

# MALIGNANT MESOTHELIOMA – UPDATE ON PATHOLOGY AND IMMUNOHISTOCHEMISTRY

Sisko Anttila, MD, PhD  
 Jorvi Hospital Laboratory of Pathology  
 Helsinki University Hospital  
 Espoo, Finland

2nd Nordic Conference on Applied Immunohistochemistry, Ålborg, Denmark, June 9-12, 2015

## MALIGNANT MESOTHELIOMA CLASSIFICATION (WHO 2015)

### WHO classification of tumours of the pleura<sup>a,b</sup>

Mesothelial tumours	Mesenchymal tumours
Diffuse malignant mesothelioma	Epithelioid hemangioendothelioma
Epithelioid mesothelioma	Angiosarcoma
Sarcomatoid mesothelioma	Synovial sarcoma
Desmoplastic mesothelioma	Solitary fibrous tumour
Biphasic mesothelioma	Malignant solitary fibrous tumour
Localized malignant mesothelioma	Desmoid type fibromatosis
Epithelioid mesothelioma	Cachyng fibrous tumour
Sarcomatoid mesothelioma	Desmoplastic round cell tumour
Biphasic mesothelioma	
Well-differentiated papillary mesothelioma	
Adenomatoid tumour	
Lymphoproliferative disorders	
Primary effusion lymphoma	
Diffuse large B-cell lymphoma associated with chronic inflammation	

<sup>a</sup> The morphology codes are from the International Classification of Diseases for Oncology (ICD-O) (4th ed). Separate designations are used for unspecified, borderline, or uncertain behaviour. <sup>b</sup> For carcinoma in situ and grade III Krukenberg tumours. <sup>c</sup> For malignant tumours. <sup>d</sup> The classification is modified from the previous WHO classification (2004), taking into account

## MALIGNANT MESOTHELIOMA CLASSIFICATION

- Epithelioid 60 - 80%
- Sarcomatoid up to 10%
- Biphasic 10 – 15%
- Desmoplastic less than 2%

## MALIGNANT MESOTHELIOMA LOCALIZATION

- Pleura
- Peritoneum
- Tunica vaginalis testis
- Pericardium

## MALIGNANT MESOTHELIOMA PRESENTATION

Unilateral pleural effusion      Thickened pleura

## MALIGNANT MESOTHELIOMA PRESENTATION

Tumor nodules in the parietal pleura

## PATTERNS OF EPITHELIOD MALIGNANT MESOTHELIOMA

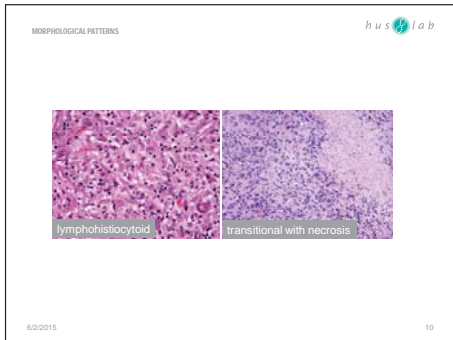
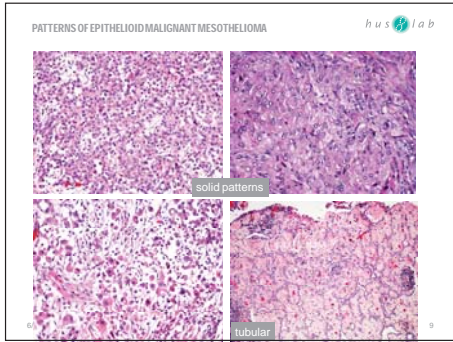
- common
  - tubulopapillary
  - microcystic
  - solid
  - trabecular
- rare
  - clear cell
  - deciduoid
  - adenomatoid (microcystic)
  - transitional
  - small cell
  - pleomorphic
  - lymphohistiocytoid

## PATTERNS OF EPITHELIOD MALIGNANT MESOTHELIOMA

epithelioid cells with myxoid stroma

clear cell

microglandular/signet ring



DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MALIGNANT MESOTHELIOMA

- metastatic carcinomas
- peritoneal/ovarian serous carcinoma
- reactive mesothelial hyperplasia
- mesothelial tumors other than malignant mesothelioma (WDPM, adenomatoid tumor)
- rare non-mesothelial neoplasms, primary and secondary (malignant melanoma, thymoma, epithelioid sarcomas, lymphomas etc.)

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

- a panel of antibodies is recommended with at least 2 positive ja 2 negative markers (+cytokeratins), the selection of markers depending on tumor localization and morphology
- sensitivity and specificity of markers 80% or higher

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### POSITIVE MARKERS - CALRETININ

Positive in MM (%)	Positive in carcinomas (%)
73-100	Lung adenocarcinoma (12-23) Lung squamous cell carcinoma (23-40) Lung large cell carcinoma (37-38) Lung small cell carcinoma (40-49) Breast cancer, various types (4-44) Renal cell carcinoma (0-17) Ovarian/peritoneal carcinoma (0-46) Endometrial carcinoma (3) Colon, adenocarcinoma (6) Hepatocellular carcinoma (2) Pancreas, adenocarcinoma (5) Stomach, adenocarcinoma (6)

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### POSITIVE MARKERS - CK 5/6

Positive in MM (%)	Positive in carcinomas (%)
53-100	Lung adenocarcinoma (5-39) Lung squamous cell carcinoma (87-100) Lung large cell carcinoma (47) Lung small cell carcinoma (27-49) Breast cancer (5-31) Renal cell carcinoma (0-37) Ovarian/peritoneal carcinoma (22-50) Endometrial carcinoma (50) Colon, adenocarcinoma (0) Hepatocellular carcinoma (4) Cholangiocarcinoma (14) Pancreas, adenocarcinoma (38) Stomach, adenocarcinoma (0)

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### POSITIVE MARKERS - WT-1

Positive in MM (%)	Positive in carcinomas (%)
72-93	Lung adenocarcinoma (0-10) Lung squamous cell carcinoma (0) Breast cancer, various types (0-8) Renal cell carcinoma (0-13) Ovarian/peritoneal carcinoma (75-83) Colon, adenocarcinoma (0)

nuclear staining

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### POSITIVE MARKERS - MESOTHELIN

Positive in MM (%)	Positive in carcinomas (%)
75-100	Lung adenocarcinoma (39-52) Lung squamous cell carcinoma (16-31) Lung large cell carcinoma (14) Lung small cell carcinoma (0) Breast cancer, various types (0-56) Renal cell carcinoma (0) Ovarian/peritoneal carcinoma (89-100) Endometrial carcinoma (87) Colon, adenocarcinoma (31) Pancreas, adenocarcinoma (91) Stomach, adenocarcinoma (50)

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM hus lab

### POSITIVE MARKERS - THROMBOMODULIN

Positive in MM (%)	Positive in carcinomas (%)
68-78	Lung adenocarcinoma (13) Lung squamous cell carcinoma (87-100) Lung large cell carcinoma (13) Lung small cell carcinoma (27) Breast cancer, various types (13-18) Renal cell carcinoma (2) Ovarian/peritoneal carcinoma (3-30)

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM hus lab

### POSITIVE MARKERS – D2-40 (PODOPLANIN)

Positive in MM (%)	Positive in carcinomas (%)
69-100	Lung adenocarcinoma (0-7) Lung squamous cell carcinoma (0-50) Breast cancer, various types (0-19) Renal cell carcinoma papillary (39) other types (0) Ovarian/peritoneal carcinoma (13-65) Endometrial carcinoma (0) Colon, adenocarcinoma (0) Pancreas, adenocarcinoma (0) Stomach, adenocarcinoma (0)

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM hus lab

### NEGATIVE MARKERS FOR PLEURAL TUMORS (1)

Tumor type	Marker	Positivity in metastatic tumors, %	Positivity in epithelioid MM, %
Lung adenocarcinoma	TTF-1	58-76	0
	CEA	83	2-5
	CD15 (LeuM1)	72	0-7
	Ber-EP4	80-100	5-26
	BG-8 (Lewis')	93-100	2-7
	MOC-31	93-100	5-13
	Claudin-4	98-100	0-29
	Napsin A	58-91	0

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM hus lab

### NEGATIVE MARKERS FOR PLEURAL TUMORS (2)

Tumor	Marker	Positivity in metastatic tumors, %	Positivity in epithelioid MM, %
Lung squamous cell carcinoma	p63	100	7
	MOC-31	97	5-13
	Ber-EP4	87	5-26
	BG-8 (Lewis')	80	2-7
	p40	97	2

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM hus lab

### NEGATIVE MARKERS FOR PLEURAL TUMORS (3)

Tumor type	Marker	Positivity in metastatic tumors, %	Positivity in epithelioid MM, %
Renal cell carcinoma	CD15 (LeuM1) <sup>b</sup>	25-100	0-3
	MOC-31 <sup>c</sup>	38-75	5-13
	RCC Ma <sup>d</sup>	50-75	8
	Ber-EP4	42	5-26
	PAX8	57-100	9 (limited data)
Breast carcinoma	PAX2	49-85	12 (limited data)
	BG-8 (Lewis')	96-100	2-7
	Claudin-4	100	0-29
	GCDFP-15	15-70	0

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM hus lab

### NEGATIVE MARKERS FOR PERITONEAL TUMORS

Marker	Positivity in ovarian/peritoneal serous carcinoma, %	Positivity in epithelioid MM, %
Ber-EP4	87-100	5-26
MOC-31	93-100	3-15
Estrogen receptor	60-100	0
B72.3	73-87	0
BG-8 (Lewis')	73	2-3
CA19-9	60-73	0
CD15 (LeuM1)	30-63	0-6
PAX8	93	0 (limited data)
Claudin-4	98	0-29

MESOTHELIAL TUMORS OTHER THAN MM hus lab

### ADENOMATOID TUMOUR

- Often incidental finding
- Benign

calretinin

MESOTHELIAL TUMORS OTHER THAN MM hus lab

### WELL-DIFFERENTIATED PAPILLARY MESOTHELIOMA

- Prognosis better than that of diffuse MM
- Peritoneal location more common than pleural

calretinin

*hus lab*

### RARE NON-MESOTHELIAL NEOPLASMS IN THE DIFFERENTIAL DG OF EPITHELIOID MM OR REACTIVE PROLIFERATIONS

- Thymic tumours
- Malignant melanoma
- Lymphoma
- Epithelioid hemangioendothelioma
- Epithelioid sarcoma
- Desmoplastic small round cell tumor

*hus lab*

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### IMMUNOHISTOCHEMISTRY OF EPITHELIOID MM (SUMMARY 1)

**Epithelioid MM**

- 'Mesothelial' markers +
- Cytokeratins + (CK 5/6, 7, 8, 18,19)

**Several tumours, other than MM, of mesothelial and non-mesothelial origin may express 'mesothelial' markers**

- Mesothelial: adenomatoid tumour, well-differentiated papillary mesothelioma
- Non-mesothelial: carcinomas, thymic tumors (CK5/6, calretinin), desmoplastic small round cell tumour, synovial sarcoma (calretinin), vascular tumours (D2-40)

*hus lab*

DIFFERENTIAL DIAGNOSIS OF EPITHELIOID MM

### EPITHELIOID MM OR ATYPICAL MESOTHELIAL HYPERPLASIA?

- morphological features favoring either benign or malignant process
- immunohistochemistry:
  - mesothelial cell markers
  - markers of malignancy
  - broad-spectrum cytokeratins for easier detection of invasion and to rule out non-epithelial tumor type

*hus lab*

REACTIVE HYPERPLASIA VS. EPITHELIOID MM

### MARKERS OF MALIGNANCY – INVASION OF PLEURAL FAT OR LUNG

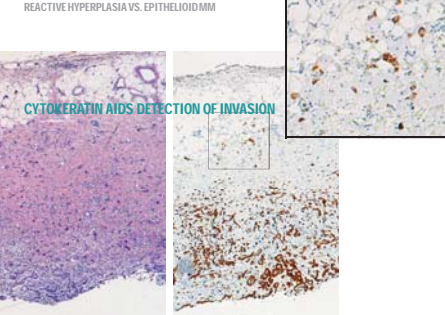


6/2/2015 28

*hus lab*

REACTIVE HYPERPLASIA VS. EPITHELIOID MM

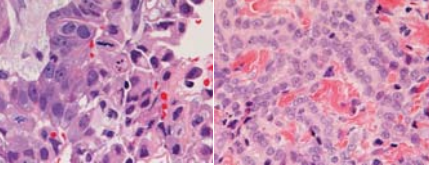
### CYTOKERATIN AIDS DETECTION OF INVASION



*hus lab*

REACTIVE HYPERPLASIA VS. EPITHELIOID MM

### CELLULAR ATYPIA

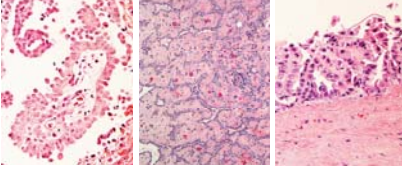


**Atypical mesothelial hyperplasia** **Epithelioid MM**

*hus lab*

REACTIVE HYPERPLASIA VS. EPITHELIOID MM

### PAPILLARY AND TUBULAR STRUCTURES

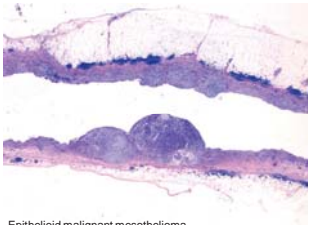


**Complex structures in epithelioid MM** **Atypical hyperplasia**

*hus lab*

REACTIVE HYPERPLASIA VS. EPITHELIOID MM

### FULL-THICKNESS CELLULARITY AND CELLULAR NODULES



**Epithelioid malignant mesothelioma**

6/2/2015 32

REACTIVE HYPERPLASIA VS. EPITHELIOID MM hus lab

### MESOTHELIAL PROLIFERATION

	Benign	Malignant
Invasion	No	Yes
Cellular atypia	Common	Often mild
Tubular & papillary structures	Simple	Complex
Full-thickness cellularity & cellular nodules	Rare	Common
Necrosis	With cellular debris and inflammation	Bland
Inflammation	Often remarkable	Often mild

REACTIVE HYPERPLASIA VS. EPITHELIOID MM hus lab

### IHC AND MOLECULAR MARKERS OF MALIGNANCY

Marker	Sensitivity	Specificity
EMA	58-100% >74%	45-100% >74%
Desmin	80-95% >74%	44-90% >74%
XIAP	80%	90%
GLUT-1	15-100%	93-100%
IMP3	32-73%	94-100%
9p21 deletion	25-67% (sarc. 96)	100%
BIP1 deletion	15 (sarc.)-69 (epith.)	96-100%

EMA, epithelial membrane antigen; XIAP, X-linked inhibitor of apoptosis; GLUT-1, glucose transporter isoform 1; IMP3, insulin-like growth factor II mRNA binding protein; BIP1, BRCA1-associated protein 1  
References: see list in handout

REACTIVE HYPERPLASIA VS. EPITHELIOID MM hus lab

### IHC AND MOLECULAR MARKERS OF MALIGNANCY

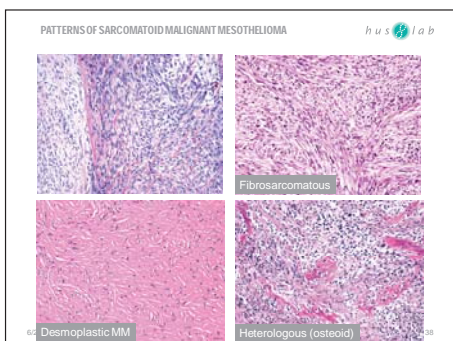
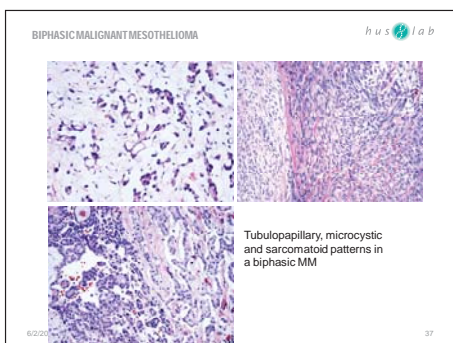
- Each laboratory should test the performance of markers with own reference materials before using them in practice
- Diagnosis cannot be based on markers only; without invasion marker-positivity may be used as a warning sign inducing follow-up or new biopsy

SARCOMATOID AND BIPHASIC MM hus lab

### SARCOMATOID AND BIPHASIC MM

- Sarcomatoid
- Desmoplastic
  - Min. 50%
- Biphasic
  - Epithelioid and sarcomatoid/desmoplastic componen – min. 10% each

6/2/2015 36

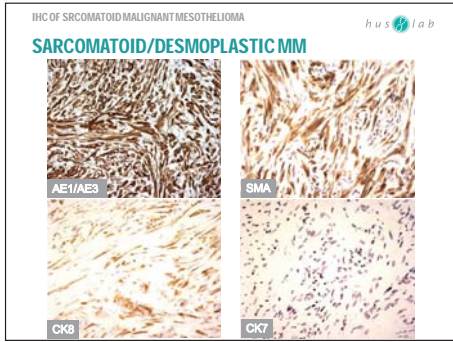


PATTERNS OF SARCOMATOID MALIGNANT MESOTHELIOMA hus lab

### CRITERIA OF DESMOPLASTIC MM

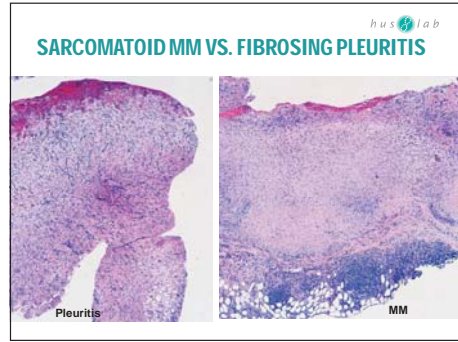
- Acellular or paucicellular areas
- Bland necrosis
- Haphazard arrangement of capillaries
- Identification of marked cellular atypia in non-desmoplastic regions
- Invasion



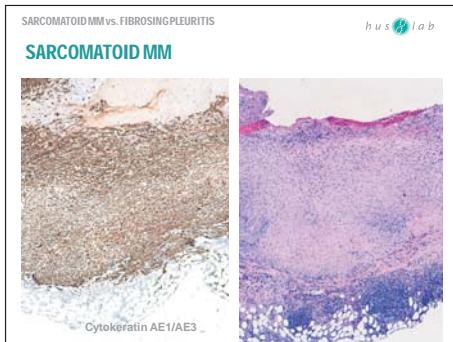
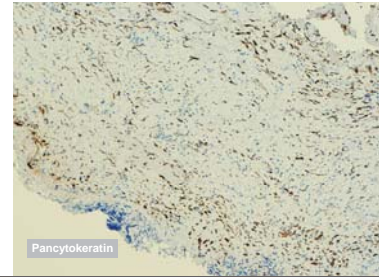


**DIFFERENTIAL DG OF SARCOMATOID AND DESMOPLASTIC MM**

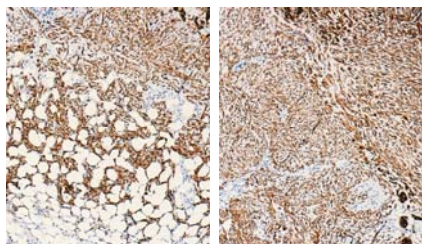
- Fibrosing pleuritis
- Solitary fibrous tumour (benign and malignant)
- Sarcomas
- Sarcomatoid carcinomas (lung, kidney)
- Desmoid tumour



**PLEURITIS**



**SARCOMATOID MM**



SARCOMATOID MM VS. FIBROSING PLEURITIS huslab

**SARCOMATOID/DESMOPLASTIC MM**

- immunohistochemistry:
  - mesothelial markers for detection of a possible small epithelioid component (be wary with reactive mesothelium) – not useful for sarcomatoid/desmoplastic component of MM
  - broad-spectrum cytokeratins for easier detection of growth patterns and invasion, and to rule out non-epithelial tumor type – CK5/6, CK7 may be negative

SARCOMATOID MM VS. FIBROSING PLEURITIS huslab

**MORPHOLOGICAL FEATURES OF BENIGN AND MALIGNANT SPINDLE CELL LESIONS**

Feature	Benign	Malignant
Typical layering of organizing fibrinous exudate	Yes	No in tumor tissue
Broad-spectrum cytokeratins	Positive cells parallel to pleural surface – no positivity in deeper fibrous tissue	Demonstrate storiform growth pattern Deep invasive tumor tissue often positive
Mesothelial markers	Positivity in reactive mesothelial cells	Sarcomatoid/desmoplastic MM often negative Help to detect a small epithelioid component – makes the diagnosis of MM confident

EPITHELIOID VS. SARCOMATOID MALIGNANT MESOTHELIOMA huslab

<p><b>EPITHELIOID MM:</b></p> <ul style="list-style-type: none"> <li>• may present with a number of different histological patterns</li> <li>• mesothelial markers and appropriate carcinoma markers are <u>helpful</u> in the differential diagnosis</li> <li>• invasion is the only reliable criterion of malignancy</li> </ul>	<p><b>SARCOMATOID MM:</b></p> <ul style="list-style-type: none"> <li>• may present with a number of different histological patterns</li> <li>• mesothelial markers are <u>not useful</u>, except for pancytokeratins</li> <li>• use pansyokeratins to detect invasion in desmoplastic MM</li> </ul>
---	---

6/2/2015 49

REFERENCES huslab

**IHC of MM** (including references in articles listed)

Ordonez NG. Hum Pathol 2013; 44:1-  
 Ordonez NG. Modern Pathol 2013; 26:553-  
 Ordonez NG & Salm AA. Hum Pathol 2014; 45:1529-  
 Henderson DW et al. J Clin Pathol 2013; 66:847-  
 Antilla S. Arch Pathol Lab Med 2012; 136:241-  
 Antilla S. in Occupational cancers, Springer 2014, p. 285-  
 WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart, 2015

**Reactive hyperplasia vs. MM** (including references in article listed)

Attanoos et al. Histopathology 2003; 43:231-  
 King et al. Histopathology 2006; 49:561-  
 Henderson DW et al. J Clin Pathol 2015; 66:847-  
 Minato H et al. Am J Clin Pathol 2014; 141:85-  
 Chang S et al. Pathol Int 2014; 64:607-  
 Lagana SM et al. Arch Pathol Lab Med 2012; 136:804-  
 Husain AN et al. Lung Cancer 2014; 53:324-  
 Takeda M. et al. Pathol Int 2010; 60:395-  
 Tochigi N et al. Arch Pathol Lab Med 2013; 137:632-  
 Ciocognetti M et al. Modern Pathol 2015; 1-15  
 Sheffield BS et al. Am J Surg Pathol 2015; -

6/2/2015 50