Il mesotelioma pleurico
Il percorso anatomo-patologico attuale. E in futuro?

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SURGICAL
CLINICS OF
NORTH AMERICA

Surg Clin N Am 82 (2002) 797–831

Malignant mesothelioma: options for management

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The management of malignant mesothelioma remains controversial, though many common themes have emerged after several decades of experience, including earlier diagnosis, the use of multimodal therapy, and the collaboration between medical centers with expertise in mesothelioma treatment to organize multicenter trials. There is no clear consensus on the treatment of malignant pleural mesothelioma, in contrast to the treatment of most other tumors. The need to find effective treatment is crucial, given the dramatically increasing incidence of mesothelioma in most western countries. This trend is expected to peak around the year 2020. It is estimated that mesothelioma deaths in men will double over the next 20 years [1].

With the new improved staging system, it may be easier to decide the best therapeutic options after delineating the extent of disease. Mesothelioma tends to remain confined to the pleural space early in its course and can remain confined for long periods of time, making it suitable for radical surgery (Figs. 1–3). For patients with stage I tumors and good performance status, pleuropneumonectomy combined with chemotherapy and radiotherapy provides the best chance of prolonged survival. Similarly, a subset of patients with epitheloid histology but advanced stages may still have some added benefit of pleuropneumonectomy. Debulking pleurectomy and decortication combined with adjuvant therapy is a worthwhile alternative for patients with more advanced disease, impaired performance status, or tumors of less favorable histology (sarcomatous or biphasic); however, further investigation is required to determine the optimum combination. Recent evidence indicates that neither radiotherapy nor chemotherapy offers worthwhile prolonged disease control when used in isolation, although both have an important role as part of multimodal therapy.

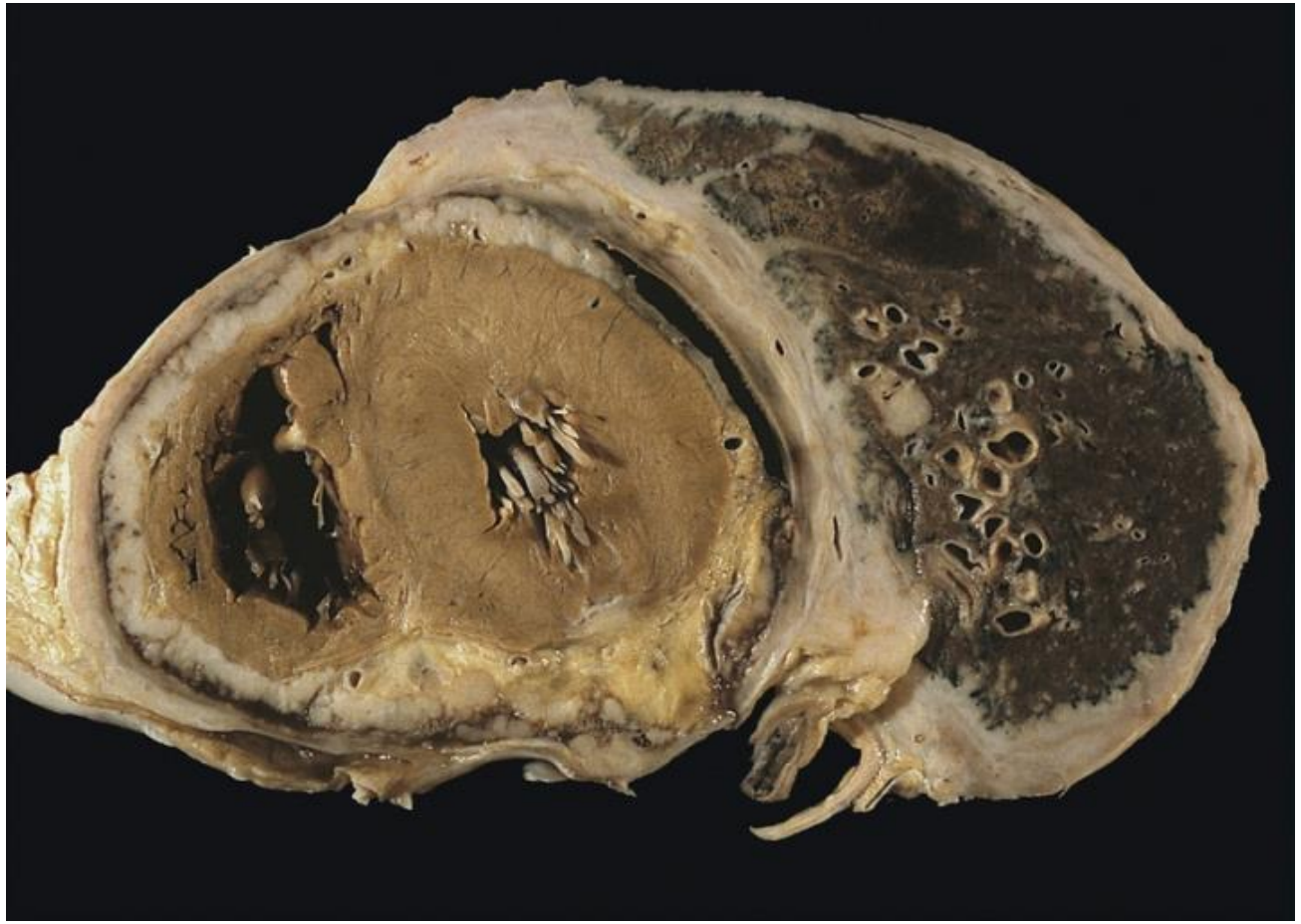

Table 1. 2015 WHO Classification of Mesothelioma

Type	Description
Diffuse malignant mesothelioma	
Epithelioid mesothelioma	Composed of rounded rather than spindle-shaped cells usually showing a cohesive architecture, although epithelioid cells can show single cell growth within fibrous stroma.
Sarcomatoid mesothelioma, including desmoplastic variant	Composed of spindle-shaped (greater than two times longer than wide). The spindle cells may lie in varying amounts of fibrous stroma, or they can form solid sheets.
Biphasic mesothelioma	Showing at least 10% of both epithelioid and sarcomatoid morphology. This rule is limited to definitive resections, namely, extended EPD and EPP. For smaller samples, until more data are collected, the group proposes that the diagnosis of "biphasic" can be rendered regardless of the percentages of each component present and that the diagnosis should be accompanied by a comment indicating the percentages of each component.
Localized malignant mesothelioma	
Epithelioid mesothelioma	
Sarcomatoid mesothelioma	
Biphasic mesothelioma	
Well-differentiated papillary mesothelioma	A rare localized mesothelial neoplasm characterized by an exophytic papillary architecture lined by relatively bland mesothelium with no or only minimal areas of invasion. Diagnosis requires exclusion of diffuse malignant mesothelioma with papillary architecture.
Adenomatoid tumor	

Adapted from the *WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart*.[1]

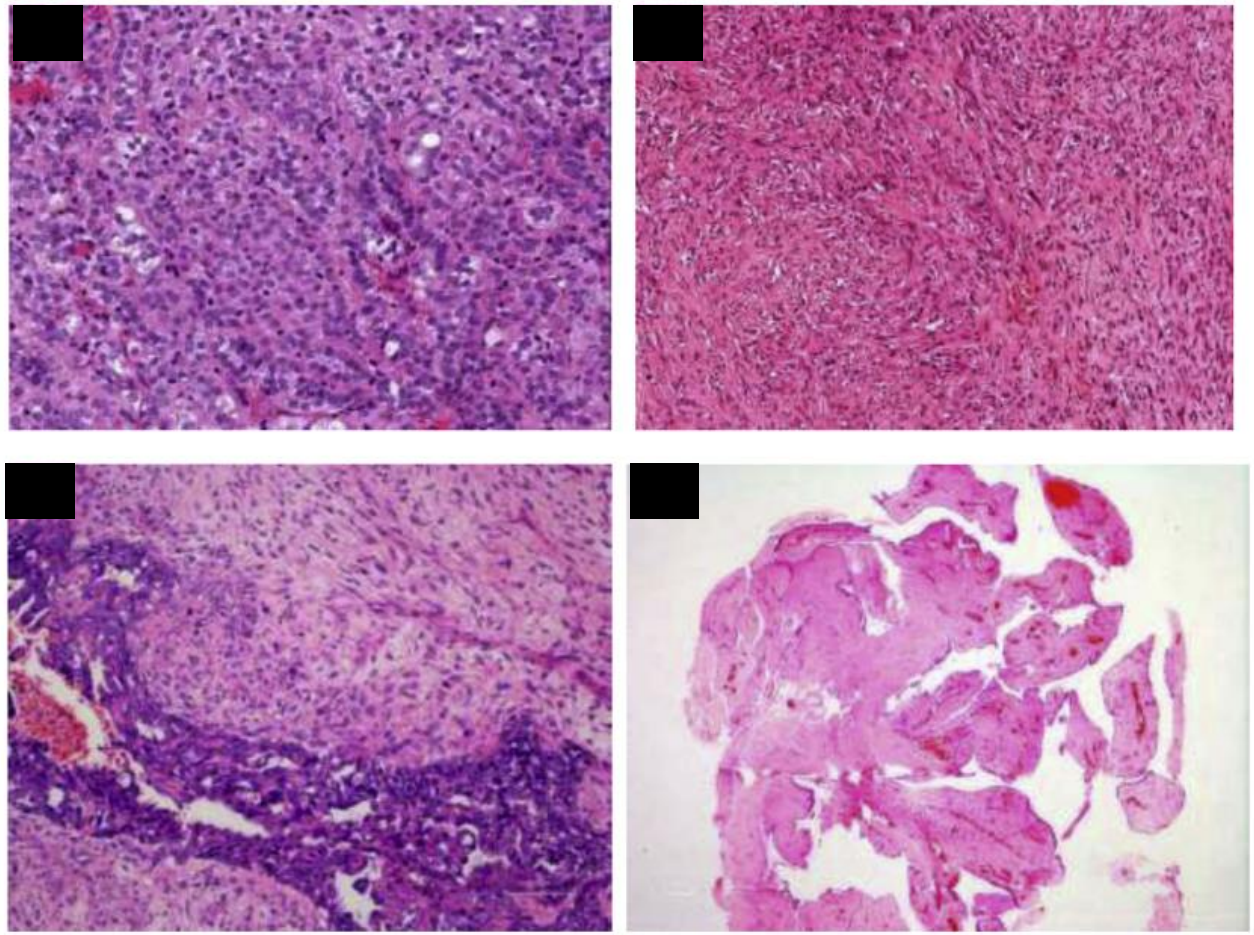

Table 2. Proposed Changes to Subtyping of Mesothelioma

Diffuse malignant mesothelioma[a]
Epithelioid malignant mesothelioma
Architectural patterns (Give percentages for EPD/EPP and document patterns present for all other samples)
Tubulopapillary
Trabecular
Adenomatoid
Microcystic
Solid
Micropapillary
Transitional pattern[b]
Pleomorphic[b]
Cytologic features (Give percentages for EPD/EPP. For all other samples, state "with ... features present")
Rhabdoid
Deciduoid
Small cell
Clear cell
Signet ring
Lymphohistiocytoid[c]
Stromal features (Give percentages for EPD/EPP. For all other samples, state "with ... features present")
Myxoid
Sarcomatoid malignant mesothelioma (Give percentages for EPD/EPP. For all other samples, state "with ... features present")
Desmoplastic
With heterologous differentiation
Lymphohistiocytoid[c]
Transitional pattern[b]
Pleomorphic[b]
Biphasic malignant mesothelioma (For EPD/EPP, any combination of patterns of epithelioid and sarcomatoid mesothelioma with at least 10% of each component. For all other samples, the consensus was to propose that the diagnosis of "biphasic" can be made regardless of percentages of each component and to include a comment indicating the percentages of each component in the sample.)
Localized malignant mesothelioma (Any of the above subtypes may be present, with tumor limited to an isolated mass lesion)
Well-differentiated papillary mesothelioma
Adenomatoid tumor

EPP, extrapleural pneumonectomy; EPD, extended pleurectomy/decortication.

[a]Some architectural patterns and cytologic and stromal features are important for prognostic significance whereas some are included only for clarity to avoid pathology misdiagnoses. When generating reports, please note that multiple architectural patterns and cytologic and stromal features may be present in a tumor and all patterns/features seen in a tumor should be included in the report.

[b]Classification of transitional and pleomorphic patterns is currently difficult due to limited data available. Therefore, the consensus is to include transitional and pleomorphic patterns under both epithelioid and sarcomatoid types until more data emerge.

[c]Histiocytoid refers to morphology of actual tumour cells, not the presence of background macrophages.

Table 3. Definitions for Architectural Patterns, Cytologic Features and Stromal Characteristics in Pleural Mesothelioma[a]

Histologic patterns

A. Tubular: Round to oval spaces surrounded by a single layer of malignant epithelioid cells.
B. Papillary: Malignant epithelioid cells growing over a fibrovascular core.
C. Tubulopapillary: In many cases, tubular and papillary patterns are seen together.
D. Trabecular: An interconnected single or dual linear arrangement of malignant epithelioid cells
E. Solid: An architectural feature comprising continuous sheets of malignant epithelioid cells.
F. Micropapillary: Small groups of epithelioid cells forming a papillary structure, but lacking a fibrovascular core. Micropapillary can also include a single cell pattern.
G. Adenomatoid: A pattern of malignant mesothelioma composed of gland-like structures lined by flat to cuboidal malignant epithelioid cells resembling adenomatoid tumor.
H. Microcystic: A cribriform network of malignant epithelioid cells with small acinar spaces forming round holes like a sieve.

Cytologic features

I. Pleomorphic: Tumor cells show marked nuclear atypia, often with bizarre nuclei and tumour giant cells.
J. Transitional: Tumor cells are intermediate between epithelioid and sarcomatoid morphologies, having lost their rounded morphology but not being overtly sarcomatoid.
K. Rhabdoid: Tumor cells resemble those seen in rhabdomyoblastic tumors, typically with a cytoplasmic eosinophilic globule that is positive for cytokeratins and generally negative for muscle markers.
L. Deciduoid: Tumors cells have a significant excess of richly eosinophilic cytoplasm resembling the decidua from the placenta. This carries no prognostic significance as a cytologic feature, but is important for avoiding misdiagnosis.
M. Small cell: Small hyperchromatic tumor cells morphologically resembling small cell carcinoma, but showing a mesothelial phenotype. This carries no prognostic significance but is important for avoiding misdiagnosis.
N. Clear cell: Tumor cells with clear cytoplasm. This carries no prognostic significance, but is important so metastatic clear cell carcinoma is not incorrectly diagnosed.
O. Signet ring: Tumor cells with intracytoplasmic vacuoles pushing the nucleus to the side. This carries no prognostic significance in mesothelioma, but is important so metastatic signet ring carcinomas from other sites are not incorrectly diagnosed.
P. Lymphohistiocytoid: This feature is seen in predominantly sarcomatoid mesothelioma where the neoplastic cells are histiocytoid in appearance but are obscured by a prominent infiltrate of lymphocytes. The morphology raises the differential diagnosis of malignant lymphoma. This definition requires that the actual tumour cells resemble histiocytes and does not simply represent prominent lymphocytic infiltration in an epithelioid mesothelioma. Focal lymphohistiocytoid features occur in otherwise conventional sarcomatoid mesotheliomas.

Stromal features

Q. Myxoid: Tumour cells lie within a pale hematoxyphilic mucoid stroma. This should be noted when > 50% of a tumor with < 50% solid component shows this feature.
R. Desmoplastic: A sarcomatoid mesothelioma with prominent dense hyaline fibrous stroma, haphazard slit-like spaces, bland collagen necrosis, cellular proliferation nodules and invasive growth.
S. Heterologous elements: Sarcomatous elements such as osteosarcoma (as seen in figure), chondrosarcoma and rhabdomyosarcoma.

[a]Table 3 defines elements shown in Figure 2.

Journal of Thoracic Oncology 2019
Vol. 15 No. 1: 29-49

Table 4. Grading of Pleural Epithelioid Malignant Mesothelioma

Nuclear Grade:
Nuclear atypia score: _____ (1 for mild, 2 for moderate, 3 for severe)
Mitotic count: ____ (1 for low [$\leq$1 per 2mm^2], 2 for intermediate [2-4 per2mm^2], 3 for high [5+ per 2mm^2])
Sum: _____ (2 or 3 = nuclear grade I, 4 or 5 = nuclear grade II, 6 = nuclear grade III)
Necrosis: Present / Absent
Low-grade = Nuclear grades I and II without necrosis
High-grade = Nuclear grade II with necrosis, Nuclear grade III with or without necrosis

MODERN PATHOLOGY (2018) 31, 598–606

Nuclear grade and necrosis predict prognosis in malignant epithelioid pleural mesothelioma: a multi-institutional study

Arch Pathol Lab Med. 2018;142:89–108

Guidelines for Pathologic Diagnosis of Malignant Mesothelioma

2017 Update of the Consensus Statement From the International Mesothelioma Interest Group

Aliya Noor Husain, MD; Thomas V. Colby, MD; Nelson G. Ordóñez, MD; Timothy Craig Allen, MD, JD; Richard Luther Attanoos, MBBS, MD, FRCPath; Mary Beth Beasley, MD; Kelly Jo Butnor, MD; Lucian R. Chirieac, MD; Andrew M. Churg, MD; Sanja Dacic, MD, PhD; Françoise Galateau-Sallé, MD; Allen Gibbs, MD; Allen M. Gown, MD; Thomas Krausz, MD; Leslie Anne Litzky, MD; Alberto Marchevsky, MD; Andrew G. Nicholson, DM; Victor Louis Roggli, MD; Anupama K. Sharma, MD; William D. Travis, MD; Ann E. Walts, MD; Mark R. Wick, MD

Mesothelioma or Carcinoma or what else ?
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Review Articles

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(Arch Pathol Lab Med. 2018;142:89–108; doi: 10.5858/arpa.2017-0124-RA

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Two mesothelial markers

Two «carcinoma» markers

Virchows Archiv (2021) 478:59–72
https://doi.org/10.1007/s00428-021-03031-7

REVIEW AND PERSPECTIVES

Pleural mesothelioma classification update

Mary Beth Beasley[1] · Francoise Galateau-Salle[2] · Sanja Dacic[3]

Received: 24 September 2020 / Revised: 23 December 2020 / Accepted: 11 January 2021 / Published online: 21 January 2021

Abstract
The 2015 WHO classification of pleural mesotheliomas includes three major histologic subtypes—epithelioid, sarcomatoid, and biphasic. Recent genomic data has supported the need for a more granular and clinically valid classification beyond the three current subtypes. Because of tumor rarity and overlapping histologic features with other tumor types, diagnostic immunohistochemical work up is essential component in establishing the final diagnosis of mesothelioma. The use of BAP1 and *CDKN2A*/MTAP improves the diagnostic sensitivity of effusion specimens and are valuable in establishing the diagnosis of epithelioid mesothelioma. The major change in the forthcoming WHO classification is the inclusion of mesothelioma in situ as a diagnostic category. In this review, we discuss recently proposed changes in the histologic classification of pleural mesothelioma, differential diagnosis, and importance of ancillary diagnostic studies.

Keywords Mesothelioma · Pleura · Histologic classification

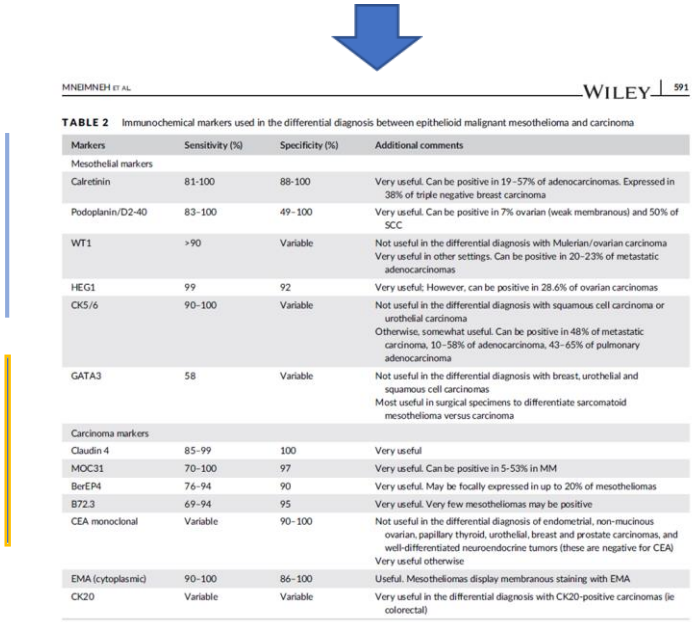

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TABLE 2 Immunochemical markers used in the differential diagnosis between epithelioid malignant mesothelioma and carcinoma

Markers	Sensitivity (%)	Specificity (%)	Additional comments
Mesothelial markers			
Calretinin	81-100	88-100	Very useful. Can be positive in 19-57% of adenocarcinomas. Expressed in 38% of triple negative breast carcinoma
Podoplanin/D2-40	83-100	49-100	Very useful. Can be positive in 7% ovarian (weak membranous) and 50% of SCC
WT1	>90	Variable	Not useful in the differential diagnosis with Mulerian/ovarian carcinoma Very useful in other settings. Can be positive in 20-23% of metastatic adenocarcinomas
HEG1	99	92	Very useful; However, can be positive in 28.6% of ovarian carcinomas
CK5/6	90-100	Variable	Not useful in the differential diagnosis with squamous cell carcinoma or urothelial carcinoma Otherwise, somewhat useful. Can be positive in 48% of metastatic carcinoma, 10-58% of adenocarcinoma, 43-65% of pulmonary adenocarcinoma
GATA3	58	Variable	Not useful in the differential diagnosis with breast, urothelial and squamous cell carcinomas Most useful in surgical specimens to differentiate sarcomatoid mesothelioma versus carcinoma
Carcinoma markers			
Claudin 4	85-99	100	Very useful
MOC31	70-100	97	Very useful. Can be positive in 5-53% in MM
BerEP4	76-94	90	Very useful. May be focally expressed in up to 20% of mesotheliomas
B72.3	69-94	95	Very useful. Very few mesotheliomas may be positive
CEA monoclonal	Variable	90-100	Not useful in the differential diagnosis of endometrial, non-mucinous ovarian, papillary thyroid, urothelial, breast and prostate carcinomas, and well-differentiated neuroendocrine tumors (these are negative for CEA) Very useful otherwise
EMA (cytoplasmic)	90-100	86-100	Useful. Mesotheliomas display membranous staining with EMA
CK20	Variable	Variable	Very useful in the differential diagnosis with CK20-positive carcinomas (ie colorectal)

Virchows Archiv (2021) 478:59–72
https://doi.org/10.1007/s00428-021-03031-7

REVIEW AND PERSPECTIVES

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Abstract
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Keywords Mesothelioma · Pleura · Histologic classification

Table 2 Pitfalls of common immunohistochemical markers used in the workup of mesothelioma

Immunostain	Diagnostic utility	Pitfalls
Calretinin*	Positive in up to 100% of EM (cytoplasmic ± nuclear)	Up to 40% of SCC positive (usually focal), breast ca
D2-40*	Positive in up to 100% of EM (membranous)	Positive in vascular tumors; up to 50% of SCC
CK5/6*	Positive in up to 100% of EM (cytoplasmic)	Positive in squamous carcinoma
WT-1*	Positive in up to 95% of EM (nuclear)	Positive in ovarian tumors, DSRCT, melanoma
Glycoprotein markers (CEA, Leu-M1, MOC-31, B72.3, BER-EP4, Claudin-4)	Positive in carcinomas	Individual markers may not be positive in all carcinomas; variable amount of positive staining (overall 10% or less, usually focal) in mesothelioma
GATA-3	Positive in breast and urothelial carcinomas	Positive in up to 50% of EM and 80–100% of SM

*Immunostains typically positive in EM may be negative or only weakly positive in the sarcomatoid variant; *SCC*, squamous cell carcinoma

Virchows Arch (2007) 451:669–680
DOI 10.1007/s00428-007-0448-x

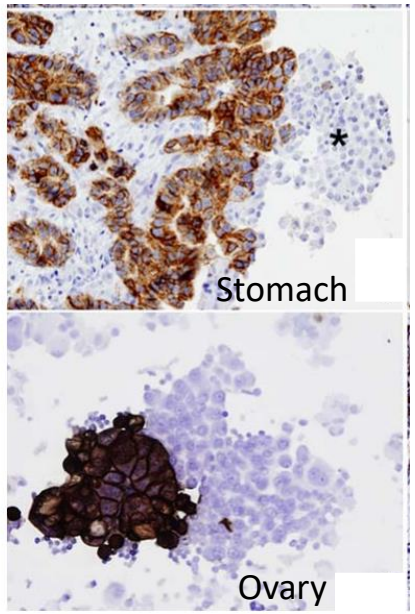
ORIGINAL ARTICLE

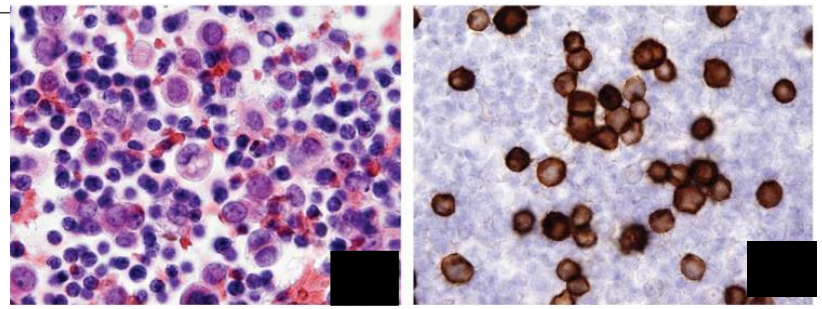
Claudin 4 identifies a wide spectrum of epithelial neoplasms and represents a very useful marker for carcinoma versus mesothelioma diagnosis in pleural and peritoneal biopsies and effusions

Fabio Facchetti · Silvia Lonardi · Francesca Gentili · Luisa Bercich · Marcella Falchetti · Regina Tardanico · Carla Baronchelli · Laura Lucini · Alessandro Santin · Bruno Murer

Received: 19 March 2007 / Revised: 30 May 2007 / Accepted: 8 June 2007 / Published online: 3 July 2007

Abstract We evaluated the usefulness of the tight-junction associated protein Claudin 4 (CL-4) in the diagnosis of mesothelioma and mimickers, analyzing biopsies from 454 tumors, including 82 mesotheliomas, 336 carcinomas of different origin (278 primary, 58 metastatic to serosae), 36 nonepithelial spindle cell neoplasms, as well as 97 cytological samples from reactive effusions (12), mesothelioma (23) and metastatic carcinomas (62). CL-4 was consistently negative in normal and reactive mesothelium, as well as in all 82 mesotheliomas. In contrast, strong reactivity was found in 57/58 serosal metastasis, and in 245/278 primary carcinomas, with uppermost expression (150/153) in those most frequently involved in the differential with mesothelioma (lung, breast, gastrointestinal tract, pancreas, ovary, primary serous papillary carcinoma of peritoneum). On effusions, reactive and neoplastic mesothelial cells were regularly negative, while metastatic tumor cells stained positively in 60/62 (96.8%) cases. Among spindle cell neoplasms, only 2/9 biphasic





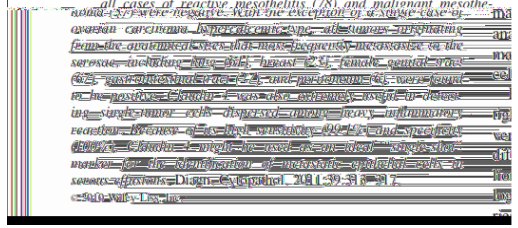
Breast

ORIGINAL ARTICLES

Usefulness of Claudin 4 in the Cytological Diagnosis of Serosal Effusions

Silvia Lonardi, B.S.,* Calogero Manera, B.S., Raffaella Marucci, B.S., Amerigo Santoro, M.D., Luisa Lorenzi, M.D., and Fabio Facchetti, M.D., Ph.D.

The identification of metastatic cells in serous effusions has prognostic and therapeutic implications, thus leading to a continuous search for improvement of the existing diagnostic procedures, including immunocytochemistry. To evaluate the usefulness of an antibody recognizing the tight junction-associated protein Claudin 4 in detecting metastatic tumor cells and in the differential with reactive and neoplastic mesothelium, we stained 345 cases of benign and neoplastic serous effusions obtained from pleura, peritoneum, and pericardium. Two-hundred and twenty-eight of 230 cases (99.1%) of epithelial metastasis of different origin were strongly stained by anti-Claudin 4, whereas all cases of reactive mesothelitis (78) and malignant mesothe-



Claudin-4 in mesothelioma diagnosis

DOI: 10.1111/j.1365-2559.2007.02743.x

 Histopathology, **51**, 258–285.

Table 1. Reactive Mesothelial Hyperplasia Versus Mesothelioma

Mesothelial Hyperplasia	Mesothelioma
• Absence of stromal invasion (beware of entrapment and en face cuts)	• Stromal invasion usually apparent (highlight with pancytokeratin staining)
• Cellularity may be prominent but is confined to the mesothelial surface/pleural space and is not in the stroma	• Dense cellularity, including cells surrounded by stroma
• Simple papillae; single cell layers	• Complex papillae; tubules and cellular stratification
• Loose sheets of cells without stroma	• Cells surrounded by stroma ("bulky tumor" may involve the mesothelial space without obvious invasion)
• Necrosis rare	• Necrosis present (occasionally)
• Inflammation common	• Inflammation usually minimal
• Uniform growth (highlighted with cytokeratin staining)	• Expansile nodules; disorganized growth (highlighted on cytokeratin staining)
Usually Not Useful	
• Mitotic activity • Mild to moderate cytologic atypia	

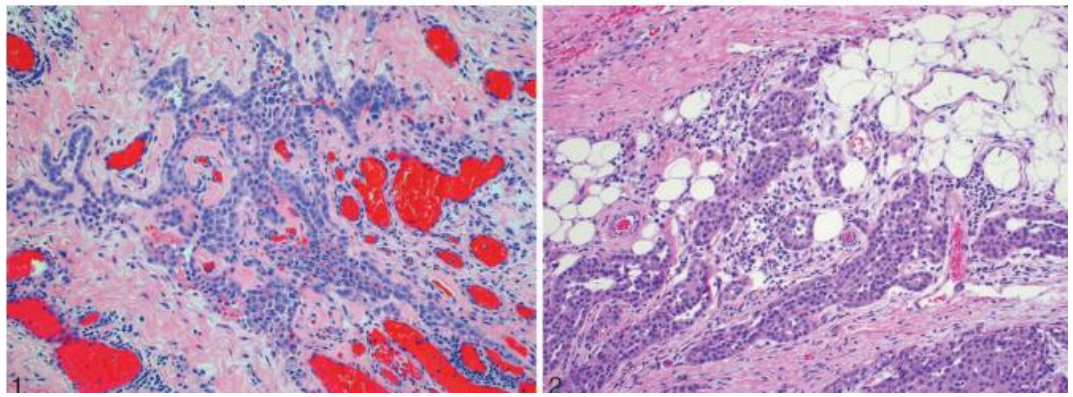
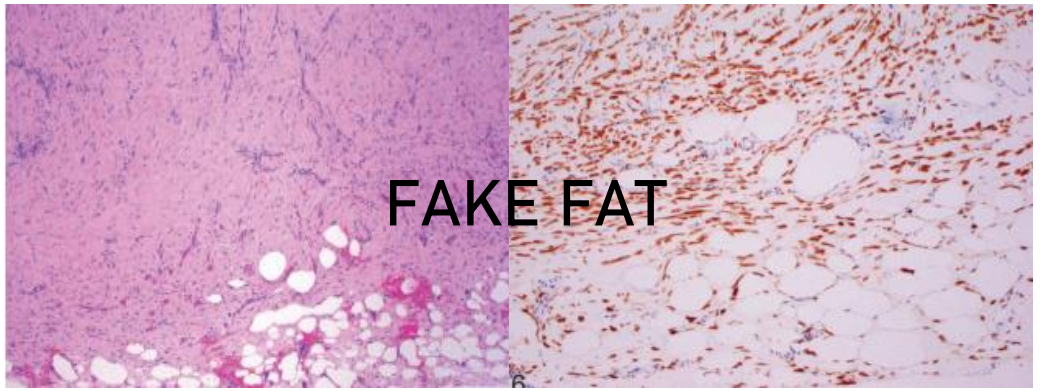
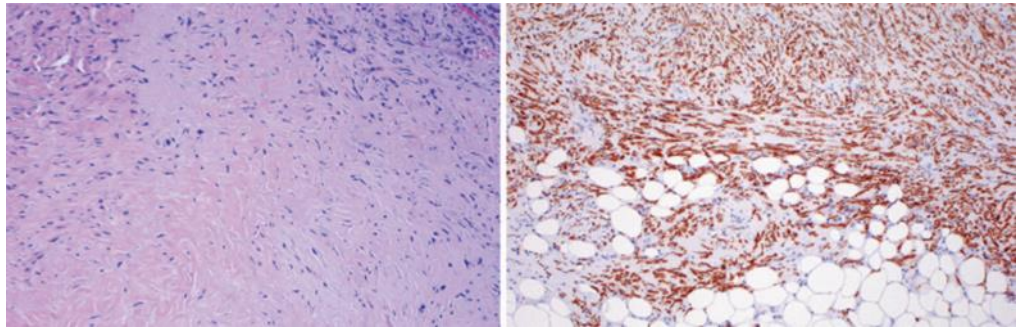


Table 2. Fibrous Pleurisy Versus Desmoplastic Mesothelioma[a]

Fibrous Pleurisy	Desmoplastic Mesothelioma
• Storiform pattern not prominent	• Storiform pattern often prominent
• Absence of stromal invasion	• Stromal invasion present (highlight with pancytokeratin staining)
• Necrosis, if present, is at the surface epithelioid mesothelial cells (where there is often associated acute inflammation)	• Bland necrosis of paucicellular, collagenized tissue
• Uniform thickness of the process	• Disorganized growth, with uneven thickness, expansile nodules, and abrupt changes in cellularity
• Hypercellularity at the surface with maturation and decreased cellularity deep (so-called zonation)	• Lack of maturation from the surface to the depths of the process
• Perpendicularly oriented vessels	• Paucity of vessels, without orientation
Usually Not Useful	
• Cellularity • Atypia (unless severe) • Mitotic activity unless numerous atypical mitotic figures	





Modern Pathology (2015) 28, 1043–1057

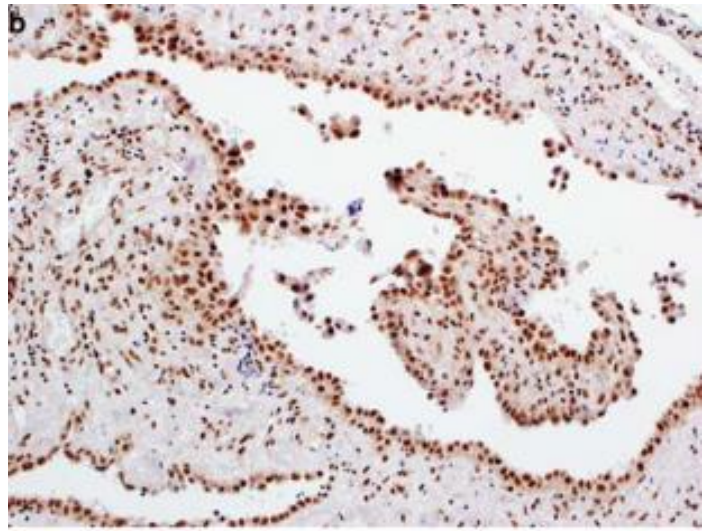
BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations

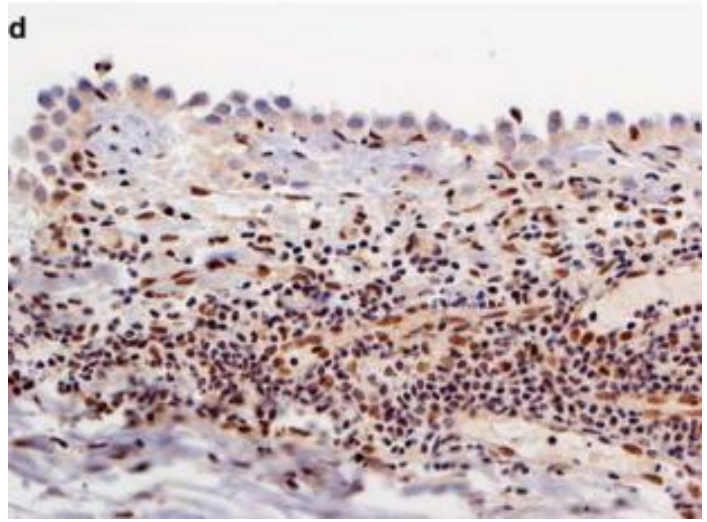
Marta Cigognetti[1], Silvia Lonardi[1], Simona Fisogni[1], Piera Balzarini[1], Vilma Pellegrini[1], Andrea Tironi[1], Luisa Bercich[1], Mattia Bugatti[1], Giulio Rossi[2], Bruno Murer[3], Mattia Barbareschi[4], Silvia Giuliani[4], Alberto Cavazza[5], Gianpietro Marchetti[6], William Vermi[1] and Fabio Facchetti[1]

[1]Department of Molecular and Translational Medicine, Section of Pathology, University of Brescia, Spedali Civili, Brescia, Italy; [2]Department of Pathology, Azienda Ospedaliero-Universitaria Policlinico of Modena, Modena, Italy; [3]Department of Pathology, Ospedale Dell'Angelo, Venezia-Mestre, Italy; [4]Unit of Surgical Pathology, S. Chiara Hospital, Trento Italy; [5]Department of Pathology, Azienda Arcispedale S. Maria Nuova IRCCS, Reggio Emilia, Italy and [6]Department of Pneumology, Spedali Civili, Brescia, Italy

The distinction between malignant mesothelioma and reactive mesothelial proliferation can be challenging both on histology and cytology. Recently, variants of the *BRCA1-associated protein 1* (*BAP1*) gene resulting in nuclear protein loss were reported in hereditary and sporadic mesothelioma. Using immunohistochemistry, we evaluated the utility of BAP1 expression in the differential diagnosis between mesothelioma and other mesothelial proliferations on a large series of biopsies that included 212 mesotheliomas, 12 benign mesothelial tumors, and 42 reactive mesothelial proliferations. BAP1 stain was also performed in 70 cytological samples (45 mesotheliomas and 25 reactive mesothelial proliferations). BAP1 was expressed in all benign mesothelial tumors, whereas 139/212 (66%) mesotheliomas were BAP1 negative, especially in epithelioid/biphasic compared with sarcomatoid/desmoplastic subtypes (69% *vs* 15%). BAP1 loss was homogeneous in neoplastic cells except for two epithelioid mesotheliomas showing tumor heterogeneity. By fluorescence *in situ* hybridization, BAP1 protein loss was paralleled by homozygous deletion of the *BAP1* locus in the vast majority of BAP1-negative tumors (31/41, 76%), whereas 9/10 BAP1-positive mesotheliomas were normal. In biopsies interpreted as reactive mesothelial proliferation BAP1 loss was 100% predictive of malignancy, as all 6 cases subsequently developed BAP1-negative mesothelioma, whereas only 3/36 (8%) BAP1-positive cases progressed to mesothelioma. On cytology/cell blocks, benign mesothelial cells were invariably positive for BAP1, whereas 64% of mesotheliomas showed loss of protein; all 6 cases showing BAP1 negativity were associated with histological diagnosis of BAP1-negative mesothelioma. BAP1 stain also showed utility in the differential of mesothelioma from most common pleural and peritoneal mimickers, such as lung and ovary carcinomas, with specificity and sensitivity of 99/70% and 100/70%, respectively. Our results show that BAP1 protein is frequently lost in mesothelioma, especially of epithelioid/biphasic subtype and is commonly associated with homozygous *BAP1* deletion. BAP1 immunostain represents an excellent biomarker with an unprecedented specificity (100%) in the distinction between benign and malignant mesothelial proliferations. Finding BAP1 loss in mesothelial cells should prompt to immediately reevaluate the patient; moreover, it might be useful in mapping tumor extent and planning surgical resection.

Modern Pathology (2015) **28,** 1043–1057; doi:10.1038/modpathol.2015.65; published online 29 May 2015





Original Article

The "Brescia Panel" (Claudin-4 and BRCA-Associated Protein 1) in the Differential Diagnosis of Mesotheliomas With Epithelioid Features Versus Metastatic Carcinomas

Livia Bernardi, BS[1]; Tommaso Bizzarro, BS[1]; Flavio Pironi, BS[2]; Stefania Szymczuk, BS[2]; Raffaella Buda, BS[1]; Enrica Fabbri, BS[2]; Giovanni Di Claudio, BS[2]; and Giulio Rossi, MD, PhD[1,2]

BACKGROUND: The distinction between mesothelioma with epithelioid features and metastatic carcinoma may be challenging, particularly on cytology. A novel *2-hit* Claudin-4 and BRCA-associated protein 1 (BAP1) panel was investigated. **METHODS:** The objective of this study was to determine the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of the panel on cytology from pleural effusions and matched biopsies, including 49 malignant mesotheliomas on cytology with 43 matched biopsies, 49 normal/reactive mesothelial proliferations, and 49 pleural metastatic carcinomas from different primaries with 21 matched pleural biopsies. The diagnostic role of the 4 categories obtained by crossing the immunostaining results was analyzed. **RESULTS:** Claudin-4 strongly stained all metastatic carcinomas and tested completely negative in normal mesothelium, benign reactive mesothelial hyperplasia, and malignant mesothelioma. All normal and benign mesothelial proliferations and all carcinomas except 1 were immunoreactive for BAP1, whereas BAP1 loss was observed in 88% of malignant mesotheliomas. The expression of Claudin-4 alone excluded all benign and malignant mesothelial growth, consistently characterizing all metastatic carcinomas. Double negativity was evident in all malignant mesotheliomas, and double positivity was observed in all metastatic carcinomas. BAP1-positive/Claudin-4–negative status was observed only in malignant mesotheliomas and benign mesothelial proliferations. A single metastatic anal squamous cell carcinoma had BAP1-negative/Claudin-4–positive staining. **CONCLUSIONS:** Claudin-4 expression was completely specific and sensitive for metastatic carcinoma, excluding mesothelial proliferations. BAP1 staining characterized 98% of metastatic carcinomas and 100% of benign mesothelial proliferations, whereas negativity was observed almost exclusively in mesotheliomas. This 2-hit panel is probably the best compromise for differentiating malignant mesothelioma and metastatic carcinoma on either cytology or biopsy specimens. ***Cancer Cytopathol* 2021;129:275-282**. © *2020 American Cancer Society*.

KEY WORDS: BRCA-associated protein 1 (BAP1); Claudin-4; diagnostic cytology; effusion cytology; immunocytochemistry; malignant mesothelioma; malignant mesothelioma versus metastatic carcinoma; metastatic carcinoma.

Editorial

The Brescia Panel and The International System (TIS) for Reporting Serous Fluid Cytopathology

Ashish Chandra, MD, FRCPath, DipRCPath (Cytol)

The distinction between mesothelial proliferations and metastatic adenocarcinoma in serous fluids remains a common and vexing issue. Whereas cytomorphology allows the identification of one cell type (mesothelial) over another (epithelial), this may be challenging when the number of lesional cells is small, when cells are associated with bland nuclear morphology accompanied by degenerative changes, or when unusual tumor subtypes present in serous fluids. For confirmation of the diagnosis, immunochemical panels using 2 epithelial immunostains and 2 mesothelial immunostains are common practice, with the choice of markers depending on availability and the experience of their usage in a particular institution.

Although the value of BRCA-associated protein 1 (BAP1) and Claudin-4 has been documented by many studies, Bernardi and colleagues were the first to draw attention to these 2 markers through their earlier publications. In this issue of *Cancer Cytopathology*, they propose the name of *Brescia panel* for the combination of these 2 markers.[1] The panel presents the opportunity to use only 2 markers, given the high sensitivity and specificity of the panel to differentiate between mesothelioma (BAP1-negative/Claudin-4–negative) from metastatic carcinoma (BAP1-positive/Claudin-4–positive).

Bernardi et al demonstrate compelling evidence through their pilot study for the cytopathology community to consider validating this panel. The pattern of staining, nuclear with BAP1 and membranous with Claudin-4, makes these immunostains easier to interpret compared with cytoplasmic staining, which is sometimes not as well localized. The panel has been applied successfully to cell block and biopsy specimens.

Incidentally, both markers are recommended by The International System (TIS) for Reporting Serous Fluid Cytopathology.[2] The system mentions Claudin-4 as a promising marker for the confirmation of metastatic carcinoma and for the exclusion of mesothelioma. BAP1 is also recommended as an immunostain of choice for the diagnosis of mesothelioma. In the absence of BAP1 loss, clinical data should be taken into account and the mesothelial proliferation should be reported as either atypia of undetermined significance or suspicious for malignancy in TIS, similar to what is proposed by the authors.

The Brescia panel holds much promise and merits further validation studies using only Claudin-4 and BAP1 instead of larger panels. This would allow more residual diagnostic material to be available for ascertaining the primary sites and for performing molecular testing of malignant cells in serous effusions.

Cancer Cytopathology April 2021

Utility of Methylthioadenosine Phosphorylase Compared With BAP1 Immunohistochemistry, and *CDKN2A* and *NF2* Fluorescence In Situ Hybridization in Separating Reactive Mesothelial Proliferations From Epithelioid Malignant Mesotheliomas

Kyra B. Berg, MD; Sanja Dacic, MD; Caitlyn Miller, BA; Simon Cheung, BSc; Andrew Churg, MD

• *Context.*—The separation of reactive from malignant mesothelial proliferations is often a difficult morphologic problem. There is contradictory information in the literature on whether methylthioadenosine phosphorylase (MTAP) immunohistochemistry can be used for this purpose.

Objective.—To determine the utility of MTAP immunohistochemistry in distinguishing reactive from malignant mesothelial proliferations.

Design.—We stained a tissue microarray containing 20 epithelioid malignant mesotheliomas and 17 reactive mesothelial proliferations. For the mesotheliomas, comparisons were made between MTAP staining and BRCA-associated nuclear protein 1 (BAP1) immunohistochemistry, cyclin-dependent kinase inhibitor 2A (*CDKN2A*) fluorescence in situ hybridization, and neurofibromin 2 (*NF2*) fluorescence in situ hybridization, which are established techniques for making this separation.

Results.—Loss of MTAP was seen in 0 of 17 reactive mesothelial proliferations and 13/20 (65%) malignant mesotheliomas. Almost all cases with loss showed loss in 100% of mesothelial cells. Background inflammatory and stromal cells served as a positive internal control. *CDKN2A* fluorescence in situ hybridization on the mesotheliomas showed concordance with MTAP staining in 14 of 17 evaluable cases. BAP1 immunohistochemistry showed loss of nuclear staining in 11 of 20 mesotheliomas (55%). No cases showed loss of *NF2*. A total of 18 of 20 mesotheliomas (90%) showed loss of either MTAP or BAP1.

Conclusions.—In the context of a mesothelial proliferation, loss of MTAP staining is 100% specific for malignant mesothelioma. In this study the combination of MTAP and BAP1 immunohistochemical staining allowed separation of reactive from epithelial malignant mesothelial proliferations in 90% of cases.

(*Arch Pathol Lab Med.* 2018;142:1549–1553; doi: 10.5858/arpa.2018-0273-OA)

Table 1. Methylthioadenosine Phosphorylase (MTAP) and BRCA-Associated Nuclear Protein 1 (BAP1) Loss by Immunohistochemistry in Reactive Mesothelial Proliferations, Malignant Epithelioid Mesotheliomas, and Lung Adenocarcinomas

	No.	MTAP Loss, No. (%)	BAP1 Loss, No. (%)	MTAP or BAP1 Loss, No. (%)
Reactive mesothelial proliferation	17	0 (0)	0 (0)	0 (0)
Malignant epithelioid mesothelioma				
Pleural	18	12 (67)	11 (61)	17 (94)
Peritoneal	2	1 (50)	0 (0)	1 (50)
Total	20	13 (65)	11 (55)	18 (90)
Lung adenocarcinoma	21	4 (14)	0 (0)	0 (0)
High-grade serous ovarian carcinoma	12	1 (8)	0 (0)	1 (8)

Table 2. Comparison of Methylthioadenosine Phosphorylase (MTAP) and BRCA-Associated Nuclear Protein 1 (BAP1) Loss by Immunohistochemistry (IHC) With Cyclin-Dependent Kinase Inhibitor 2A (*CDKN2A*) and Neurofibromin 2 (*NF2*) Deletion by Fluorescent In Situ Hybridization (FISH)[a]

		MTAP IHC	BAP1 IHC	*CDKN2A* FISH	*NF2* FISH
1	Pleural	Lost	Intact	Deleted	Intact
2	Pleural	Lost	Intact	Deleted	Intact
3	Pleural	Lost	Intact	Deleted	Intact
4	Pleural	Lost	Lost	—	—
5	Pleural	Lost	Lost	Deleted	Intact
6	Pleural	Intact	Lost	Intact	Intact
7	Pleural	Lost	Lost	Deleted	Intact
8	Pleural	Lost	Lost	Deleted	Intact
9	Pleural	Intact	Intact	Intact	Intact
10	Pleural	Intact	Lost	Deleted	Intact
11	Pleural	Intact	Lost	Intact	—
12	Pleural	Lost	Intact	Deleted	Intact
13	Pleural	Lost	Lost	Deleted	Intact
14	Pleural	Intact	Lost	Deleted	Intact
15	Pleural	Lost	Lost	Deleted	Intact
16	Pleural	Lost	Intact	Deleted	Intact
17	Pleural	Lost	Intact	—	—
18	Pleural	Intact	Lost	—	Intact
19	Peritoneal	Intact	Lost	Intact	Intact
20	Peritoneal	Lost	Intact	Intact	Intact

[a] — indicates cases that were not evaluable by FISH.

Lung Cancer 104 (2017) 98–105

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Immunohistochemical detection of MTAP and BAP1 protein loss for mesothelioma diagnosis: Comparison with 9p21 FISH and BAP1 immunohistochemistry

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ARTICLE INFO

Article history:
Received 18 October 2016
Received in revised form
15 December 2016
Accepted 21 December 2016

Keywords:
Malignant pleural mesothelioma
MTAP
BAP1
Immunohistochemistry
9p21 FISH
Diagnosis

ABSTRACT

Objectives: Differentiating malignant pleural mesothelioma (MPM) from reactive mesothelial hyperplasia (RMH) is still challenging. Detection of homozygous deletion (HD) of 9p21 region including $p16^{INK4A}$ (*p16*) by fluorescence *in situ* hybridization (FISH) and immunohistochemical detection of loss of BRCA1 associated protein 1 (BAP1), are reliable markers for MPM diagnosis. However, not all laboratories are equipped to perform 9p21 FISH; immunohistochemistry (IHC) is a more common and feasible technique. Thus, we sought to develop a IHC-based method that could predict the deletion of *p16* in MPM in concordance with 9p21 FISH.

Materials and methods: We examined the expression of the 9p21.3-related proteins (p14, p15, p16, and methylthioadenosine phosphorylase (MTAP)) and BAP1 using IHC in 51 MPM and 25 RMH cases, and assessed their correlation with HD of *p16* detected by FISH. The diagnostic usefulness of IHC of the 9p21.3-related proteins and BAP1 and their combinations was assessed using the cut-off values set by receiver operating characteristic (ROC) analysis.

Results: Among the 9p21.3-related proteins, MTAP IHC findings showed best concordance with 9p21 FISH results (kappa coefficient of 0.69) and a specificity of 100%. We also examined the combinations of MTAP IHC with the other products. The loss of p16 and MTAP had better concordance (kappa coefficient of 0.71), although lower specificity (85%). For differentiating MPM from RMH, only MTAP showed 100% specificity among the 9p21.3-related proteins, as did BAP1 IHC and 9p21 FISH. Among BAP1 combinations, only that of BAP1 with MTAP showed 100% specificity. Its sensitivity was 76.5%, which was lower than BAP1 IHC and 9p21 FISH combination (84.3%), but higher than BAP1 IHC alone (60.8%) or 9p21 FISH alone (60.8%).

Conclusions: A combination of MTAP or BAP1 loss detected by IHC can likely detect MPM with good sensitivity and 100% specificity, and serve as useful ancillary IHC for discriminating MPM from RMH.

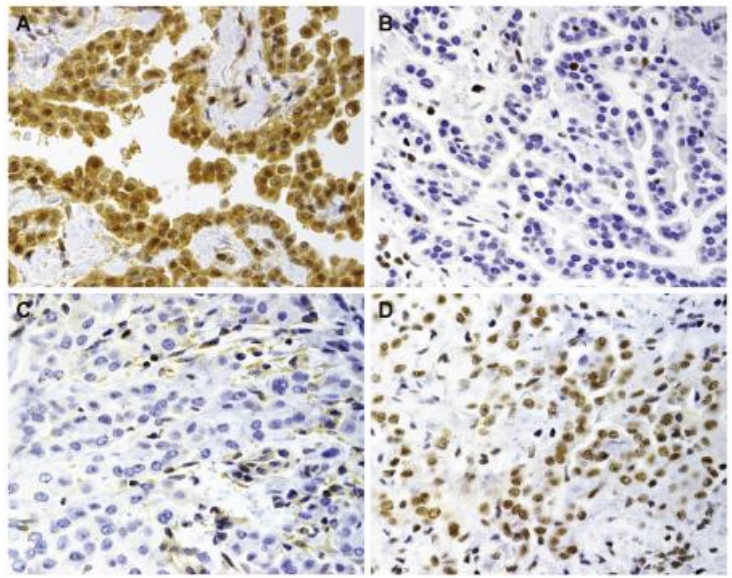


Fig. 4. Examples of immunohistochemistry (IHC) of methylthioadenosine phosphorylase (MTAP) and BAP1 in malignant pleural mesothelioma (MPM) cases. The top row shows a MPM case with preserved staining of MTAP (A) and loss/decreased staining of BAP1 (B). In contrast, the case in the bottom row exhibits loss/decreased staining of MTAP (C) but preserved staining of BAP1 (D). Original magnifications × 400.

Sarcomatoid mesothelioma
Differential diagnosis

- Pleural metastasis
- Benign organizing pleuritis

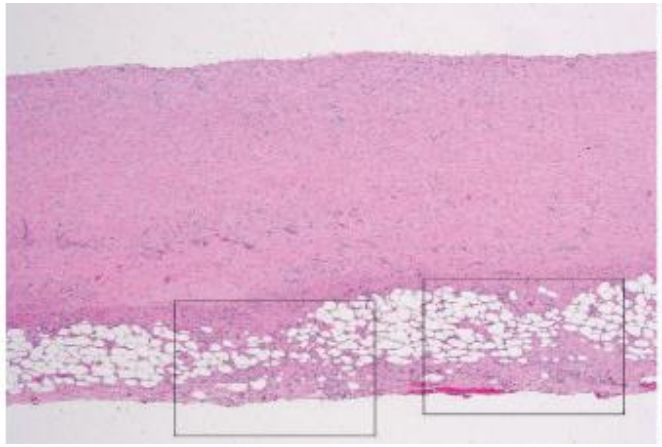
Up to 100%

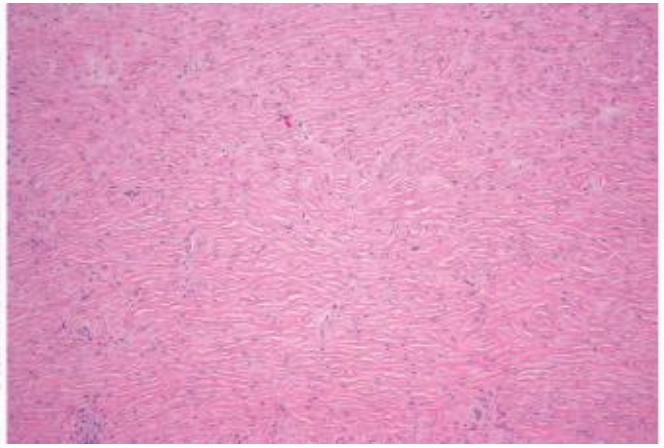
- Presence of a homozygous deletion of CDKN2a (p16) (FISH) or MTAP (IHC) loss

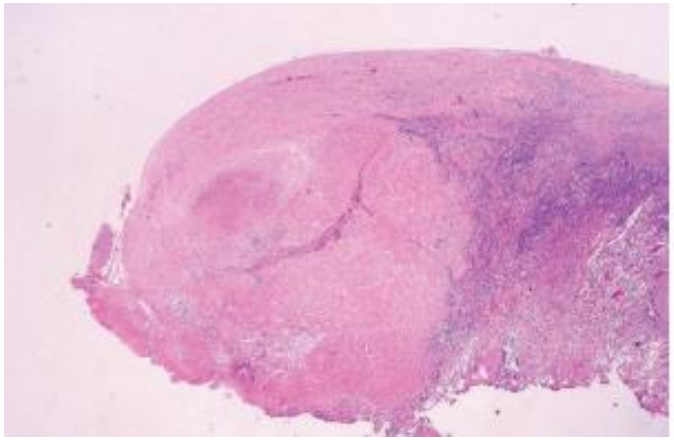
- BAP1 loss: uncommon in sarcomatoid mesothelioma and less useful in distinction from benign processes

Sarcomatoid «desmoplastic» mesothelioma

A variant characterized by spindle cells with minimal atypia arranged haphazardly in a so-called patternless pattern within a dense hyalinized stroma that resemble pleural hyaline plaque. The presence of obvious sarcomatoid areas is very helpful in establishing the diagnosis, as this variant may easily be misdiagnosed as benign.







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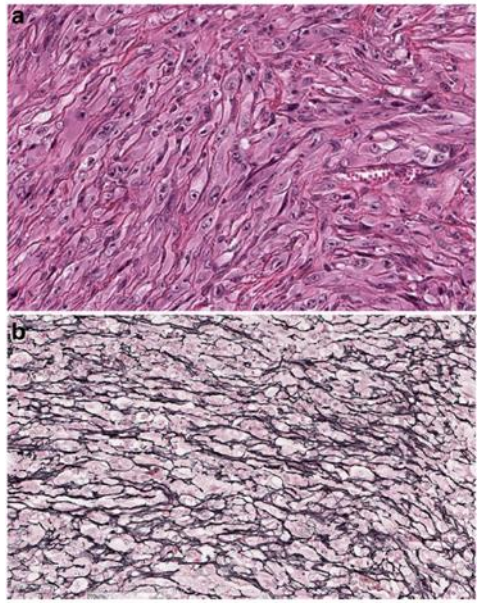

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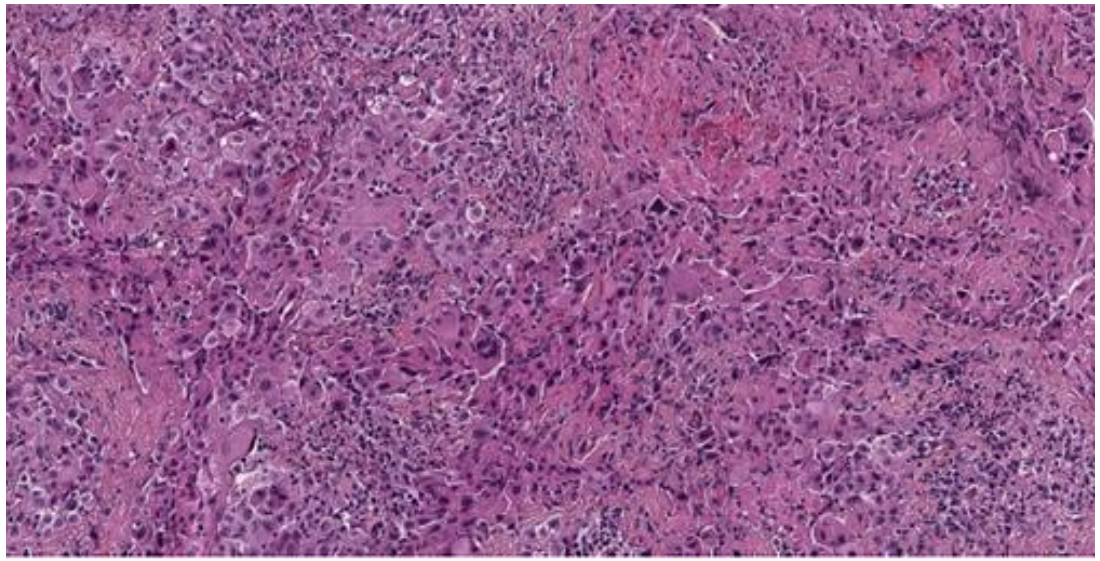


Whitaker 1992

Modern Pathology (2020) 33:297–302
https://doi.org/10.1038/s41379-019-0347-0

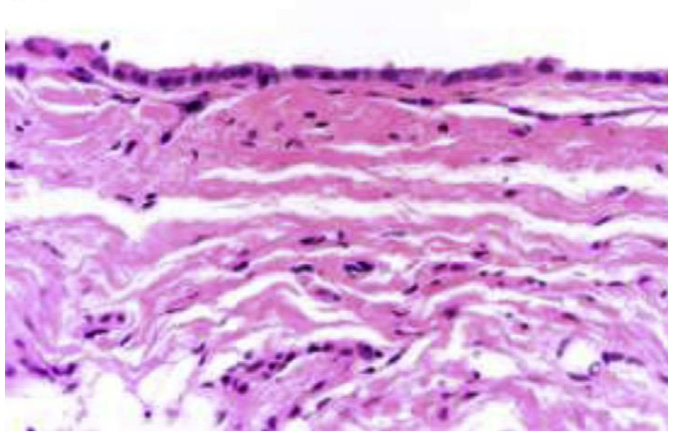
USCAP

ARTICLE

Malignant mesothelioma in situ: morphologic features and clinical outcome

Andrew Churg[1] · Francoise Galateau-Salle[2] · Anja C. Roden[3] · Richard Attanoos[4] · Jan H. von der Thusen[5] · Ming-Sound Tsao[6] · Nina Chang[6] · Marc De Perrot[7] · Sanja Dacic[8]

Received: 11 July 2019 / Revised: 23 July 2019 / Accepted: 23 July 2019 / Published online: 2 August 2019



Abstract

The existence of an in situ phase of malignant mesothelioma has long been postulated but until recently has been impossible to prove. Here we describe ten patients with mesothelioma in situ, defined by a single layer of surface mesothelial cells showing loss of BAP1 nuclear immunostaining, no evidence of tumor by imaging and/or by direct examination of the pleura/peritoneum, and no invasive mesothelioma developing for at least 1 year. Nine cases were pleural and one peritoneal. Most patients were biopsied for repeated effusions of unknown etiology; in two patients mesothelioma in situ was found incidentally in lung cancer resections. In addition to surface mesothelium with BAP1 loss, one case had a surface papillary proliferation with BAP1 loss, and two cases had a small (few millimeter) nodule with BAP1 loss. CDKN2A was deleted by FISH in one of eight cases. Methylthioadenosine phosphorylase showed partial loss in the surface mesothelium by immunohistochemistry in three cases. Invasive malignant mesothelioma developed in seven patients with time between biopsy and invasive disease from 12 to 92 (median 60) months. Invasive mesothelioma has not developed in the other three patients at 12, 57, and 120 months, but the latter patient, who has pleural plaques, still has repeated pleural effusions, probably representing a so-called "benign asbestos effusion." We conclude that mesothelioma in situ, as diagnosed using the criteria outlined above, is associated with a high risk of developing invasive mesothelioma, but typically over a relatively protracted time, so that curable interventions maybe possible.

Modern Pathology (2020) 33:297–302
https://doi.org/10.1038/s41379-019-0347-0

ARTICLE

Malignant mesothelioma in situ: morphologic features and clinical outcome

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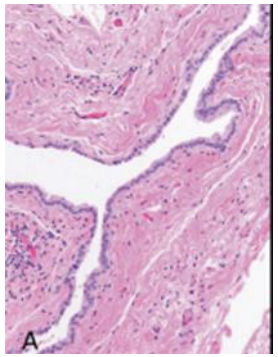
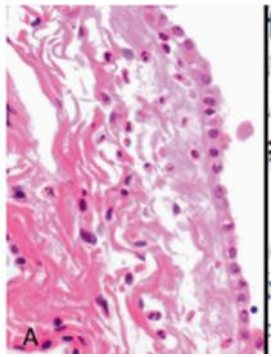
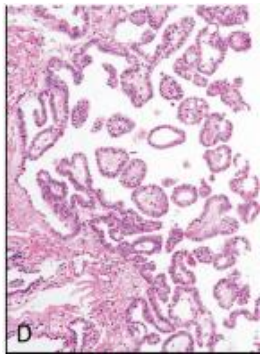
(1) a surface proliferation of mesothelial cells in the form of a single layer of mesothelial cells that had lost BAP1;

(2) no evidence of invasive tumor by imaging and/or direct visual inspection of the pleura or peritoneum at the time of biopsy;

(3) no invasive mesothelioma diagnosed for at least 1 year after the biopsy.







BAP1 loss (IHC)
and/or
Presence of a homozygous deletion of CDKN2a (p16) (FISH) or MTAP (IHC)

Use of Diagnostic and Predictive IHC and Molecular Assays

?

- BAP1 IHC
- CDKN2a (p16) FISH and or MTAP IHC for CDKN2a deletion
- PD-L1 IHC (Chapel DB and al. *Hum Pathol 2019; 87; 11-17*)
- ... Serum levels of calretinin differential diagnosis between histological MPM types

2019

SPECIAL ARTICLE

IASLC

EURACAN/IASLC Proposals for Updating the Histologic Classification of Pleural Mesothelioma: Towards a More Multidisciplinary Approach

Check for updates

Journal of Thoracic Oncology Vol. 15 No. 1: 29-49

2020

SPECIAL ARTICLE

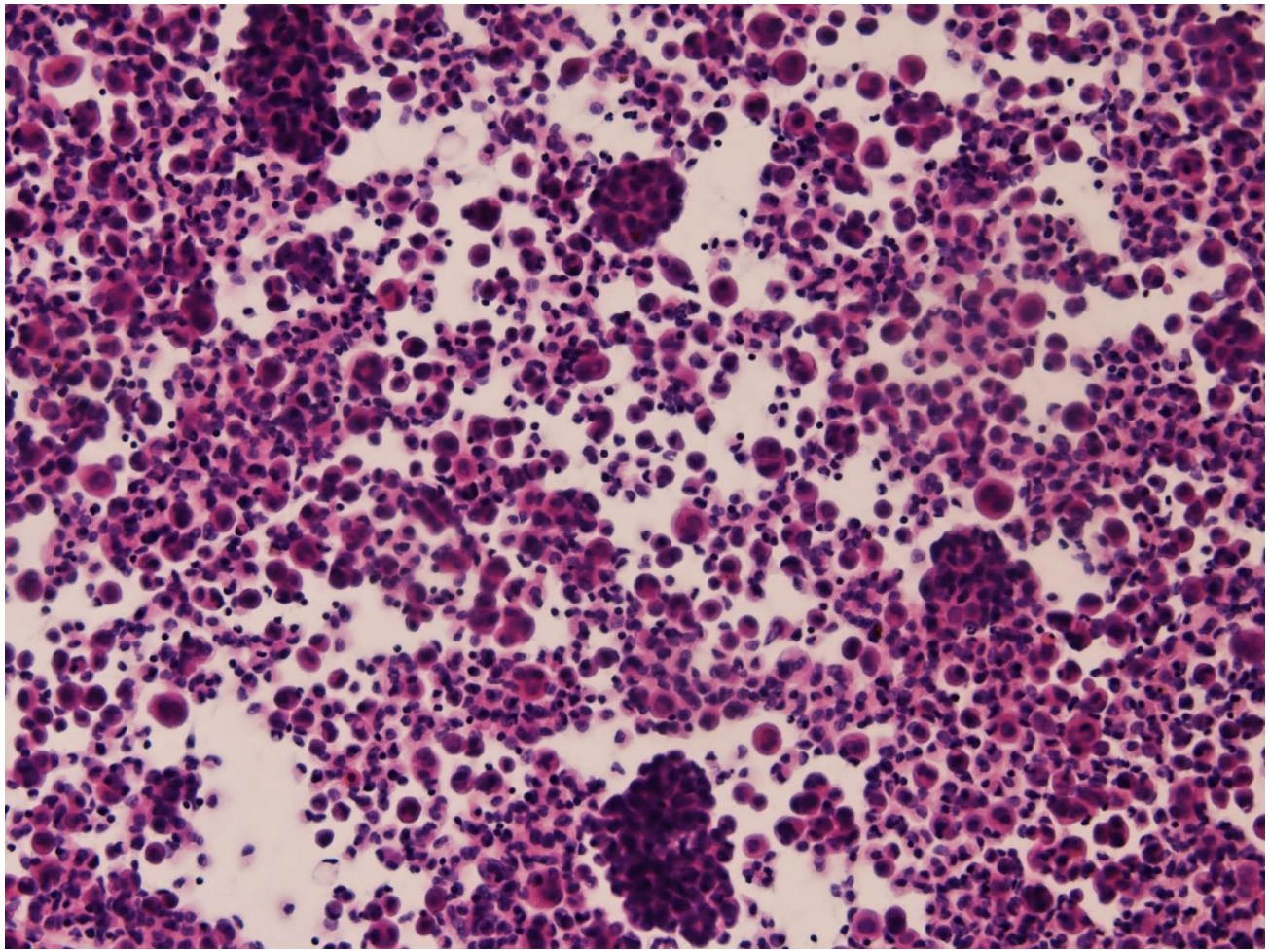
The Separation of Benign and Malignant Mesothelial Proliferations

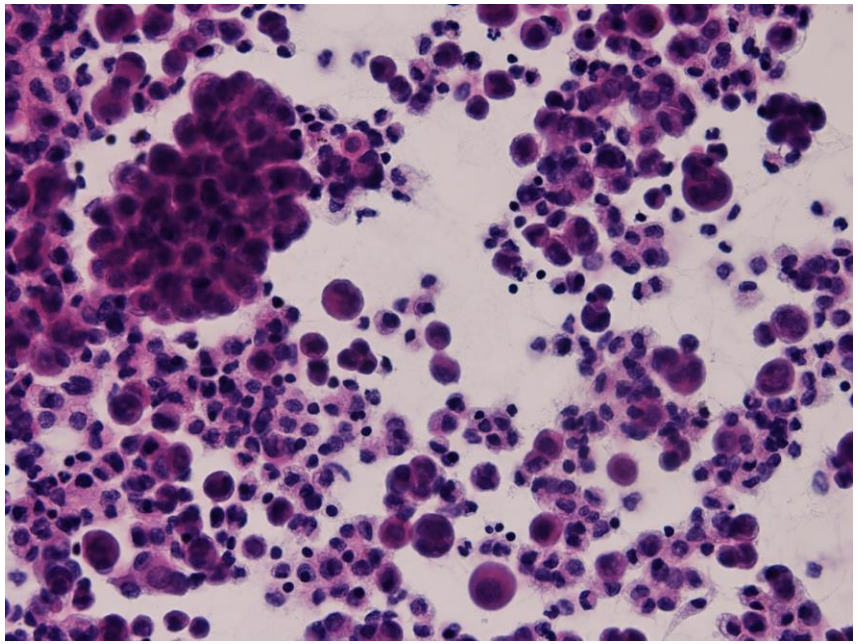
New Markers and How to Use Them

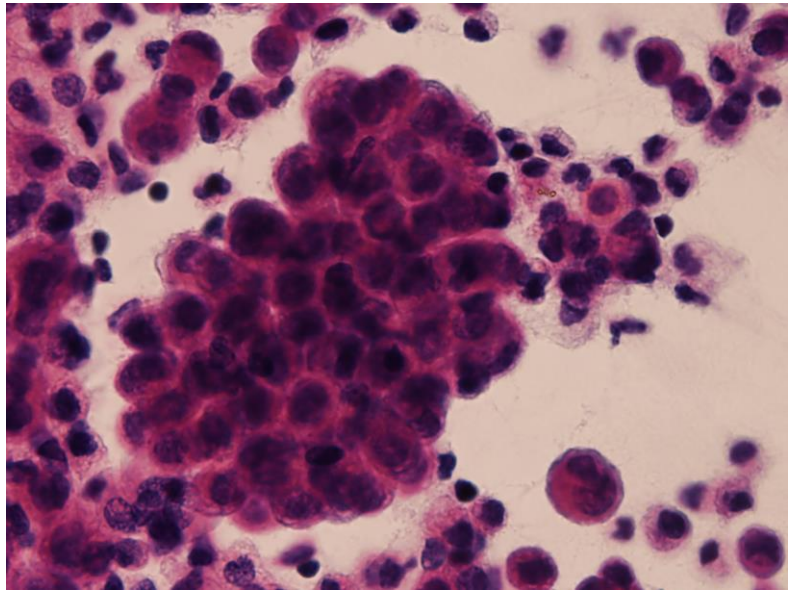
Andrew Churg, MD† and Julia R. Naso, MD, PhD*†*

Issues for The Future

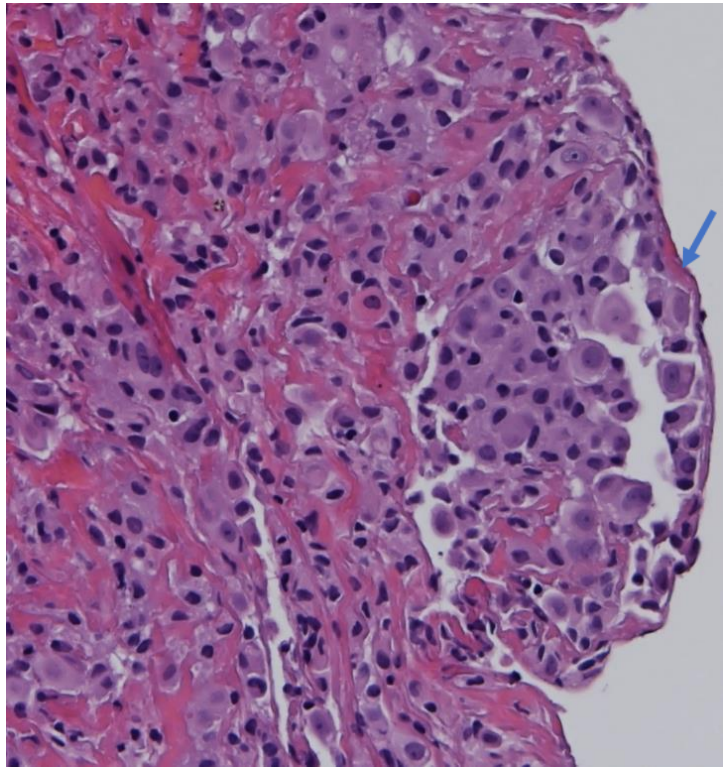
- Updated histological classification WHO 2015
- Mesotelioma in situ: additional category
- Grading of epithelioid malignant pleural mesotheliomas should be routinely reported
- Favourable/unfavourable histologic characteristics should be routinely reported
- Other molecular data should be thoughtful (PDL1, BAP1 e CDKN2A –p16) and added as parte of future trials
- Staging of resection specimens
- At least three separate areas should be sampled from the pleural cavity
- «Multidisciplinary tumor board»
- All histologic sybtypes should be considered potential candidates for chemiotherapy
- Systematic screening of all patients for germline mutations in not recommended in the absence of a family history suspicious for BAP1 syndrome

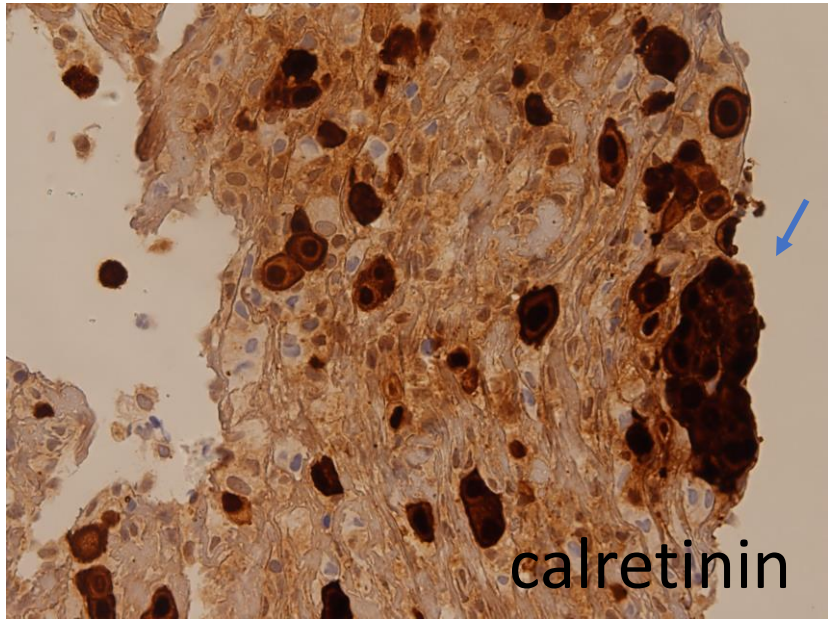


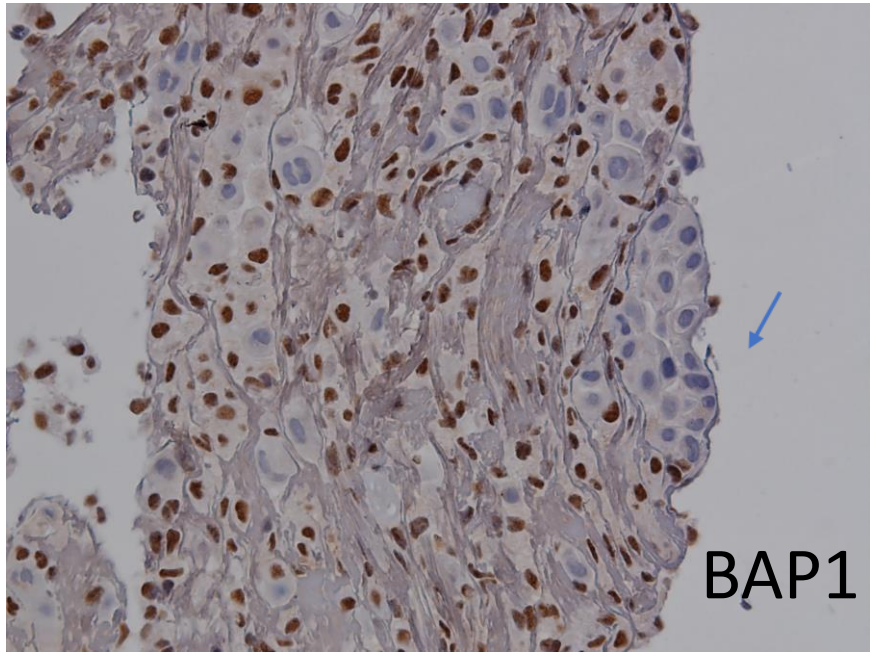




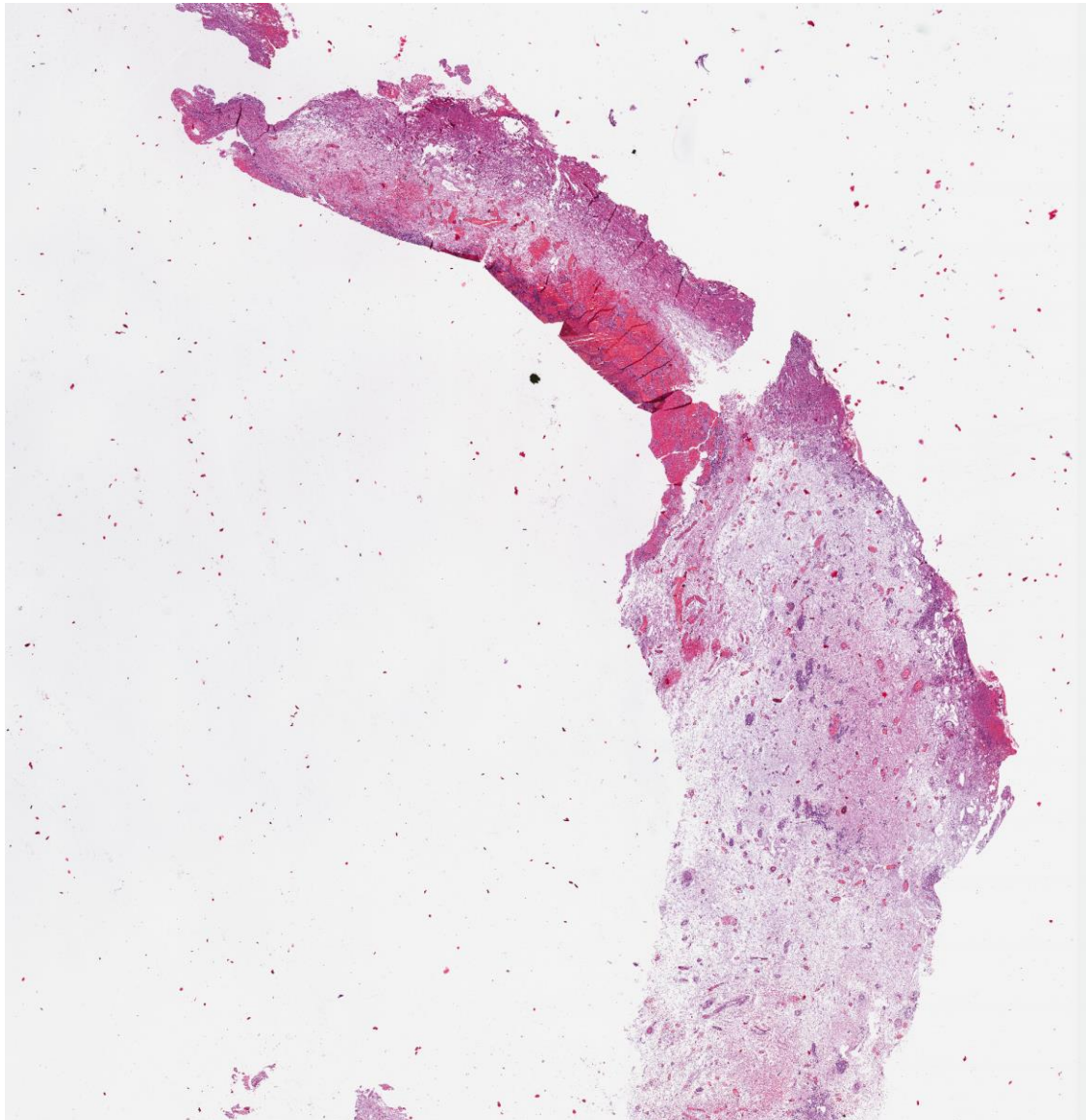
Male 54 ys Pleural effusion

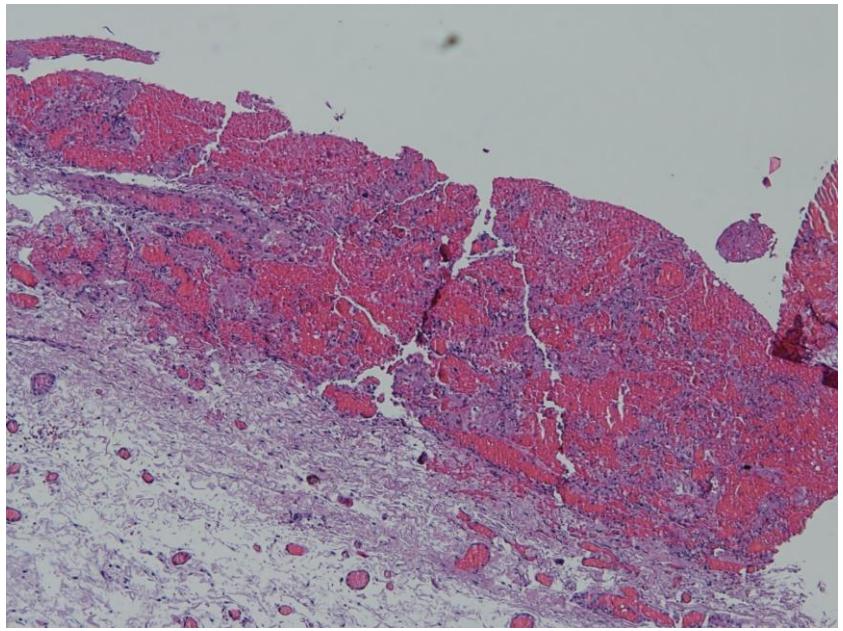


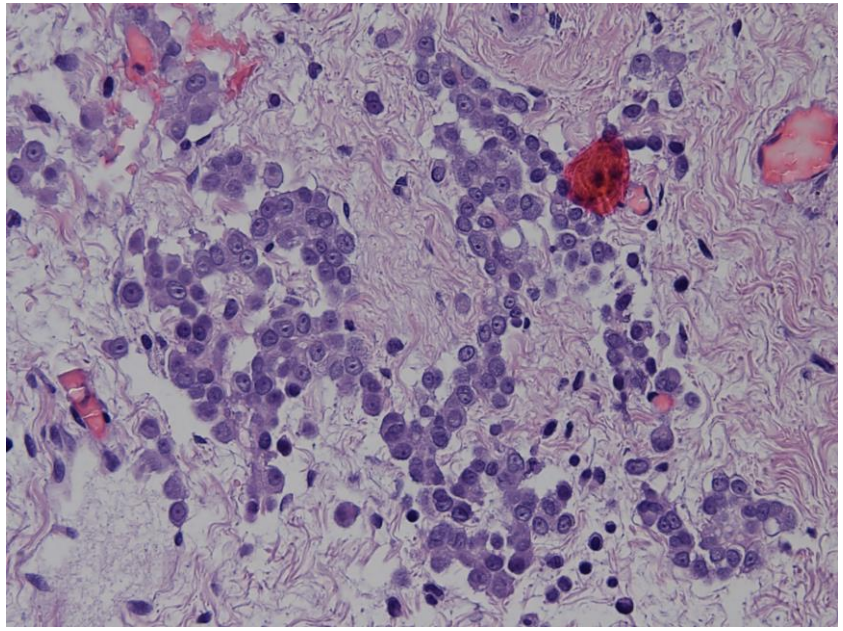


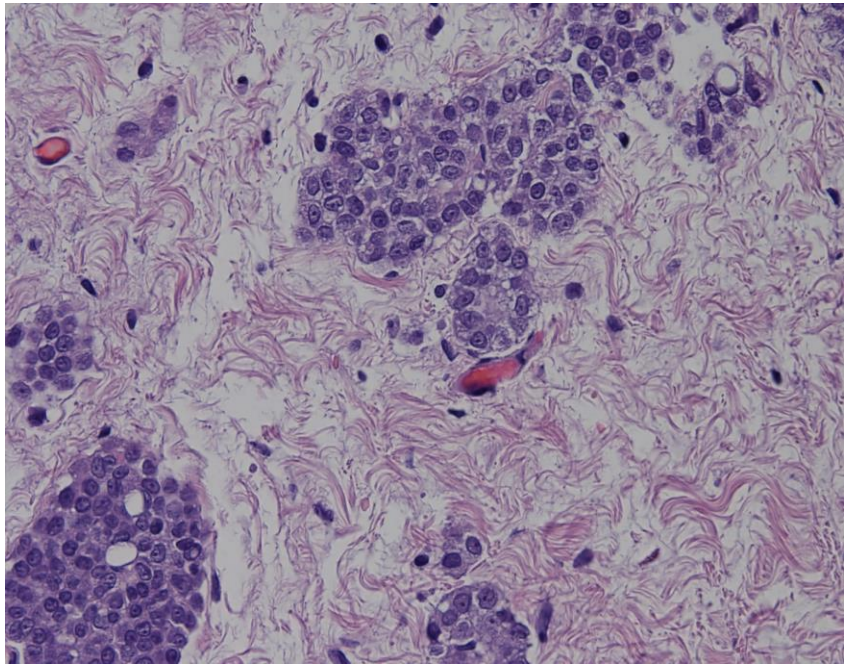


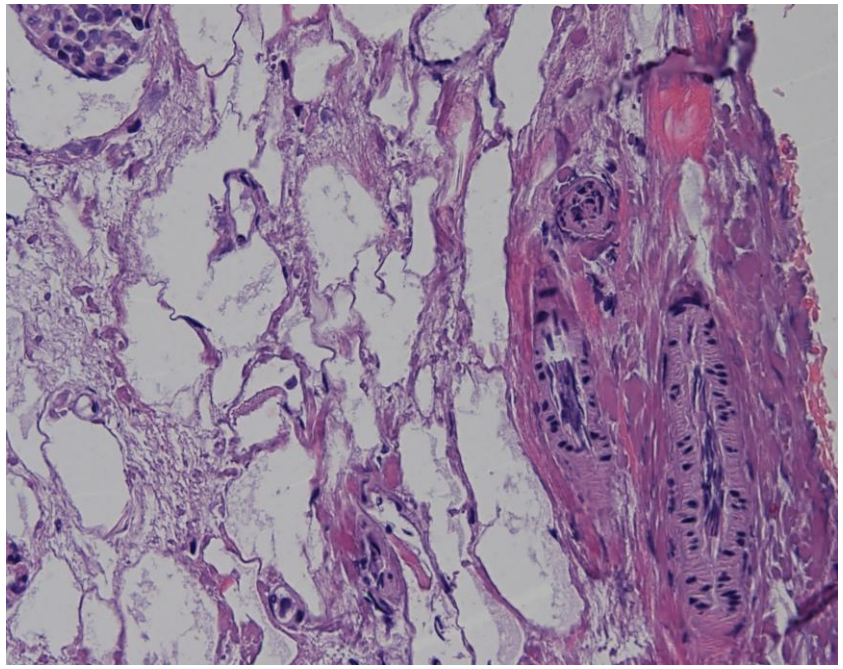
Diagnosis: neoplastic: mesothelioma

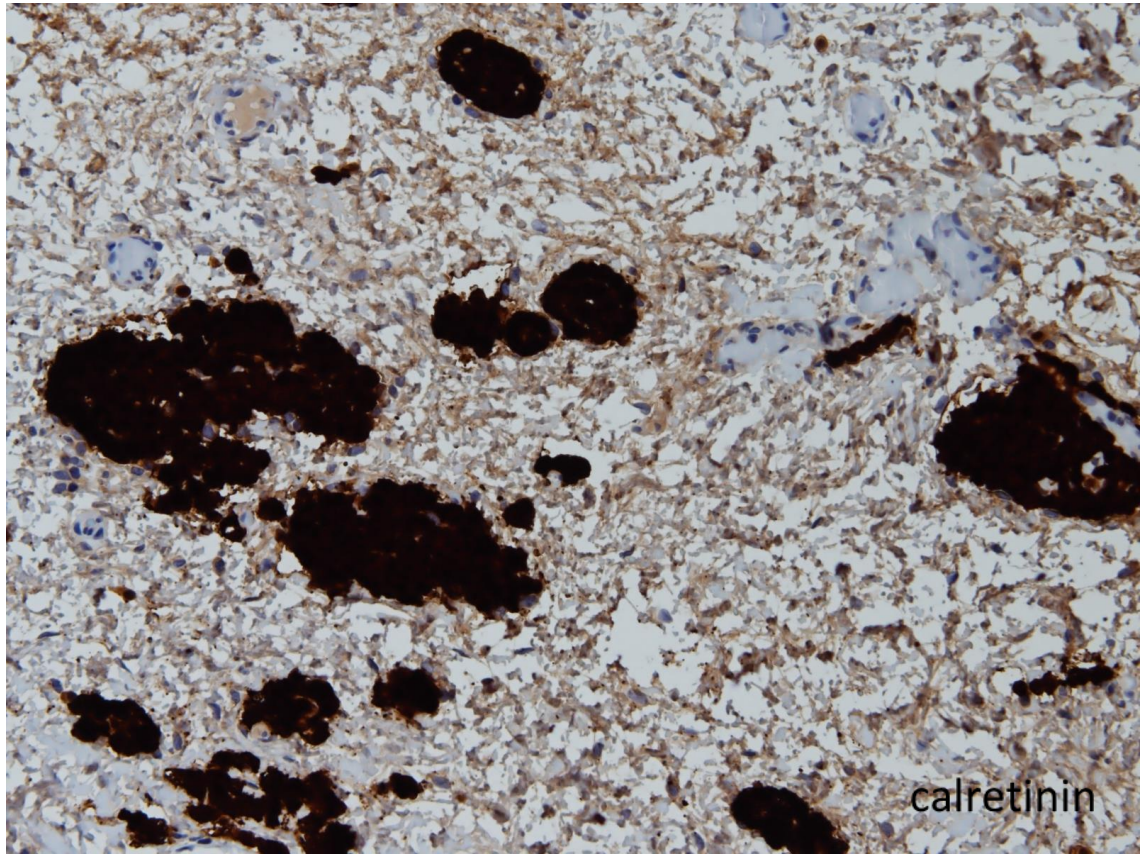


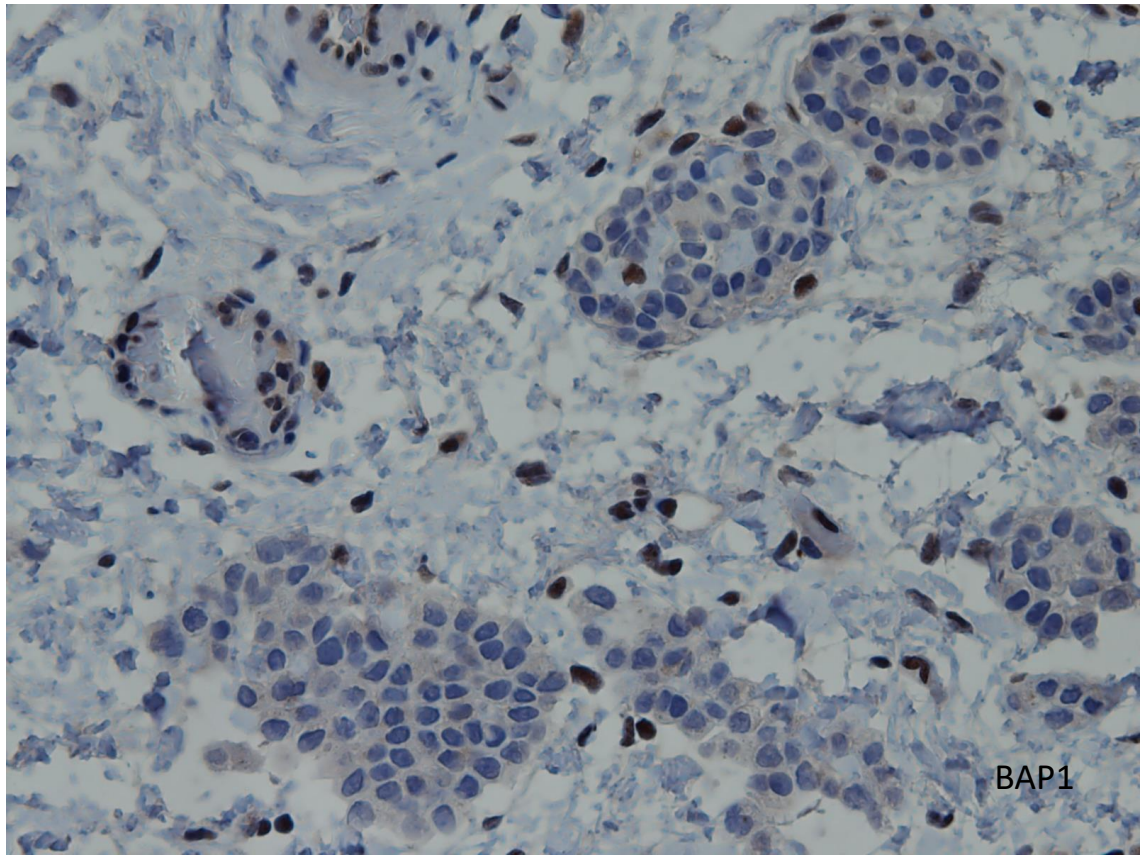












Very suspicious for mesothelioma

GRAZIE