MACROSCOPIC, HISTOLOGIC, HISTOCHEMICAL, IMMUNOHISTOCHEMICAL AND ULTRASTRUCTURAL FEATURES OF MESOTHELIOMA

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INTRODUCTION

The celomic cavity develops early in embryogenesis and is divided by partitioning membranes into the pleural, pericardial and peritoneal cavities. These body cavities are lined by tissue referred to as serosa that have a visceral and parietal layer. The serosal tissue is composed of a layer of epithelial mesothelial cells separated from the underlying connective tissue component by a basement membrane. Mesotheliomas arise from cells forming this serosal membrane. The majority of mesotheliomas (90-95%) arise in the pleural cavity whereas about 5 to 10% arise in the peritoneal cavity. Primary pericardial mesotheliomas are extremely uncommon. Mesotheliomas can arise in the tunica vaginalis which is an invagination of the peritoneum.

Serosal tissue is an extremely reactive type of tissue and shows a prominent reaction to almost any form of injury. Epithelial mesothelial cell hypertrophy and hyperplasia can become extremely severe and be confused with epithelial mesothelioma. Likewise, multipotential subserosal cells proliferate forming a highly cellular invasive appearing type process. One of the most difficult areas in “mesothelioma pathology” is differentiating reactive epithelial mesothelial cell proliferation from an epithelial mesothelioma and from differentiating reactive multipotential subserosal cell proliferation from a sarcomatoid or desmoplastic mesothelioma.

MACROSCOPIC FEATURES OF MESOTHELIOMA

At the time most pleural mesotheliomas are diagnosed, they are composed of multiple small nodules studding the visceral and parietal pleural surface. These nodules range from 1 mm. to occasionally 1 cm. In the majority of cases, this proliferation is associated with a pleural effusion, the pleural fluid usually having the features of an exudate.

As time progresses, the nodules coalesce to form solid tumors that in the case of pleural mesotheliomas encase the lung and obliterate the pleural cavity. Mesotheliomas frequently invade chest wall skeletal muscle and sometimes directly invade skin and subcutaneous tissue. They likewise invade lung parenchyma. It is not uncommon for mesotheliomas to show variability in the thickness of the rind of tumor that encases the lung. In general, the tumor is usually much thicker at the base of the pleural cavity than it is at the apex. Frequently, mesotheliomas have a nodular morphology and if the rind of tumor is relatively thin, these nodules can be confused with primary lung cancers. Occasionally, mesotheliomas metastasize to hilar lymph nodes and produce a hilar mass that is significantly more recognizable radiographically than the thin rind of tumor that encases the lung. Mesotheliomas also frequently directly invade pericardium and sometimes myocardium. It is not uncommon for pleural mesotheliomas to invade through the hemidiaphragms and extend into the abdominal cavity.

Some epithelioid mesotheliomas produce excess amounts of hyaluronic acid and proteoglycans. Tumors that produce these substances are “slick” and “slimy”. They often have large cystic areas filled with a tannish gelatinous material.

Peritoneal mesotheliomas are similar to pleural mesotheliomas in that they also begin as multiple small nodules that over a period of time coalesce to form a rind of tumor tissue that encase various organs within the abdominal cavity. Sometimes this can be so extensive that the bowel and other organs are compressed to the point of being nonexistent. As with pleural mesotheliomas, most peritoneal mesotheliomas initially are associated with an effusion.

Primary mesotheliomas that arise in the tunica vaginalis often present as a mass in that location. They sometimes remain localized, although not infrequently invade the peritoneal cavity and extensively involve it.

Primary pericardial mesotheliomas are rare. To diagnose a primary pericardial mesothelioma, one has to be certain that the tumor involving the pericardium does not represent an extension of a pleural mesothelioma. Pericardial mesotheliomas are like other mesotheliomas in that they start out as small nodules that coalesce to form a rind of tumor around the heart with obliteration of the pericardial cavity.

Rarely, mesotheliomas occur as localized masses rather than diffusely involving a body cavity. These occur most frequently in the pleural cavity and are called localized malignant mesotheliomas.

Symptoms referable to the site that mesotheliomas begin are often so dominating that metastases are not searched for in mesothelioma. However, metastases are relatively common in mesothelioma, although not as common as one sees in primary lung cancers. The most common site mesotheliomas metastasize to is bronchopulmonary and hilar lymph nodes. The next most common site is to the pleural surface of the lung not involved by tumor. Mesothelioma metastases can involve almost any organ, including adrenal glands, liver, kidneys, etc. There have been about 20 or 25 reported cases of mesotheliomas metastasizing to brain. Desmoplastic mesotheliomas have a propensity to metastasize to bone and can be a diagnostic dilemma because they resemble benign fibrous tissue.

HISTOLOGIC TYPES OF MESOTHELIOMA

Mesotheliomas are subtyped into four major categories:

1. Epithelial
2. Sarcomatoid – fibrous
3. Biphasic – mixed
4. Desmoplastic (this is considered a variant of a sarcomatoid mesothelioma)

This classification scheme is extremely simple compared to what actually exists. There are numerous subtypes of epithelial mesothelioma (Table 1) and there are numerous patterns that one sees with sarcomatoid mesotheliomas and biphasic mesotheliomas. When large tissue samples are available such as a pleural pneumonectomy specimen or an autopsy specimen, it is common to see variable differentiation. One can often see five or six histologic types of differentiation by the tumor and the more sections one takes, the more likely the tumor is found to be biphasic. Sarcomatoid mesotheliomas can show homologous or heterologous differentiation including osteocartilaginous and lipomatous differentiation. It is debatable whether they show vascular differentiation.

Desmoplastic mesotheliomas are probably the most difficult of all mesotheliomas to diagnose. They should not be diagnosed from a needle core biopsy. The primary differential diagnosis is fibrosing pleuritis. The criteria for diagnosing desmoplastic mesothelioma include:

1. Over 50% of the tumor has to be composed of relatively dense hypocellular fibrous tissue that not infrequently forms vague nodules.
2. Areas of increased cellularity that have the features of a sarcomatoid mesothelioma.
3. Focal areas of stellate necrosis.
4. Invasion of subparietal pleural fat/chest wall or invasion of the lung (most important).

In fibrosing pleuritis, there are more reactive tissue changes with capillary proliferation, inflammation and fibrin deposition. The capillaries that proliferate in the pleura are usually perpendicular to the surface of the pleura which is not seen in desmoplastic mesothelioma.

One has to remember that when desmoplastic mesotheliomas invade or metastasize, they can look extremely bland and can be misdiagnosed as benign fibrous tissue.

HISTOCHEMICAL FEATURES

Histochemistry is infrequently used at this point in time in diagnosing mesotheliomas, although occasionally it can be helpful. Histochemistry is used primarily to differentiate epithelial mesotheliomas from mucin producing adenocarcinoma such as primary pulmonary mucin producing adenocarcinoma. The general rule of thumb is that most epithelial mesotheliomas do not produce mucin and therefore are PAS diastase, mucicarmine and Alcian blue/colloidal iron negative. Epithelial mesotheliomas frequently contain glycogen and are PAS positive with this reaction eradicated with pretreatment with diastase. Likewise, the epithelial mesotheliomas that produce abundant hyaluronic acid or proteoglycans frequently stain strongly positive with Alcian blue/colloidal iron with this reaction often being eradicated by pretreatment of the tissue with hyaluronidase. Approximately 2-5% of all epithelial mesotheliomas stain positive with a mucin stain such as mucicarmine, PAS diastase and Alcian blue/colloidal iron even after pretreatment with hyaluronidase. These mesotheliomas are ones referred to as mucin positive epithelial mesotheliomas. When evaluated ultrastructurally, they frequently show crystalloid material which is discussed below under the heading “Ultrastructural Features”. The mucin positive epithelial mesotheliomas are the ones that often will show focal positive staining for immunohistochemical markers that are often associated with primary pulmonary adenocarcinoma such as CEA, LeuM1, and B72.3.

IMMUNOHISTOCHEMICAL MARKERS

There is extensive literature on the immunohistochemistry of mesothelioma. Immunohistochemistry is most useful in differentiating epithelial mesothelioma from other types of an epithelial neoplasm. Epithelial mesotheliomas characteristically express broad spectrum cytokeratin, cytokeratin 5/6, cytokeratin 7 and about 5 to 10% will show staining for cytokeratin

20. Epithelial mesotheliomas likewise express calretinin in a nuclear and cytoplasmic distribution and show cell membrane staining for HBME-1 and epithelial membrane antigen. About 20% of epithelial mesotheliomas show cell membrane staining for BerEP4 and thus finding a BerEP4 positive tumor does not rule out mesothelioma. Occasional epithelial mesotheliomas show diffuse cell membrane staining for BerEP4. Other antibodies that are used to diagnose epithelial mesothelioma include thrombomodulin, WT-1, mesothelin and N-Cadherin. The antibodies we use in evaluating mesothelioma are shown in tables 3 and 4.

Immunohistochemistry is much less useful in sarcomatoid mesotheliomas, although in the majority of cases, the neoplastic spindle cells coexpress broad spectrum keratin and vimentin. In approximately 30% of the cases, the spindle cells express cytokeratin 7 and only rarely do the neoplastic spindle cells express cytokeratin 5/6. Vimentin staining is seen in essentially 100% of sarcomatoid mesotheliomas. About 30 to 40% of sarcomatoid mesotheliomas express alpha actin. The intensity of the staining can vary from being low intensity to high intensity. Rare sarcomatoid mesotheliomas do not express keratin.

As time has progressed, epithelial and sarcomatoid mesotheliomas have been identified to express other substances including a number of “cluster designation” antigens. Also, epithelial mesotheliomas express neuroendocrine markers. Small cell mesotheliomas are characteristically stated to not express neuroendocrine markers, although I have seen at least one case where the small cell mesothelioma expressed neuroendocrine markers and also expressed typical epithelial markers of mesothelioma, specifically calretinin and CK5/6. Caution is urged in interpreting immunohistochemical markers and it is always better to do a fairly large battery of tests in trying to determine if the tumor is a mesothelioma or some other type of neoplasm.

ULTRASTRUCTURAL FEATURES

As the majority of people attending this conference know, electron microscopy is extremely useful in diagnosing mesothelioma, primarily well to moderately well-differentiated epithelial mesotheliomas. These mesotheliomas characteristically have fairly long sinuous microvilli that are not covered by a glycocalyx. They are not associated with rootlets in the underlying tumor cells and characteristically do not contain mucus granules. Epithelial mesotheliomas frequently show large desmosomes and prominent junctional complexes. They not infrequently show what is referred to as microvillous matrix interaction in which the microvilli directly “penetrate” adjacent collagen fibers. The tonofilaments that are identified in neoplastic epithelial mesothelial cells frequently are in a perinuclear distribution, although sometimes they are distributed throughout the cytoplasm. Remember that some primary pulmonary adenocarcinomas have long microvilli, but these microvilli are invariably covered by a glycocalyx. Epithelial mesotheliomas frequently form intracellular canaliculi that is not a specific finding, but may be more common in epithelial mesothelioma than pulmonary adenocarcinoma. Epithelial mesotheliomas produce excess amounts of hyaluronic acid that appears as a medium electron dense material that covers the microvilli. The proteoglycan granules are not specific for mesothelioma, but are not infrequently seen in glandular lumens of mesothelioma and by electron microscopy have a somewhat stellate appearance and are electron dense.

Mucin positive epithelial mesotheliomas are frequently associated with extracellular and sometimes intraluminal crystalloid structures that in my experience are 100% unique for mucin positive epithelial mesotheliomas. These crystalloid structures occasionally can be seen in the cytoplasm of the neoplastic mesothelial cells. In cross section, they somewhat resemble chrysotile asbestos fibers in that have a scroll like appearance.

Rare mesotheliomas have a Gauchier-like appearance that ultrastructurally is associated with a unique crystalloid material within the cisternae of the rough endoplasmic reticulum of the neoplastic cells. These often form large scroll-like structures that in my experience are unique for mesotheliomas.

DIFFERENTIAL DIAGNOSIS

Epithelial mesotheliomas have to be differentiated from adenocarcinomas and other epithelial neoplasms. Small cell mesotheliomas have to be differentiated from neuroendocrine neoplasms. There is a type of primary lung cancer called pseudomesothelioma that look identical to mesothelioma macroscopically, but are formed by tumor cells that usually show glandular differentiation and have the characteristic features of an adenocarcinoma. Sometimes, these tumors can be metastatic from sites outside of the chest cavity and can be a difficult diagnostic dilemma. With respect to sarcomatoid mesotheliomas, one has to be aware that sarcomatoid carcinomas of the kidney and pancreas can metastasize to the lung and form a macroscopic pattern characteristic of a mesothelioma (pseudomesotheliomatous metastatic sarcomatoid carcinoma).

Some synovial sarcomas fairly extensively involve the pleura and can be extremely difficult to differentiate from a sarcomatoid mesothelioma or a biphasic mesothelioma. With respect to biphasic mesothelioma, the epithelial component of a synovial sarcoma can have many of the same immunostaining patterns as an epithelial component of a mesothelioma. In cases where this is a question of synovial sarcoma, cytogenetic studies are the only certain way to determine if a tumor is or is not a synovial sarcoma.

A number of other rare sarcomatoid tumors occur in the pleura are pseudomesotheliomatous epithelioid hemangioendotheliomas, primary desmoid tumors of the pleura, calcifying fibrous pseudotumor of the pleura, primary pleural thymomas and pleural pulmonary blastomas.

Lymphomas rarely involve the lung and pleural surface. When they do, they can occasionally be mistaken for a mesothelioma, although with immunohistochemistry and EM, this usually is not a problem.

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TABLE 1

Epithelial Mesothelial Subtypes

1. Tubulopapillary
2. Glandular
3. Histiocytoid
4. Adenoid cystic
5. Microcystic
6. Macrocystic
7. Signet ring
8. Single file
9. Diffuse – NOS
10. Glomeruloid
11. In association with excessive amounts of hyaluronic acid/proteoglycan
12. Small cell
13. Poorly differentiated (Large cell)/Pleomorphic
14. Deciduoid
15. Mucin Positive
16. Gaucher cell-like
17. In-situ

18. TABLE 2

ANTIBODY DIRECTED AGAINST	*CLONE*	*CHARACTERISTICS OF ANTIGENS RECOGNIZED*	*IMMUNOGEN*	*MANUFACTURER*	*DILUTION*	*TYPE OF ANTIGEN RETRIEVAL*
Keratin	AE1/AE3	Keratins – Moll numbers 1-5, 6, 8, 9, 10, 14-16, 18	Human Epidermal Keratin	DAKO	1:200	HIER
Keratin	MAK-6	Keratins – Moll numbers 8, 14-16, 18 and 19	Extracellular antigen from MCF-tissue culture and from human sole epidermis	Zymed	1:100	HIER
Keratin	CAM5.2	Keratins – Moll numbers 8 & 18	Colorectal cancer cell line	Becton-Dickinson	1:100	HIER
Keratin	35βH11	Keratin – Moll number 8	Hep3B hepatocellular carcinoma cell line	DAKO	1:50	HIER
Keratin	34BE12	Keratins – Moll numbers 1, 5, 10 and 14	Human stratum corneum keratin	DAKO	1:100	HIER
Cytokeratin 5/6	D5/16B4	Keratins – Moll numbers 5, 6, and to a slight degree, 4	Purified cytokeratin 5	Biocare Medical	1:100	HIER
Cytokeratin 7	OV-TL 12/30	Keratin – Moll number 7	OTN 11 ovarian carcinoma cell line	DAKO	1:100	HIER
Cytokeratin 20	K 20.8	Keratin – Moll number 20	Villi of human duodenal mucosa	DAKO	1:100	HIER
Vimentin	Vim3B4	Intermediate filament 57 kilodaltons	Vimentin from bovine eye lens	DAKO	1:100	HIER
Alpha Actin	1A4	Alpha-smooth muscle isoform of actin	N-terminal decapeptide of human α smooth muscle actin	DAKO	1:100	HIER
Muscle Specific Actin	HHF35	42 kd protein in preparations of purified skeletal muscle actin and extracts of aorta, uterus, diaphragm and heart	SDS extracted protein fraction of human myocardium	DAKO	1:400	HIER
Desmin	D33	53 kd intermediate filament in muscle cells, recognizing 18 kd rod piece of molecule	Desmin purified from porcine stomach	DAKO	1:80	HIER
Calretinin	-----	29 kd calcium-binding protein	Human recombinant calretinin	Zymed	1:50	HIER
Mesothelioma antigen	ABME-1	Antigen present in membrane of mesothelial cells	Suspension of human mesothelial cells from malignant epithelial mesothelioma	DAKO	1:500	HIER
Thrombomodulin	1009	Transmembrane glycoprotein of 75 kd molecular weight containing 6 repeated domains homologous with epidermal growth factor	Recombinant thrombomodulin	DAKO	1:50	HIER
Epithelial Membrane Antigen (EMA)	E29	250-400 kd glycoprotein of milk fat globule protein family	Delipidated extract of human milk fat	DAKO	1:100	HIER
Human Milk Fat Globule Protein-2 (HMFG-2)	115D8	MAM-6 mucus glycoprotein of > 400 kd in glycocalyx of epithelial cells	Purified human milk fat globule protein	BioGenex	1:25	HIER
N-Cadherin	389	Transmembrane glycoprotein involved in calcium dependent cell adhesion	Intracellular domain of chicken N-cadherin	Zymed	1:100	HIER
Polyclonal Carcinoembryonic Antigen (CEA)	-----	CEA and CEA-like proteins including nonspecific cross-reacting substance and biliary glycoprotein	Human CEA isolated from metastatic colonic adenocarcinoma	DAKO	1:16,000	HIER
CD15 (LeuM1)	C3D-1	3-fucosyl-N-acetyl-lactosamine	Purified neutrophils from normal human peripheral blood	DAKO	1:20	HIER
Tumor Associated Glycoprotein	B72.3	Tumor-associated glycoprotein of wide variety of human adenocarcinomas	Membrane-enriched fraction of metastatic breast cancer	BioGenex	1:100	HIER
Human Epithelial Antigen	Ber-EP4	34-& 49 kd glycoproteins on the surface and in	MCF-7 cell line	DAKO	1:100	HIER

		cytoplasm of most epithelial cells, except squamous epithelium, hepatocytes and parietal cells				
Thyroglobulin	-----	Thyroglobulin	Thyroglobulin from human thyroid glands	DAKO	1:16,000	HIER
Thyroid Transcription Factor (TTF-1)	8G7G3/1	40 kd member of NKχ2 family of homeodomain transcription factors	Rat TTF-1 recombinant protein	Biocare Medical	1:200	HIER
Prostate Specific Antigen (PSA)	ER-PR8	33 kd prostate specific antigen	Purified human prostate specific antigen	DAKO	1:100	HIER
Prostatic Acid Phosphatase (PAP)	PASE/4LJ	52 kd human prostatic acid phosphatase	Purified prostatic acid phosphatase from human seminal plasma	DAKO	1:16,000	HIER
Human Epithelial Related Antigen	MOC-31	40 kd transmembrane glycoprotein present on most normal and malignant epithelial cells	Neuraminidase treated cells from small-cell carcinoma cell line	DAKO	1:50	HIER
Lewis Y Antigen	BG8-F3	Difucosylated tetrasaccharide found on type 2 blood group oligosaccharide	SK-LU-3 lung cancer cell line	Signet	1:40	HIER
E-Cadherin	4A2C7	Transmembrane glycoprotein in calcium-dependent cell adhesion	Recombinant protein of human E-cadherin	Zymed	1:100	HIER
Gross Cystic Disease Fluid Protein-15 (BRST-2)	D6	Pathologic secretion of breast composed of several glycoproteins including 15 kd monomer protein	Gross cystic disease fluid protein-15	Signet	1:50	HIER
Estrogen Receptor Protein	1D5	86 kd protein member of nuclear hormone receptor that act as ligand-activated transcription factors	Human recombinant estrogen receptor protein	Biocare Medical	1:200	HIER
c-erbB-2 Oncoprotein	-----	190 kd protein product of c-erbB-2 proto-oncogene	Synthetic human c-erbB-2 oncoprotein peptide	DAKO	1:500	HIER
Human Leukocyte Antigen CD45	DAKO-LCA	Five or more high molecular weight glycoproteins on the surface of the majority of human leukocytes	Human peripheral blood lymphocytes maintained in T-cell growth factor	DAKO	1:200	HIER
CD20 Human B Lymphocyte Antigen	L26	33 kd non-glycosylated membrane spanning protein	Human tonsil B lymphocyte	DAKO	1:800	HIER
CD3 Human T Lymphocyte Antigen	-----	Intracytoplasmic portion of CD3 antigen	Synthetic human CD3 peptide	DAKO	1:100	HIER
CD30 Ki-1 Antigen	Ber-H2	120 kd transmembrane glycoprotein	Co cell lines cells	DAKO	1:20	HIER
bcl-2 Oncoprotein	124	25 kd integral protein localized in mitochondria that inhibits apoptosis	Synthetic peptide sequence amino acids 41-54 of bcl-2 protein	DAKO	1:20	HIER
Neuron-specific Enolase	-----	Gamma subunit of enolase	Neuron-specific enolase isolated from human brain	DAKO	1:400	HIER
Chromogranin-A	DAK-A3	Member of secretogranin/chromogranin class of proteins in secretory granules of endocrine and neuron cells	C-terminal 20 kd fragment of chromogranin-A	DAKO	1:100	HIER
Synaptophysin	-----	38 kd membrane component of neuron synaptic vesicles	Synthetic human synaptophysin peptide coupled to ovalbumin	DAKO	1:100	HIER
S100 Protein	-----	S100 Protein A and B	S100 protein isolated from cow brain	DAKO	1:3000	HIER
Melanoma Antigen	HMB45	Neuraminidase-sensitive oligosaccharide side chain of glycoconjugate in immature melanosomes	Extract of pigmented melanoma metastases from lymph nodes	DAKO	1:200	HIER
CD34	My10	105-120 kd single-chain transmembrane glycoprotein associated with human hematopoietic progenitor cells	CD34 antigen	Becton-Dickinson	1:50	HIER
CD31	JC/70A	100 kd glycoprotein in endothelial cells and 130 kd glycoprotein in platelets	Membrane preparation of spleen from patient with hairy cell leukemia	DAKO	1:40	HIER
Factor VIII Antigen	-----	Human von Willebrand Factor	von Willebrand factor isolated from human plasma	DAKO	1:2000	HIER

TABLE 3

	ANTIBODY DIRECTED AGAINST													
TYPE OF NEPLASM	AE1/AE3 Ker	LMWK	HMWK	Ker 7	Ker 5/6	CEA	CD15/ LeuM1	B72.3	BerEP4	TTF-1	Calretinin	HBME-1	EMA	HMFG-2
Well-moderately well differentiated epithelial mesothelioma	+	+	+	+	+/-	R	R	R	-/+	N	+/-	* +/-	* +/-	* +/-
Well-moderately well differentiated pulmonary adenocarcinoma	+	+	+/-	+	R	+	+/-	+/-	+/-	+/-	R	R	** +/-	** +/-

Abbreviations:

LMWK **= low molecular weight keratin**
HMWK **= high molecular weight keratin**
CEA **= carcinoembryonic antigen**
TTF-1 **= thyroid transcription factor-1**
EMA **= epithelial membrane antigen**
HMFG-2 **= human milk fat globule protein-2**

Reactivity:

+ **almost always diffuse strong positivity**
+/- **variable staining, mostly positive**
-/+ **variable staining, mostly negative**
R **rare cells positive**
N **almost always negative**

Note:

***** **Cell membrane distribution**
****** **Cytoplasmic distribution**

TABLE 4

CYTOKERATIN MOLL NUMBER, MOLECULAR WEIGHT AND ISOELECTRIC pH																				
TYPE OF NEPLASM	1 68 kd 7.8	2 65.5 kd 7.8	3 63 kd 7.5	4 59 kd 7.3	5 58 kd 7.4	6 56 kd 7.8	7 54 kd 6.0	8 52.5 kd 6.1	9 64 kd 5.4	10 56.5 kd 5.3	11 56 kd 5.3	12 55 kd 4.9	13 54 kd 5.1	14 50 kd 5.3	15 50 kd 4.9	16 48 kd 5.1	17 46 kd 5.1	18 45 kd 5.1	19 40 kd 5.2	20 46 kd
Primary Pulmonary Adenocarcinoma	N	N	N	N	N	N	+/-	+/-	N	N	N	N	N	N	N	N	N	+/-	+/-	R
Epithelial Mesothelioma	N	N	N	N	+/-	+/-	+/-	+/-	N	N	N	N	N	+/-	N	N	+/-	+/-	+/-	R
Primary Pulmonary Squamous Cell Carcinoma	N	N	N	+/-	+/-	+/-	R	-/+	N	N	N	N	N	+/-	-/+	-/+	+/-	-/+	+/-	R

<u>Reactivity Designation:</u>

+	**almost always diffuse strong positivity**
+/-	**variable staining, mostly positive**
-/+	**variable staining, mostly negative**
R	**rare cells positive**
N	**almost always negative**

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