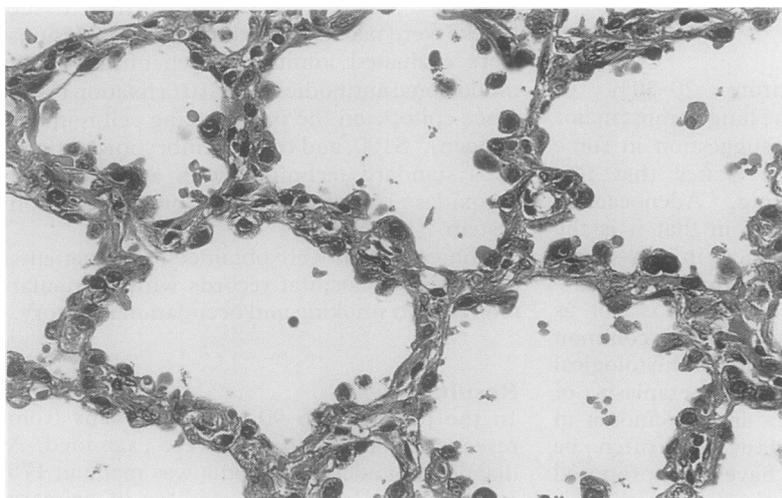


Figure 2 At high power the alveoli are lined by plump, cytologically atypical epithelial cells showing considerable nuclear pleomorphism (haematoxylin and eosin $\times 250$).

possible deregulation of expression of the proliferating cell nuclear antigen gene. This phenomenon has been described in other neoplasms.⁶ All of the epithelial lesions contained occasional interdigitating S100 positive cells, a pattern similar to that described in many pulmonary adenocarcinomas.⁷ Review of gross specimens showed that some lesions could be identified macroscopically. These were impalpable and pale in colour, and had rather ill defined edges. None measured more than 5 mm maximum diameter. The morphological features of these lesions suggest that they are a manifestation of atypical hyperplasia of alveolar lining cells and, as such, may be of interest in relation to pathogenesis of primary pulmonary adenocarcinoma.

The macroscopically and clinically obvious adenocarcinomas for which resection had been performed in the cases described here were all situated in a peripheral, subpleural, location with no obvious bronchial origin. The tumours showed varying degrees of differentiation. All cases showed some degree of alveolar wall spread at the tumour edge but none were true bronchioloalveolar carcinomas.

Seven of the 10 patients were women. All were smokers or had smoked up to two years before surgery. The possibility that the tumours were metastatic was excluded clinically. There was no obvious exposure to industrial carcinogens in any case. Interestingly, in two of the patients a clinically unexpected second (synchronous) primary carcinoma was identified in the surgical resection specimen. In one case the second tumour was a moderately differentiated squamous carcinoma; in the other a separate adenocarcinoma of different histological subtype was seen arising in the middle lobe of a right pneumonectomy specimen for a right lower lobe tumour.

Discussion

In the World Health Organisation classification of lung cancer four histological subtypes of adenocarcinoma are recognised: acinar, papillary, bronchioloalveolar, and solid carcinoma with mucin secretion.⁸ This classification has been criticised because it does not take tumour heterogeneity into account and because the subtypes do not have clear prognostic significance.^{9,10} Edwards¹⁰ has proposed that adenocarcinomas should be categorised as bronchial or parenchymal. The second (67% of his series) were characterised by their peripheral location and by the lack of an obvious bronchial origin whereas the bronchial adenocarcinomas (13%) arose at the hilum. The importance of distinguishing between these groups is that parenchymal tumours have a fairly good prognosis in the absence of hilar node metastases, whereas bronchial adenocarcinomas in general have a poor outlook.¹⁰ Our study describes a potential precursor lesion seen in the pulmonary parenchyma of patients undergoing resection for the parenchymal type of adenocarcinoma. This lesion, which is anatomically distinct from the associated tumour, is characterised by cytological atypia

in alveolar lining cells and by active cell proliferation as assessed by expression of the PC10 antigen. The distinctive cytological features of these lesions and the lower level of proliferating cell nuclear antigen expression when compared with the associated adenocarcinomas make it unlikely that we are seeing a manifestation of intrapulmonary tumour spread. The classification and nomenclature of these lesions is difficult in the absence, as yet, of data firmly establishing a causal association with adenocarcinoma. The morphological features are similar to those seen in the lungs of rodents exposed to carcinogenic dusts.¹¹ In the human context the degree of cytological atypia is reminiscent of preneoplastic states found in association with adenocarcinomas of, for example, the oesophagus and cervix uteri.^{12 13} The descriptive term "atypical hyperplasia" is perhaps best in this regard.

Occasional reports of similar morphological abnormalities in association with pulmonary adenocarcinoma have been traced in other published work. Miller *et al*¹⁴ described five cases of "bronchioloalveolar tumours of uncertain potential" in a study of synchronous adenocarcinomas in the lung and Nakanishi¹⁵ has reported a range of typical and atypical changes in the alveolar epithelium from patients coming to surgery for pulmonary adenocarcinoma. At least some of the abnormalities found in these studies correspond to the atypical hyperplasia presented here. In both the studies quoted it is notable that specimens were examined after formalin inflation and serial slicing in a manner similar to the practice in our laboratory. It seems likely that more widespread use of such techniques will reveal more of these subtle parenchymal abnormalities. It is also probable that the incidence of atypical hyperplasia reported here (about 5% of adenocarcinomas) is an underestimate and that a systematic prospective study will produce more of these lesions. Such work is under way in our department. Miller, in a more extensive study of 23 patients,¹⁶ has proposed the term "bronchioalveolar cell adenoma" to describe the lesions referred to here as atypical hyperplasia. We believe that such categorisation of these abnormalities as benign neoplasms of bronchioalveolar type is premature in that, unlike comparable lesions in, for example, the colon, they have not been described except in association with a carcinoma. Further, the associated carcinomas, in our experience, are of parenchymal type, not of the classical bronchioloalveolar morphology.

The concept of a "field change" in an epithelium exposed to carcinogens, with progression from dysplasia and carcinoma in situ to invasive malignancy, is recognised in association with many human and animal tumours.^{17 18}

Such a progression is well recognised in the case of squamous carcinomas of the lung.³ Indeed bronchial carcinoma in situ is known to be particularly extensive in cases of synchronous multiple primary squamous carcinomas.¹⁹ These changes are strongly related to smoking history. An in situ stage for adenocarcinoma of the lung is not recognised. It is in this context that we describe a dysplastic change in peripheral lung that is strongly associated with parenchymal adenocarcinoma. We believe that these lesions may be important in the pathogenesis of such adenocarcinomas. Further morphological and epidemiological investigation of this disease association will be of great interest.

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