The value of anticytokeratin antibodies in differentiating mesothelioma from lung carcinoma

V M Joglekar, D Oliver, M Harris

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Monoclonal anticytokeratin and glial acidic protein. I. A study of 35 cases of pleural mesothelioma and lung carcinoma.

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Monoclonal anticytokeratin and glial acidic protein. I. A study of 35 cases of pleural mesothelioma and lung carcinoma.
Further 4 μ sections were cut for the alkaline phosphatase anti-alkaline phosphatase (APAAP) immunostaining technique. Eight pleural biopsy cases now had insufficient cells for immunostaining and these were excluded from the study leaving 40 pleural biopsies for analysis (13 carcinomas, 17 mesotheliomas). The sections were labelled numerically by one of us (DO), who was aware of the diagnosis. The sections were mounted with starch adhesive and allowed to dry for 30 minutes at 60°C. Sections were treated with trypsin for 20 minutes, stained by the AAPAP immunooalkaline staining method as previously described, and mounted with glycerine jelly.

The stained sections were then assessed independently and blindly by two of us (VMJ, MH). Staining was considered positive when most cells showed the reddish reaction product or negative if no reaction was observed. The two assessments were then correlated with each other and with the pleural biopsy and postmortem diagnosis at the end of the study.

Table 1 Antibody results for postmortem material from 113 cases

<table>
<thead>
<tr>
<th>Tumour type (No of cases)</th>
<th>Antikeratin AE1 (% No)</th>
<th>HMFG 2 (% No)</th>
<th>CEA (% No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma (53)</td>
<td>+ 40 (75-5)</td>
<td>10 (18-9)</td>
<td>2 (3-8)</td>
</tr>
<tr>
<td></td>
<td>- 40 (66-7)</td>
<td>29 (48-3)</td>
<td>22 (36-7)</td>
</tr>
<tr>
<td>Carcinoma (60)</td>
<td>+ 20 (33-3)</td>
<td>31 (51-7)</td>
<td>38 (63-3)</td>
</tr>
</tbody>
</table>

Table 2 Antibody results for pleural biopsy material from 40 cases

<table>
<thead>
<tr>
<th>Tumour type (No of cases)</th>
<th>Antikeratin AE1 (% No)</th>
<th>HMFG 2 (% No)</th>
<th>CEA (% No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesothelioma (26)</td>
<td>+ 17 (65-4)</td>
<td>6 (23-1)</td>
<td>4 (15-4)</td>
</tr>
<tr>
<td></td>
<td>- 11 (78-6)</td>
<td>6 (42-6)</td>
<td>5 (35-7)</td>
</tr>
<tr>
<td>Carcinoma (14)</td>
<td>+ 9 (34-6)</td>
<td>20 (76-9)</td>
<td>22 (84-6)</td>
</tr>
<tr>
<td></td>
<td>- 3 (21-4)</td>
<td>8 (57-4)</td>
<td>9 (64-3)</td>
</tr>
</tbody>
</table>
APAAP technique has been tried previously on histological material from lung carcinoma and mesothelioma. In our experience the intensity of the staining reaction did not appear to deteriorate in postmortem material and the red staining reaction was easier to interpret compared with the brown reaction product of the immunoperoxidase method.

Necropsy Study

AntiCEA

Table 1 shows that antiCEA is by far the most useful antibody, 51 out of 53 (96-2%) mesotheliomas staining negatively. In our study antiCEA was also absent, however, in many cases of carcinoma (38 of 60; 63-3%). This is a higher percentage of negative carcinomas than in previous reports, which show a range between 0\(^\text{12}\) and 28\%. Initial reports\(^\text{3,12}\) gave conflicting results, perhaps due to the use of trypsin, different polyclonal antisera, or different staining techniques, or due to non-specific, cross reacting antigen. When this was absorbed by spleen powder and when monoclonal antiCEA with prior trypsin digestion (as in this study) was used, mesotheliomas were usually negative. The occurrence of a high proportion of antiCEA negative adenocarcinomas in our study obviously reduces the value of the reaction as a discriminant between carcinoma and mesothelioma.

HMFG2

The next most useful antibody was HMFG2, 43 out of 53 (80-1%) mesotheliomas staining negatively. Fifty two per cent of carcinomas were also negative, however. Early studies gave differing results with HMFG2; thus Battifora and Kopinski\(^\text{9}\) found negative staining for HMFG2 in mesothelioma (0/16), whereas Marshall et al\(^\text{8}\) (12/16) and Stickler et al\(^\text{6}\) (6/6) found positive staining with the same antibody. Our results differ from these studies in that HMFG2 positivity occurred in a minority of mesotheliomas but was more likely to be negative. Conflicting results in earlier studies may have been due to the small sample analysed compared with the amount in our study. A contributory factor may be the affinity of the sera used, as the HMFG2 molecule is a large one with multiple binding sites.\(^\text{2}\) Our results indicate that HMFG2 would be a useful second antibody in the diagnosis of mesothelioma in combination with antiCEA.

Antikeratin

Although an early report\(^\text{1}\) suggested that antikeratin profiles helped to distinguish adenocarcinoma from mesothelioma, later studies\(^\text{5,9,12}\) failed to support this view. A reason for this may have been the use of polyclonal antisera in the early study or the testing of only a small number of mesotheliomas. Our study with a monoclonal antiserum shows that antikeratin antibodies are not useful in distinguishing mesothelioma from lung carcinoma, similar staining reactions occurring in both situations. An immunoperoxidase study\(^\text{14}\) of 30 cases of sarcomatoid, and mixed types of diffuse malignant mesothelioma, however, showed that it helps to distinguish this group from other spindle cell lung neoplasms. Our 10 cases in this group did not provide a result that was as clear cut.

Biopsy Autopsy Correlation

The pleural biopsy part of this study showed that in any individual case the main problem was the inadequate harvest of diagnostic cells; of the original 60 cases 20 had to be eliminated for this reason. When tumour was present in sufficient quantity the antiCEA and HMFG2 reaction correlated reasonably well with the postmortem results. A practical point is that normal alveolar lining cells stain positively for HMFG2 so that care must be taken to ensure that only tumour cells are evaluated in the pleural biopsy. Also leucocytes sometimes stain positively for antiCEA although these were not likely to be confused with tumour cells.

In general the three antibodies showed the same trends found in the postmortem series. When the pleural biopsy series was compared with the postmortem results, complete agreement was found with the three antibodies tested in 26 out of 40 cases (65%; 15 mesotheliomas, 11 carcinomas). Discrepancies in the 14 cases between the two series occurred in the antikeratin reactions (11 mesotheliomas, one carcinoma), HMFG2 (five mesotheliomas, one carcinoma), and antiCEA (one mesothelioma, one carcinoma). In every case the discrepancy resulted from a negative biopsy reaction and a positive postmortem reaction suggesting a sampling problem in the pleural biopsy.

The diagnosis of pleural mesothelioma at necropsy examination is an important problem for the pathologist as the success or failure of individual compensation claims can hinge on that person's conclusions. In this study we have shown that in most cases immunohistochemistry on material from necropsy accurately reflects the results obtained in biopsies from the same patients, suggesting that it is a valid diagnostic procedure. Although our results confirm that antiCEA and HMFG2 are useful in distinguishing mesothelioma from carcinoma, we found a smaller proportion of carcinomas in general and adenocarcinomas in particular staining with the two antibodies than most other workers. This, taken together with our finding and those in other series that a number of mesotheliomas are positive for antiCEA and HMFG2 reduces the value of the staining reactions when applied to the individual case. They should not, therefore, be used as the sole criteria by medical panels in deciding the origin of a given tumour for mesothelioma compensation claims.
We thank the Northern Regional Health Authority research committee for providing the funds to conduct this project.

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Accepted 11 June 1990
The value of anticarcinoembryonic antigen, human milk factor globulin, and antikeratin antibodies in differentiating mesothelioma from lung carcinoma.

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doi: 10.1136/oem.48.1.34

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