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Original Article

Do mesothelin/MUC16 interactions facilitate adenocarcinoma metastases to intracranial meningiomas?

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Abstract

Background: Meningiomas have been shown to express mesothelin, a high affinity binding site for MUC16, a transmembrane protein on adenocarcinoma cells. The mechanisms underlying adenocarcinoma metastases to meningiomas may provide insight into tumor-to-tumor metastases and adenocarcinoma metastases to leptomeningeal cells.

Methods: Two meningiomas containing metastases from adenocarcinomas were identified and evaluated immunohistochemically for the expression and localization of mesothelin and MUC16.

Results: Both meningiomas show extensive mesothelin immunoreactivity, and the adenocarcinomas metastatic to the meningiomas show mesothelin and MUC16 immunoreactivity at the interface with meningioma.

Conclusions: Interactions between MUC16 and/or mesothelin on the cell membrane of adenocarcinoma cells with mesothelin on meningioma cells may facilitate adenocarcinoma metastases to meningiomas and possibly the leptomeninges.

Key Words: Meningiona, mesothelin, metastasis, MUC16, tumor-to-tumor

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INTRODUCTION

Adenocarcinomas are one group of carcinomas known to metastasize to the leptomeninges.[24,25,28] Several reports suggest that they represent the majority of tumors metastasizing to extant meningiomas in the leptomeninges.[2,4,6,8,11,15,17,20,22,27] The mechanisms underlying this this tumor-to tumor metasatases are not known. Identifying these factors may facilitate the development of therapies for these metastases.

Transmembrane mucins such as MUC1 and MUC16 are thought to facilitate the metastases of many carcinomas, including pulmonary adenocarcinomas.[7,10,21,30] These bind to a number of membrane proteins in recipient tissues.[7,10,21,30]

Mesothelin is a 40kDa glycosyl-phosphatidylinositol-anchored cell surface protein that has been identified in low levels in mesothelial cells of the pleura, pericardium, and peritoneum.[7,9,27] Mesothelin is a potential adhesion molecule for itself and is a receptor for MUC16. It is commonly expressed by adenocarcinoma

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cells. Previously, we found widespread expression of mesothelin in leptomeninges and meningiomas.[12,13] It is also overexpressed in mesotheliomas, pancreatic, and pulmonary adenocarcinomas and squamous cell carcinomas of the head, neck, lung, esophagus, cervix, and vulva.[5,16,29] The functions of mesothelin are not established, however, it may function as a binding site for transmembrane mesothelin and mucins expressed by tumor cells.[5,16]

Recently, it has been shown that mesothelin binds MUC16, a type I transmembrane protein that belongs to the mucin family of glycoproteins. It is also called CA125.[10] In the peritoneum, mesothelin binds MUC16/CA125 with high affinity anchoring ovarian adenocarcinoma facilitating carcinomatous peritonitis.[7,21] In the present study, we evaluated whether two meningiomas with intratumoral metastasis from adenocarcinomas co-express mesothelin and MUC16/CA125 and whether this co-localized at the sites of metastasis.

MATERIALS AND METHODS

Two meningiomas with intratumoral adenocarcinoma were identified in the University of Rochester archives and consultative material after obtaining Institutional Review Board approval. The first was from a 74-year-old male with a right frontal transitional meningioma. He had a known lung mass. The second patient was a 66-year-old female with a left sphenoid wing meningioma and an adenocarcinoma identified 2 years earlier.

Immunohistochemistry

Each case was analyzed with a monoclonal antibody to human mesothelin.[18,19] The mesothelin antibody is made against 100 amino acid sequence present in the membrane-bound form of mesothelin (clone 5B2, Novo Castra, Newcastle upon Tyne, UK), which has been characterized previously.[18,19] MUC16 (OV185:1, Santa Cruz Biotechnology Inc. Santa Cruz, CA) was prepared with streptavidin-biotin immunohistochemistry, as described previously.[12,13]

RESULTS

Pathology

Patient 1. The sections revealed a transitional, meningioma containing a relatively circumscribed, poorly differentiated adenocarcinoma with clear cell features and necrosis. The metastasis exhibited vimentin, cytokeratin 7, TTF-1, and AE1/AE3, however, no cytokeratin 20 or S-100 immunoreactivity. The adenocarcinoma had clear periodic acid schiff (PAS) and dPAS negative cytoplasm, large pleomorphic nuclei with prominent nucleoli, and focal glandular formation and necrosis. Ki-67 labeling was brisk in the metastasis and approximately 6% in the meningioma. The meningioma had numerous whorls and rare mitoses, but no loss of lobularity, with only modest cellularity and no definite small cell component. The PAS/PAS-D stain revealed no clear cell component.

Patient 2. The meningioma was transitional with atypical features, including hypercellularity, focal loss of lobular pattern, small cell change, and focal necrosis. The meningioma showed extensive epithelial membrane antigen (EMA) but no CAM 5.2, cytokeratin 7, TTF-1, napsyn, or PAS staining. The metastatic adenocarcinoma shows gland formation. The epithelioid cells had prominent nucleoli, high mitotic activity, and necrosis and Kreyberg staining. The carcinoma cells showed EMA, Cam 5.2, cytokeratin 7, napsyn, TTF-1, and Ki-67 labeling of 60%.

Immunohistochemistry

Mesothelin immunoreactivity was detected in both meningiomas and was extensive [Figure 1a and 2a].High mesothelin expression was also seen in the adenocarcinoma metastases to the meningiomas [Figure 1c and 2c].

Muc16 immunoreactivity was not detected in either meningioma [Figure 1b and 2b], however, was variably detected in both adenocarcinomas, including focal areas with mesothelin in the carcinoma and interface with the meningioma immunoreactivity [Figure 1d and 2d].

DISCUSSION

Previously, we have demonstrated mesothelin expression in the majority of meningioma and 30% of human leptomeninges tested.[12] Several groups have suggested that adenocarcinomas may metastasize frequently to the peritoneum and pleura due to interactions between

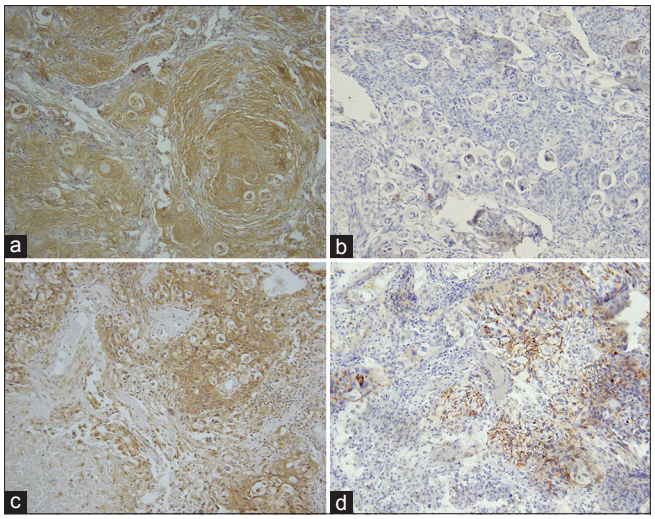

Figure 1: Mesothelin and MUC16 expression in meningiomas with adenocarcinoma metastasis in patient 1. Meningioma with mesothelin immunoreactivity (a) but no MUC16 (b). Metastatic adenocarcinoma to meningioma showing mesothelin (c) and MUC16 (d) Hematoxylin counterstain and diaminobenzidine chromagen (Original magnification, ×400)

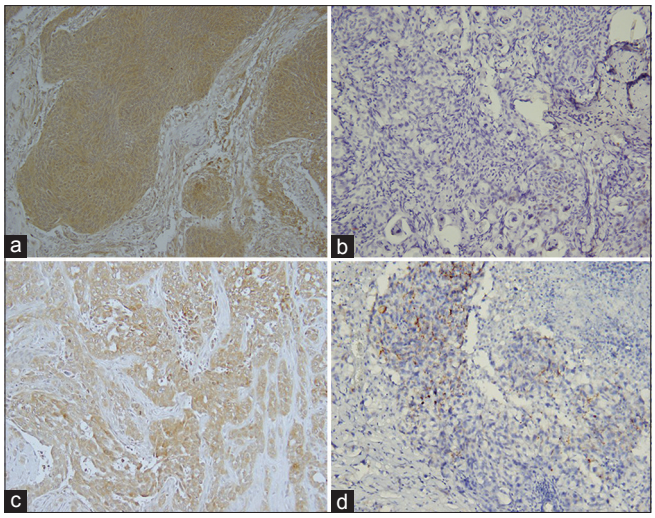

Figure 2: Mesothelin and MUC16 expression in meningiomas with adenocarcinoma metastasis in patient 2. Meningioma with mesothelin immunoreactivity in meningioma (a) and in adenocarcinoma metastatic to meningioma (c). Lack of MUC 16 in meningioma (b) but extensive immunoreactivity in adenocarcinoma (d) Hematoxylin counterstain and diaminobenzidine chromagen (Original magnification, ×400)

mesothelin and MUC16. High concentrations of mesothelin in these tissues as well as its high affinity for MUC16 have been noted;[7,21] we have also reported the same observation.[13] Some, but not all, MUC16 adenocarcinoma also metastasized to the leptomeninges, however, not in significantly higher numbers than MUC16 adenocarcinomas spreading to the peritoneum and pleura.[13] This may reflect the limited expression of mesothelin the leptomeninges, and thus limited binding sites.[12]

In contrast, meningiomas show widespread mesothelin expression and may have more favorable binding sites for MUC16-expressing carcinomas. Consistent with this is our finding of widespread mesothelin in both meningiomas as well as MUC16 in both carcinomas. Thus, these interactions may represent another mechanism by which tumors metastasize to remote tissues (and tumors).[1]

Mesothelin may also facilitate metastases by other mechanisms. Recent studies have shown that mesothelin induces expression of metaloproteinase MMP9, which has been implicated in tumor invasion.[3,23,24] Numerous other factors may also contribute to this tumor-to-tumor metastasis. For example, proportionately higher blood flow to the meningioma than to the leptomeninges or brain may influence the site of metastasis. In addition, changes in e-cadherin-catenin complex expression, expression of other adhesion molecules with receptors on endothelial cells, paracrine expression of various growth factors, and stromal proteases affecting transmigration across blood vessel/endothelial barriers likely have complex effects on this tumor-to-tumor metastases.[26,28] Nonetheless, analyses of these is beyond the scope of this study.

Targeting mesothelin with an anti-mesothlin immunotoxin SS1P binding has been shown to cause regression of mesothelin-expressing tumors in athymic mice. It also has exhibited tumoricidal effects on mesotheliomas and ovarian carcinomas.[5,14,18] Vaccines against mesothelin are also being developed.[5,18] Because of the low level of mesothelin expression in a limited number of normal tissues, as well as high levels of expression in some tumors, such as seen here, these therapies may prove to be relatively specific and are in phase I and II clinical trials.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Agalioti T, Giannou AD, Stathopoulos. Pleural involvement in lung cancer. J Thor Dis 2015;7:1021-30.
2. Bhargava P, McGrail KM, Manz HJ, Baidas S. Lung carcinoma presenting as metastasis to intracranial meningioma: Xase report and review of the literature. Am J Clon Oncol 1999;22:199-202.
3. Brown GT, Muttay GI. Current mechanistic insights into the roles of matrix metalloproteinases in tumor invasion and metastasis. J Pathol 2015;237:273-81.
4. Carr K, Hwe L, Weaver K, Highfield Nickols H. Renal cell carcinoma metastatic to meningioma: Tumor-tumor metastasis. Clin Neuropathol 2014;33:152-6.
5. Chang K, Pastan I. Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas and ovarian cancers. Proc Natl Acad Sci U S A 1996;93:136-40.
6. Glass R, Hukku S, Gershenhorn B, Alzate J, Tarr B. Metastasis of adenosquamous carcinoma to meningioma: Case report with literature review. Int J Clin Exp Pathol 2013;6:2625-30.
7. Gubbels JA, Belisle J, Onda M, Rancourt C, Migneault CM, Ho M, *et al.* Mesothelin- MUC16 binding is a high affinity, N-glycan dependent interaction that facilitates peritoneal metastasis of ovarian tumors. Mol Cancer 2006;5:50-65.
8. Hamperl M, Goehre F, Schwan S, Jahromi BR, Ludka CM, Mendel T, *et al.* Tumor-to-tumor metastasis - Bronchial carcinoma in meningioma. Clin Neuropathol 2015;34:302-6.
9. Hassan R, Bera T, Pastan I (2004) Mesothelin: A new target for immunotherapy. Clin Cancer Res 2004;10:3937-42.
10. Hollingsworth MA, Swanson BJ. Mucins in cancer: Protection and control of the cell surface. Nat Rev Cancer 2004;4:45-60.
11. How E, Lee R, Kasem K, Withers T. Surprise within a meningioma: Case report of a signet ring cell carcinoma in a meningioma. ANZ J Surg 2015:10:1111.
12. Johnson MD, O'Connell M, Vito F. Mesothelin in leptomeninges and meningiomas. J Histochem Cytochem 2008;56:579-85.
13. Johnson MD, Vito F, Xu H. MUC16 Expression and Risk of Adenocarcinoma Metastases to Peritoneum, Pleura, Leptomeninges and Brain. J Appl Immunohistochem Mol Morphol 2010;18:250-3.
14. Kelly RJ, Sharon E, Pastan IR, Hassan R. Mesothelin-targeted agents in clinical trials and in preclinical development. Mol Cancer Ther 2012;11:517-25.
15. Kim KH, Hong EK, Lee SH, Yoo H. Non small cell carcinoma metastasis to meningioma. J Korean Neurosurg Soc 2013;53:43-5.
16. Kojima T, Oh-eda M, Hattori K, Taniguchi Y, Tamura M, Ochi N, *et al.* Molecular cloning and expression of megakaryocyte potentiating factor cDNA. J Biol Chem 1995;270:21984-90.

17. Okada E, Nakamura M, Koshida Y, Mukai K, Toyama Y, Matsumoto M. Breast carcinoma metastasis to meningioma in the thoracic spine: A case report and review of the literature. J Spinal Cord Med 2015;38:231-5.
18. Onda M, Willingham M, Nagata S, Bera TK, Beers R, Ho M, Hassa*et al*. New monoclonal antibodies to mesothelin useful for immunohistochemistry, fluorescence-activated cell sorting, western blotting and ELISA. Clin Cancer Res 2005;11:5840-6.
19. Ordonez, NG. Application of mesothelin immunostaining in tumor diagnosis. Am J Surg Pathol 2003;27:1418-28.
20. Ravnik J, Ravnik M, Bunc G, Glumbic I, Tobi-Veres E, Velnar T. Metastasis of an occult pulmonary carcinoma into meningima: A case report. World J Surg Oncol 2015;13:292.
21. Rump A, Morikawa Y, Tanaka M, Minami S, Umesaki N, Takeuchi M, *et al*. Binding of ovarian cancer cell antigen CA125/MUC16 to mesothelin mediates cell adhesion. J Biol Chem 2004;279:9190-8.
22. Sayegh ET, Henderson GA, Burch EA, Reis GF, Cha S, Oh T, *et al*. Intrameningioma metastasis of breast carcinoma. Rare Tumors 2014;6:5313.
23. Servais EL, Colovos C, Rodriquez LA, Bograd AJ, Nitadori J, Sima C, *et al*. Mesothelin overexpression promotes mesothelioma cell invasion and MMP-9 secretion in an orthotopic mouse model and in epithelioid pleural mesothelioma patients. Clin Cancer Res 2012;18:2478-89.
24. Smalley RV, Malmud LS, Ritchie WG. Preoperative scanning: Evaluation for metastatic disease in carcinoma of the breast, lung, colon and prostate. Semin Oncol 1980;7:358-69.
25. Svokos KA, Salhia B, Toms SA. Molecular biology of brain metastasis Int J Mol Sci 2014;15:9519-30.
26. Talukdar A, Khanra D, Mukhopadhay S, Bose D. Tumor-to-tumor metastasis: Adenocarcinoma of lung metastatic to meningioma. J Post Grad Med 2014;60:403-5.
27. Weible UH, Birzele F, Kollmorgen G, Ruger R. Dissection of the process of brain metsatasis reveals targets and mechanisms for molecular-based intervention. Cancer Genomics Proteomics 2016;13:245-58.
28. Wesseling P, von Deimling A, Aldape KD, Preusser M. Metastatic tumours of the CMS. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, editors. Tumours of the Nervous System. Geneva, Switzerland: WHO Press; 2016. p. 338-41.
29. Yamaguchi N, Hatori K, Oh-eda M, Kojima T, Imai N, Ochi N. A novel cytokine exhibiting megakaryocyte potentiating activity from a human pancreatic tumor cell line HPC-Y5. J Biol Chem 1994;269:805-8.
30. Yonezawa S, Goto M, Yamada N, Higashi M, Nomoto M. Expression profiles of MUC1, MUC2, and MUC4 mucins in human neoplasms and their relationship with biological behavior. Proteomics 2008;8:3329-41.