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Original contribution

Diagnostic utility of immunohistochemistry in distinguishing between epithelioid pleural mesotheliomas and breast carcinomas: a comparative study☆,☆☆

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Summary Epithelioid mesotheliomas and breast carcinomas can present a variety of morphologic patterns. Because of this, breast carcinomas that metastasize to the pleura and lung may be confused with mesotheliomas. The aim of the present study is to compare the immunohistochemical markers currently available for the diagnosis of these 2 malignancies and to determine the best panel of markers that can be used to assist in discriminating between them. Sixty epithelioid mesotheliomas and 80 breast carcinomas (40 triple negative and 40 estrogen receptor positive) were investigated for expression of the positive mesothelioma markers calretinin, keratin 5/6, mesothelin, podoplanin, thrombomodulin, and WT1; the positive carcinoma marker claudin 4; and the breast-associated markers gross cystic disease fluid protein 15 (GCDFP-15), mammaglobin, and GATA3. All of the epithelioid mesotheliomas reacted for calretinin and keratin 5/6, 93% for WT1; 88% for podoplanin; 77% for thrombomodulin; 23% for GATA3; and 0% for claudin 4, GCDFP-15, and mammaglobin, respectively. Of the triple-negative breast carcinomas, 100% expressed claudin 4; 5%, keratin 5/6; 30%, GATA3; 18%, mammaglobin; 15%, GCDFP-15; 56%, mesothelin; 38%, calretinin; 18%, thrombomodulin; 5%, WT1; and 3%, podoplanin. Among the estrogen receptor–positive breast carcinomas, 100% were claudin 4 and GATA3 positive; 70% expressed GCDFP-15; 63%, mammaglobin; 13%, calretinin; 13%, thrombomodulin; 8%, WT1; 5%, keratin 5/6; 3%, mesothelin; and 0%, podoplanin. It is concluded that podoplanin and WT1 are the best positive mesothelioma markers for differentiating epithelioid mesotheliomas from breast carcinomas. An accurate differential diagnosis can be reached with the use of these two markers in combination with the breast-associated markers GCDFP-15, mammaglobin, and GATA3.

1. Introduction

Breast carcinomas can metastasize to virtually any organ of the body, including the serosal membranes. Adenocarcinomas of the lung, breast, and gastrointestinal tract are the most common types of tumors that metastasize to the pleural membranes and cavity [1]. A diffuse involvement of the pleura is a common feature of mesothelioma; however,

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localized malignant mesotheliomas and nonmesotheliomatous tumors demonstrating a diffuse growth (pseudomesotheliomatous) pattern, including various types of carcinomas [2], primary pleural sarcomas [3,4], cystosarcoma phyllodes of the breast [5], thymic epithelial tumors [6], and lymphomas [7], have been described. The most common pseudomesotheliomatous carcinomas of the pleura are peripheral lung carcinomas, particularly adenocarcinomas, but squamous cell carcinomas, small cell carcinomas, basaloid carcinomas, and carcinosarcomas as well as nonpulmonary metastatic carcinomas, including breast carcinomas, transitional cell carcinomas of the bladder, renal cell carcinomas, pancreatic and prostatic adenocarcinomas, Merkel cell carcinomas, and squamous cell carcinomas of the head and neck, have also been reported [2,8-10]. Because mesotheliomas can present a diverse array of cytomorphologic features and grow in a wide range of histologic patterns, they can resemble a variety of carcinomas, including those of the breast. When the patient has a history of breast carcinoma, the differential diagnosis between a metastatic breast carcinoma and an epithelioid mesothelioma is relatively easy; however, if the patient's history is unavailable to the pathologist at the time of the evaluation of the biopsy or cytology specimen or if the patient has no known history of breast carcinoma, the differential diagnosis can become difficult. In addition, cases of synchronous epithelioid malignant mesothelioma and breast carcinoma in individuals exposed to asbestos [11] as well as rare cases of breast carcinoma metastasizing to a malignant mesothelioma [8] have been documented in the literature.

Over the past 2 decades, numerous studies have been published on the value of immunohistochemistry as an ancillary technique in the diagnosis of mesothelioma. The primary focus of these studies has been on the distinction between epithelioid pleural mesotheliomas and metastatic lung adenocarcinomas [12], squamous cell carcinomas [13], or renal cell carcinomas [14] as well as on the value of immunohistochemistry in discriminating between epithelioid peritoneal mesotheliomas and serous carcinomas involving the peritoneum [15]. It has recently been reported that the so-called positive mesothelioma markers calretinin and keratin 5/6, which are frequently used to assist in the differential diagnosis of mesothelioma, are also frequently positive in some subgroups of breast carcinomas, and because of this, some breast carcinomas can potentially be misdiagnosed as a mesothelioma [16,17]. The purpose of the present article is to investigate the frequency with which various commonly used positive mesothelioma markers are expressed in breast carcinomas, particularly triple-negative breast carcinomas, which are the ones that can potentially cause the most diagnostic difficulty because of their lack of estrogen and progesterone receptors, and the frequent presence of a basal-like phenotype in a subgroup of these tumors, including the expression of keratin 5/6, which is found in a large percentage of triple-negative breast carcinomas, and to determine the best markers that can be used for assisting in distinguishing between epithelioid pleural mesotheliomas and breast carcinomas involving the lung and pleura. Also investigated is the expression of various breast-associated carcinoma markers, including the recently available GATA3. To our knowledge, a comprehensive study primarily focused on comparing the immunoprofile of epithelioid pleural mesothelioma with that of breast carcinoma, including triple-negative breast carcinoma, has not yet been published.

2. Materials and methods

This study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center. The material used in this study was obtained from the files of the Department of Pathology at this institution. It consisted of 60 epithelioid pleural mesotheliomas and 80 invasive breast carcinomas. In all of the mesothelioma cases, the diagnosis was confirmed by the use of histologic and immunohistochemical criteria combined with clinical and radiologic information. The breast carcinomas consisted of 40 cases of triple-negative breast carcinoma, which were defined by the lack of estrogen receptor (ER), progesterone receptor, and HER2 together with aggressive clinical behavior, and 40 ER-positive breast carcinomas, which were included for comparison purposes.

Immunohistochemical studies were performed on 5-μm-thick, formalin-fixed, paraffin-embedded tissue sections using the polymeric biotin-free horseradish peroxidase method on a Leica Microsystems BOND-MAX Stainer (Bannockburn, IL). The primary antibodies used are listed in Table 1. In brief, slides were deparaffinized and hydrated, followed by heat-induced antigen retrieval in which either a citrate buffer solution, pH 6.0, or a Tris-EDTA solution, pH 8.0, was used. Incubation with the primary antibody was followed by development of the immunostaining using either 3,3′-diaminobenzidine or 3-amino-9-ethylcarbazole as chromogen. The secondary antibody and detection were applied as per instructions from the manufacturer (Leica Biosystems). To evaluate the specificity of the immunoreaction, known positive and negative tissues were used as controls. The immunostaining was graded on a sliding scale of 1+ to 4+ according to the percentage of reactive cells (1+, 1%-25%; 2+, 26%-50%; 3+, 51%-75%; 4+, >75%).

3. Results

The immunostaining results are summarized in Table 2.

3.1. Calretinin

All 60 mesotheliomas (100%) reacted for calretinin. The staining was strong and diffuse (3+ or 4+) and occurred in both the cytoplasm and nucleus (Fig. 1A). Of the triple-negative breast carcinomas, 15 (38%) were calretinin