

論 文 内 容 要 旨

Mucin 21 is a novel, negative immunohistochemical marker for epithelioid mesothelioma for its differentiation from lung adenocarcinoma

(上皮型中皮腫と肺腺癌の鑑別診断における新規マーカーMUC21の有用性)

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Introduction The prognosis of malignant mesothelioma is extremely poor and its incidence has been increasing worldwide. Treatments for mesothelioma, including surgery, chemotherapy, radiotherapy, and immunotherapy, have been developed. For the adequate treatment of malignant mesothelioma, an early, accurate pathological diagnosis is essential. Among three histologic subtypes of malignant mesothelioma: epithelioid, sarcomatoid, and biphasic, epithelioid mesothelioma is occasionally misdiagnosed as lung adenocarcinoma and vice versa owing to the similarity of the histomorphological patterns between them. Therefore, immunohistochemical markers are necessary for the precise diagnosis of epithelioid mesothelioma. Currently, the International Mesothelioma Interest Group (iMig) recommends various immunohistochemical markers of epithelioid mesothelioma and lung adenocarcinoma. Calretinin, podoplanin (D2-40), wilms tumour (WT1), and cytokeratin5/6 are positive mesothelioma markers and carcinoembryonic antigen (CEA), claudin-4, thyroid transcription factor-1 (TTF-1), and napsin-A are positive lung adenocarcinoma markers. Combinations of these markers have advanced our diagnostic capabilities. However, there are no absolute immunohistochemical markers to definitively diagnose epithelioid mesothelioma. Therefore, the search for the novel immunohistochemical markers is still desirable. In this study, we evaluated the utility of MUC21 expression as an immunohistochemical marker to differentiate epithelioid mesothelioma from lung adenocarcinoma.

Materials and Methods We reanalysed the microarray gene expression data for epithelioid mesothelioma and lung adenocarcinoma that we had published previously and determined the differentially expressed genes, based on those that exhibited more than a 2-fold change. Gene expression analysis was also validated with MUC21 expression in mesothelioma cell lines and lung adenocarcinoma cell line by western blotting. The utility of MUC21 in the differential diagnosis of epithelioid mesothelioma and lung adenocarcinoma was examined by an immunohistochemistry.

Results Of the 58 genes that were differentially expressed, based on an at least 2-fold increase between epithelioid mesothelioma and lung adenocarcinoma, 35 were upregulated in epithelioid mesothelioma and 23 upregulated in lung adenocarcinoma. MUC21 expression exhibited very low expression signals in all 6 epithelioid mesothelioma cases and was present in many of the 6 lung adenocarcinoma samples. Western blot analysis showed the presence of MUC21 protein expression in lung adenocarcinoma cell line (A549), while no expression was observed for mesothelioma cell lines (ACC-MESO-1 and CRL-5915). Next, we investigated 70 cases of epithelioid mesothelioma and 70 cases of lung adenocarcinoma for MUC21 expression by the use of immunohistochemistry, and compared to other previously reported markers (CEA, claudin-4, TTF-1, napsin-A, and MUC4). MUC21 expression was

observed in the membrane of the lung adenocarcinoma tumour cells.

In lung adenocarcinoma cases, MUC21, CEA, claudin-4, TTF-1, napsin-A, and MUC4 expression was present in 67 (96%), 68 (97%), 68 (97%), 65 (93%), 58 (83%), and 53 (76%), respectively. All cases of lung adenocarcinoma with negative immunoreactivity for CEA (2 cases), claudin-4 (2 cases), TTF-1 (5 cases), napsin-A (12 cases), or MUC4 (17 cases) showed positive immunoreactivity for MUC21.

In epithelioid mesothelioma cases, MUC21 and claudin-4 expression was present in 2 (3%). Expression of CEA, TTF-1, napsin-A, and MUC4 was absent in all of the epithelioid mesothelioma cases.

The sensitivity, specificity, and accuracy of negative MUC21 expression for differentiating epithelioid mesothelioma from lung adenocarcinoma were 97%, 96%, and 96%, respectively. The sensitivity of negative MUC21 expression (97%) was lower than that of negative CEA, TTF-1, napsin-A, and MUC4 expression. However, the specificity of negative MUC21 expression (96%) was better than that of negative TTF-1, napsin-A, and MUC4 expression and comparable to that of negative CEA and claudin-4 expression.

Discussion-MUC21, formerly called as epiglycanin, was reported as a glycoprotein expressed on the surface of highly malignant TA3-Ha cells of A/HeHa mice. Itoh et al. identified a human counterpart of mouse mucin 21 (Muc21) and termed as MUC21. The mRNA expression of epiglycanin/MUC21 is found in the lung, thymus, and colon.

The sensitivity of negative MUC21 for the diagnosis of epithelioid mesothelioma from lung adenocarcinoma was slightly inferior to that of negative CEA, TTF-1, napsin-A, and MUC4 expression. However, the specificity was better than that of negative TTF-1, napsin-A, and MUC4 expression. The diagnostic accuracy of negative MUC21 expression (96%) was similar to that of CEA, claudin-4, and TTF-1 and better than that of napsin-A or MUC4. We also found MUC21 expression in the lung adenocarcinoma cases with no expression of either CEA, claudin-4, TTF-1, napsin-A, or MUC4. Moreover, two lung adenocarcinoma cases, one negative for both CEA and claudin-4 and the other negative for both CEA and TTF-1, had MUC21 expression. Various lung adenocarcinomas showing only a +1 score for CEA, claudin-4, TTF-1, napsin-A, or MUC4 showed a MUC21 expression of score of 2+ or 3+. Thus, by using MUC21, we can reduce the number of false-negative cases of lung adenocarcinoma. Therefore, the addition of MUC21 immunohistochemistry will aid in the precise diagnosis of epithelioid mesothelioma.

Conclusion We propose MUC21, identified by gene expression analysis, as an additional novel negative marker for epithelioid mesothelioma for the differentiation of epithelioid mesothelioma from lung adenocarcinoma. Further validation is required to support our findings in other laboratories.