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# What are the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma? A review and update

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**Summary** Numerous immunohistochemical markers that can assist in the diagnosis of epithelioid mesotheliomas, some of which have only recently been recognized, are currently available. Because the various types of carcinomas express these markers differently, their selection for inclusion in a diagnostic panel can vary according to the differential diagnosis. This article provides a critical review of all of the information that is presently available on those markers that are believed to have the greatest potential for assisting in distinguishing between epithelioid mesotheliomas and those carcinomas with which they are most likely to be confused. Information is also provided regarding the panels of immunohistochemical markers that are, at present, recommended in these differential diagnoses.


## 1. Introduction

The diagnosis and management of mesotheliomas continue to be a major problem for both clinicians and pathologists. The accuracy of the histopathologic diagnosis of this malignancy is critical to the successful evaluation of clinical trials and is of paramount importance in the determination of a compensation settlement for those individuals with a history of asbestos exposure. Despite the existence of a large volume of literature on the pathology of mesotheliomas describing the histomorphology of these tumors, it is not always possible to reach a firm diagnosis by the study of routine histologic or cytologic light microscopic preparations. The inherent ability of the cells of the serosal membranes to alter their appearance and phenotype, as is frequently manifested in the tumors arising from these structures, and the occurrence of morphologic variants compound the difficulties encountered in diagnosing these neoplasms. An important characteristic of mesotheliomas is their ability to exhibit a broad range of cytomorphological features and to grow in a wide variety of histologic patterns. When presenting a tubular or papillary pattern, mesotheliomas can be confused with adenocarcinomas, and when they present a sarcomatoid morphology, they can often be confused with sarcomatoid carcinomas or sarcomas composed of spindle cells or having pleomorphic features. Of the various ancillary techniques that have been used in the differential diagnosis of mesotheliomas, immunohistochemistry has been recognized as having the most practical utility, especially when distinguishing epithelioid mesotheliomas from peripheral adenocarcinomas of the lung involving the pleura and from metastatic carcinomas arising from a distant organ, such as, the kidney. In the peritoneum, epithelioid mesotheliomas may resemble papillary peritoneal serous carcinomas or metastatic serous carcinomas of the ovary.

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Because an absolutely specific and sensitive marker for mesotheliomas has not yet been recognized, the immunohistochemical diagnosis of epithelioid mesotheliomas largely depends on the use of panels of markers that are frequently expressed in mesotheliomas (positive mesothelioma markers) combined with those that are commonly expressed in carcinomas (positive carcinoma markers). These panels, however, are continually changing as a result of the identification of new markers that could be useful in the differential diagnosis of these tumors and the publication of new information regarding the value of individual markers. The purpose of this article is to review the information available for those markers that have, for some time, been used in the diagnosis of epithelioid mesotheliomas and to determine their current diagnostic value when compared with markers that have recently become available. Particular emphasis will be placed on those newly recognized markers for which there is some evidence that they could be useful in distinguishing epithelioid mesotheliomas from the different types of carcinomas with which they may be confused. To facilitate the discussion of the markers and to make such a discussion easier for the reader to follow, the various markers have been subdivided into 3 groups: positive mesothelioma markers, positive carcinoma markers, and miscellaneous markers. It should be mentioned that the placement of some of these markers, especially those in the miscellaneous group, is somewhat arbitrary because, in some instances, various individual markers could also be regarded as either a positive mesothelioma marker or a positive carcinoma marker.

## 2. Positive mesothelioma markers

Markers that are commonly expressed in mesotheliomas, but not in carcinomas, have only relatively recently been recognized. A list of these markers, which are often referred to as *positive mesothelioma markers*, is shown in Table 1.

### 2.1. Podoplanin

Podoplanin is the most recently recognized of the positive mesothelioma markers. It is a 38-kd mucin-type transmembrane glycoprotein with extensive O-glycosylation and a high content of sialic acid. In 1996, Wetterwald et al [41] were the first to identify this protein, which they designated E11 antigen, in lymphatic endothelial cells, epithelial cells of the choroid plexus, alveolar type I cells, osteoblasts, and peritoneal mesothelial cells [41]. Subsequently identified on the surface of rat glomerular epithelial cells (podocytes), this protein was named podoplanin because it was found to be involved in the flattening of foot processes in puromycin-induced nephrosis [42]. Recent investigations have demonstrated that podoplanin, the so-called oncofetal M2A antigen expressed in germ cell tumors that is recognized by the recently commercially available D2-40 antibody, and the type I alveolar cell marker

**Table 1** Positive mesothelioma markers that have been suggested to be useful in the diagnosis of epithelioid mesotheliomas

| Marker | Current value/comments | Selected references |
|---|---|---|
| Podoplanin | Very useful for distinguishing mesotheliomas from lung adenocarcinomas or renal cell carcinomas, but its value for discriminating mesotheliomas from serous or squamous carcinomas is limited. | [1-6] |
| Calretinin | Very useful for distinguishing mesotheliomas from lung adenocarcinomas or renal cell carcinomas, but its value for discriminating mesotheliomas from serous or squamous carcinomas is limited. | [5-18] |
| Keratin 5/6 | Very useful for distinguishing mesotheliomas from lung adenocarcinomas or renal cell carcinomas, but it has no utility in discriminating mesotheliomas from serous or squamous carcinomas. | [5,11,13,15-23] |
| WT1 protein | Very useful for distinguishing mesotheliomas from lung adenocarcinomas or squamous carcinomas. It may also have some utility for discriminating between mesotheliomas and renal cell carcinomas, but it is not useful for assisting in the differential diagnosis between mesotheliomas and serous carcinomas. | [5,6,17,18,24-30] |
| Thrombomodulin | Limited utility. It was the first positive mesothelioma marker that proved to be useful in distinguishing these tumors from lung adenocarcinomas and from serous carcinomas. It may also assist in discriminating between mesotheliomas and renal cell carcinomas, but it has no value in distinguishing mesotheliomas from squamous carcinomas. | [5,11,13,14,17,18,31-37] |
| Mesothelin | Limited utility for distinguishing between mesotheliomas and adenocarcinomas and squamous carcinomas of the lung. It can be useful in discriminating between mesotheliomas and renal cell carcinomas, but has no utility in distinguishing between mesotheliomas and serous carcinomas. Because of its high sensitivity for mesotheliomas, it may help when the standard battery is equivocal; a negative staining is a strong indication against the diagnosis of mesothelioma. | [6,18,38-40] |