Staining pattern of type IV collagen and prognosis in early stage adenocarcinoma of the lung

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Abstract

Aims—To examine the prognostic value of basement membrane expression in early stage adenocarcinoma of the lung.

Methods—Using antibodies to type IV collagen, basement membrane expression at the tumour-stromal border was immunohistochemically analysed in 30 patients with early stage adenocarcinoma of the lung (pstage I and pstage II). Two patterns of staining for type IV collagen were observed: in the first one the staining line was conserved or partially fragmented; in the second the staining line was widely fragmented or absent in more than 10% of the tumour area. The first staining pattern was categorised as continuous and the second as discontinuous.

Results—Of the 24 patients with pstage I adenocarcinoma, 12 (50%) cases showed a continuous pattern. In only one (16.7%) of the six patients with pstage II adenocarcinoma was this pattern evident. Five year survival was greater in pstage I adenocarcinoma (65%) than in pstage II adenocarcinoma (17%), but the difference was not significant. When the analysis was restricted to the 24 patients with pstage I adenocarcinoma, five year survival was better in continuous pattern cases (88%) than in discontinuous pattern cases (20-5%) (p < 0.05). The survival curve of 12 patients with pstage I adenocarcinoma and a discontinuous pattern resembled that of the six patients with pstage II adenocarcinoma.

Conclusion—These findings suggest that patients with pstage I adenocarcinoma and a discontinuous pattern have histopathologically unrecognized micrometastasis when they come to surgery. The staining pattern of type IV collagen could help in the prognosis of pstage I adenocarcinoma of the lung after surgery.

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The survival curves of the patients were drawn using the Kaplan-Meier method, and statistical evaluation was carried out using the Wilcoxon test.

Results
All basement membranes in normal tissues were strongly and continuously stained using this method. But in the 30 lung adenocarcinomas different staining patterns were observed in the basement membrane, and the staining line looked either conserved or fragmented or even absent. As the staining pattern of type IV collagen was nearly always heterogeneous in a tumour we defined two main patterns. In the continuous pattern (fig 1A) staining was either conserved or occasionally fragmented in up to 10% of the tumour area. In the discontinuous pattern (fig 1B) staining was either absent or widely fragmented in more than 10% of the tumour area and, generally, the staining pattern was abnormal in over 80% of the tumour area. All our continuous pattern cases had over 90% normal staining (conserved or fragmented in a limited area of the tumour) and discontinuous pattern cases had over 80% abnormal staining (fragmented across extensive parts of the tumour foci, or absent).

Of the 24 patients with pstage I adenocarcinoma, 12 (50%) showed a continuous pattern and 12 (50%) a discontinuous pattern. Of the six patients with pstage II adenocarcinoma, only one (16-7%) showed a continuous pattern (table). Better five year survival trends were observed in the group with pstage I adenocarcinoma (65%) than in the group with pstage II adenocarcinoma (17%). However, no significant difference in survival was observed between the pstage I and II adenocarcinoma groups (fig 2).

When the analysis was restricted to the 24 patients with pstage I adenocarcinoma, a better five year survival was observed for patients with continuous patterns (88%) than for patients with discontinuous patterns (20-5%) (p < 0-05) (fig 3). The survival curve of 12 patients with pstage I adenocarcinoma and a discontinuous pattern of type IV collagen...
staining resembled that of the six patients with stage II adenocarcinoma (fig 3).

Discussion

Many authors have stated that TNM stage is an important prognostic factor in adenocarcinoma of the lung. The five year survival of patients with stage I adenocarcinoma was only about 60–70%. However, tumour recurrence in patients whose disease was categorized as stage I indicates the existence of prognostic factors other than TNM. Besides TNM-related factors, the following prognostic factors have been mentioned: histological subtype; degree of differentiation; vascular invasion; the degree of collagenisation; mitotic index; and nuclear DNA content.

Recent reviews have shown that the changes in basement membrane distribution are related to prognosis in carcinomas of various organs, such as colorectal carcinoma and bladder carcinoma. But very few reports have been published about basement membrane expression in early stage lung cancer, especially stage I adenocarcinoma of the lung.

Invasion and metastasis are hallmarks of malignant neoplasia and frequently determine the course of the disease. Invasion precedes metastasis and interactions between tumour cells and the extracellular matrix are involved in this dynamic process. In carcinoma the first step is penetration through the epithelial basement membrane.

The difference of the type IV staining patterns observed in our cases was obvious and the intratumour heterogeneity of the staining was such that no mistakes could be made. The most interesting and important finding was the correlation of basement membrane staining pattern with prognosis in stage I adenocarcinoma. The 12 patients with a continuous pattern of type IV staining had a significantly better prognosis than the 12 patients with a discontinuous pattern. Moreover, the survival curve of the 12 patients with a discontinuous pattern in stage I adenocarcinoma resembled that of the six patients with stage II adenocarcinoma. These findings suggest that patients with stage I adenocarcinoma and a discontinuous pattern have histopathologically recognised lymph node metastasis (micrometastasis) at the point of surgery.

From this limited study we cannot explain with certainty why prognosis in stage I adenocarcinoma of the lung seems to be different between the two groups of patients, as defined by the staining pattern for type IV collagen.

However, several factors must be considered to understand the correlation between alterations in basement membrane components and poorer prognosis. In tumours there seems to be a balance between the synthesis of these components by epithelial malignant cells and the degradation of basement membrane by various tumour derived proteases. Extensive basement membrane expression in a neoplasm is probably a sign of a competent host response or of limited metastatic capability.

We can't explain why this imbalance occurs in stage I lung adenocarcinomas. We are now studying the expression of some tumour derived proteases to elucidate this.

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