

Primer of Immunohistochemistry (Epithelial Markers)

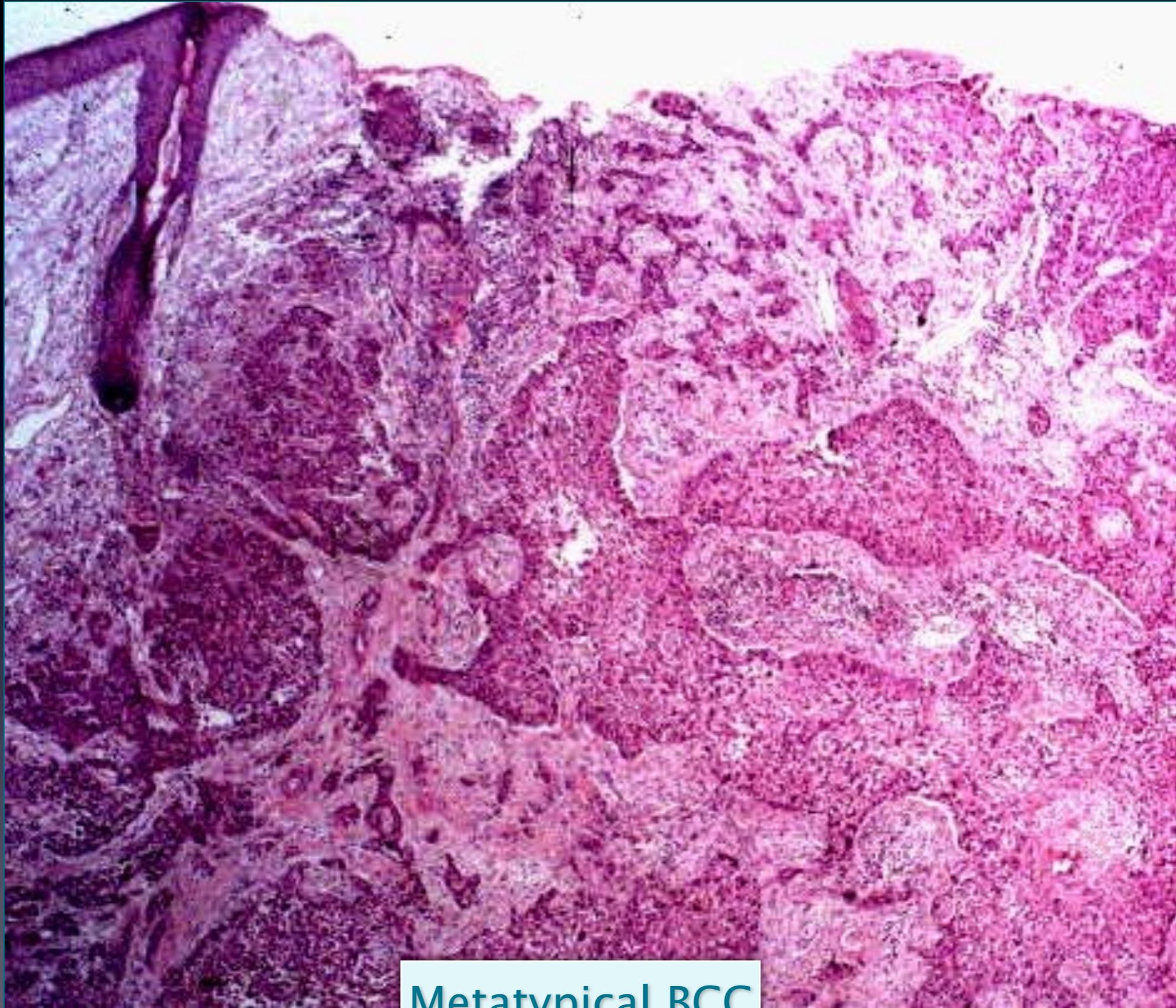
Paul K. Shitabata, M.D.
Dermatopathology Institute
Torrance, CA

DETERMINANTS OF VALUE IN DDX OF SQUAMOID BCC VARIANTS VS. SQUAMOUS CARCINOMA

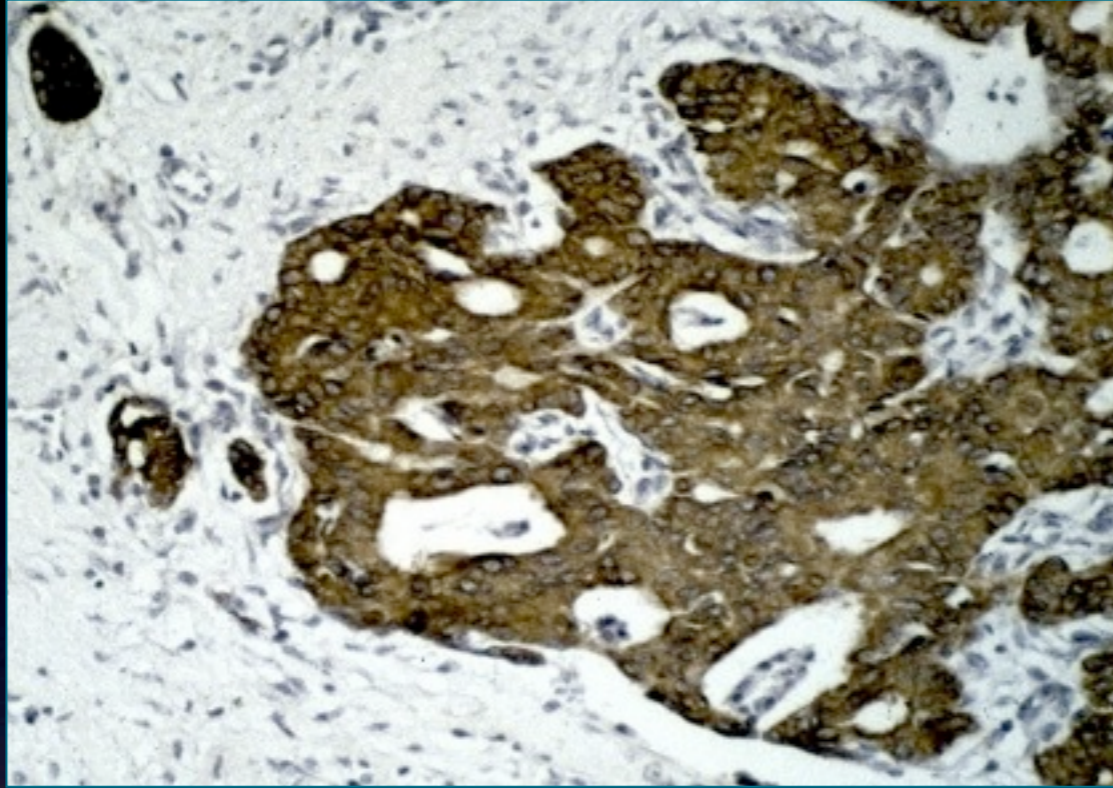
- ***bcl-2 Protein***
 - Functions in the governance of apoptosis, together with products of *bax*, p53, and other genes
 - Expressed by basal cell carcinoma (*Br J Dermatol 1993; 131:28*) but not by squamous cell carcinoma

BER-EP4

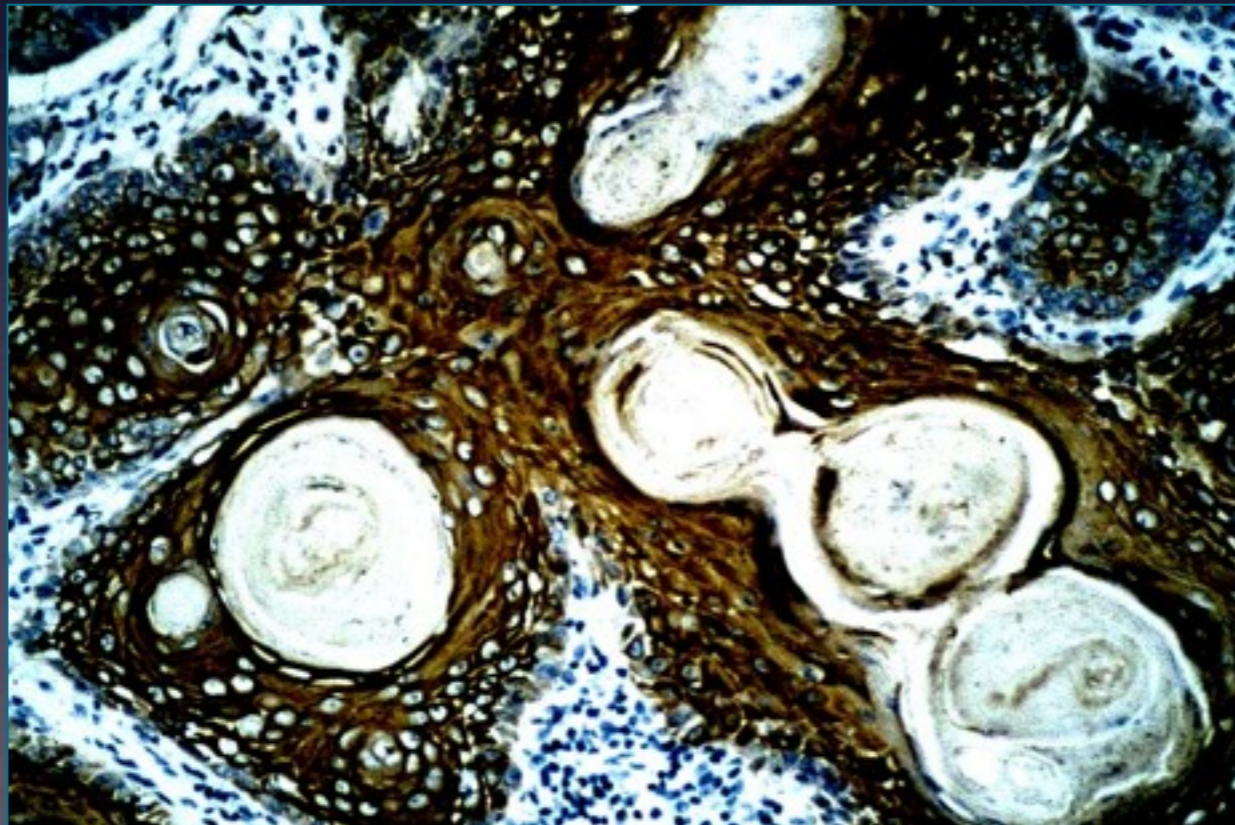
- Monoclonal antibody directed against a cell surface glycoprotein found on most but not all epithelial cells
- Expressed by basal cell carcinoma (*Am J Dermatopathol 1993; 15:45*) but not by squamous cell carcinoma



Metatypical BCC



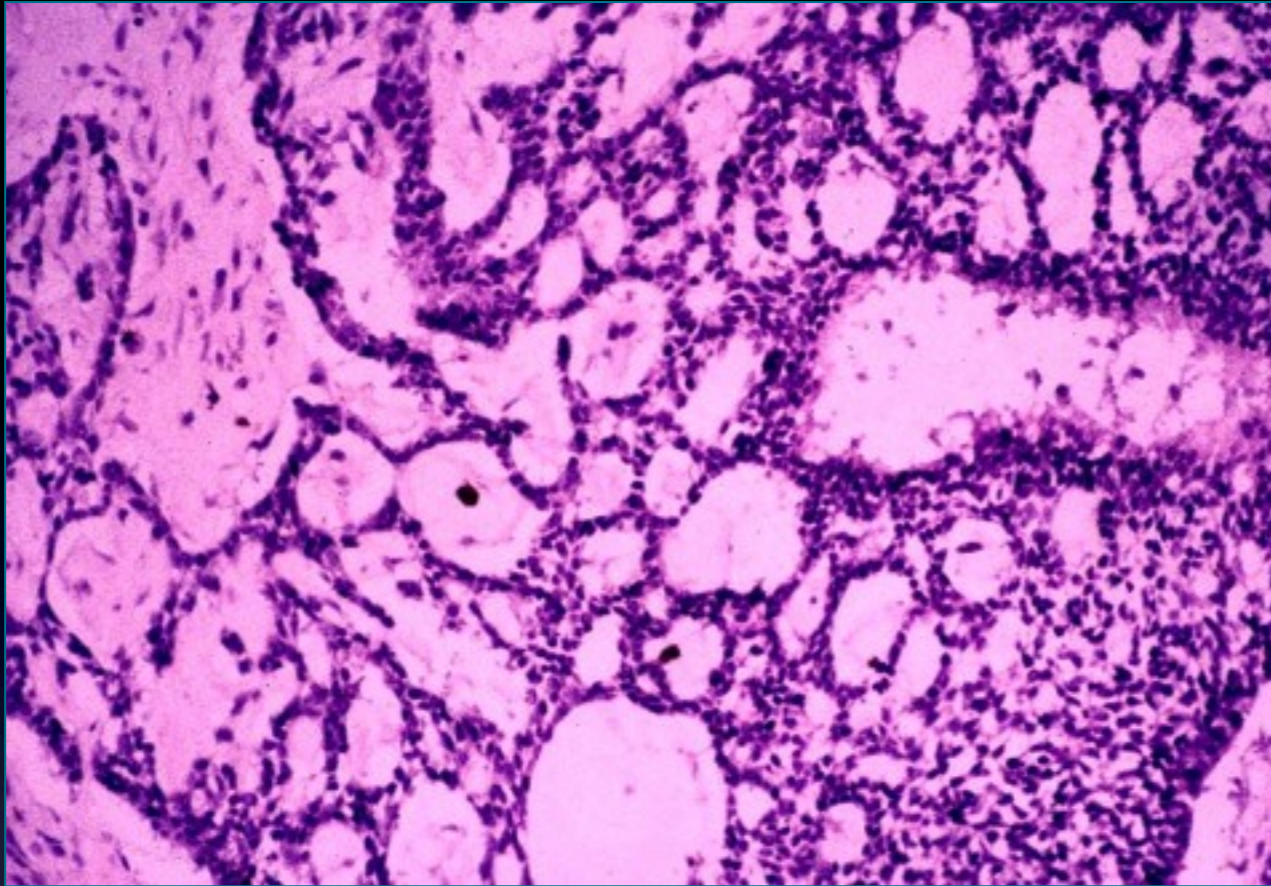
bcl-2 Protein



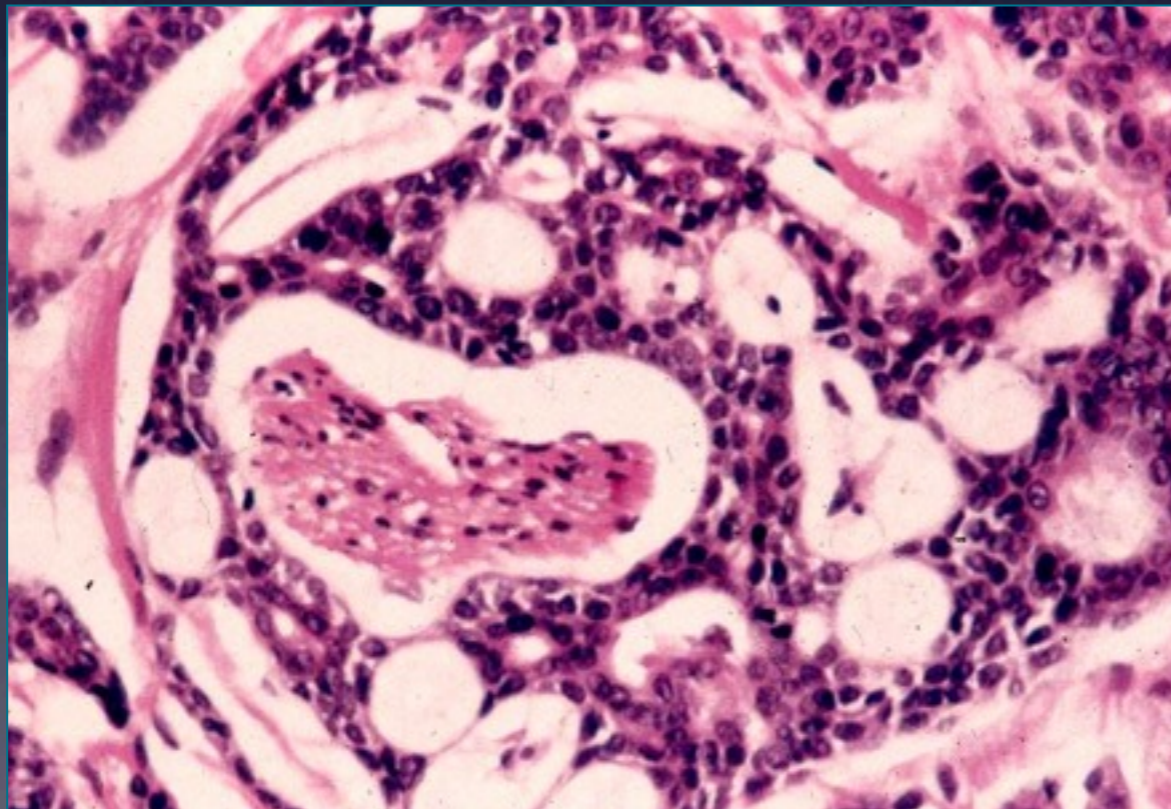
Ber-EP4

IMMUNOHISTOLOGIC DDX OF BCC AND ADNEXAL CARCINOMAS OF THE SKIN

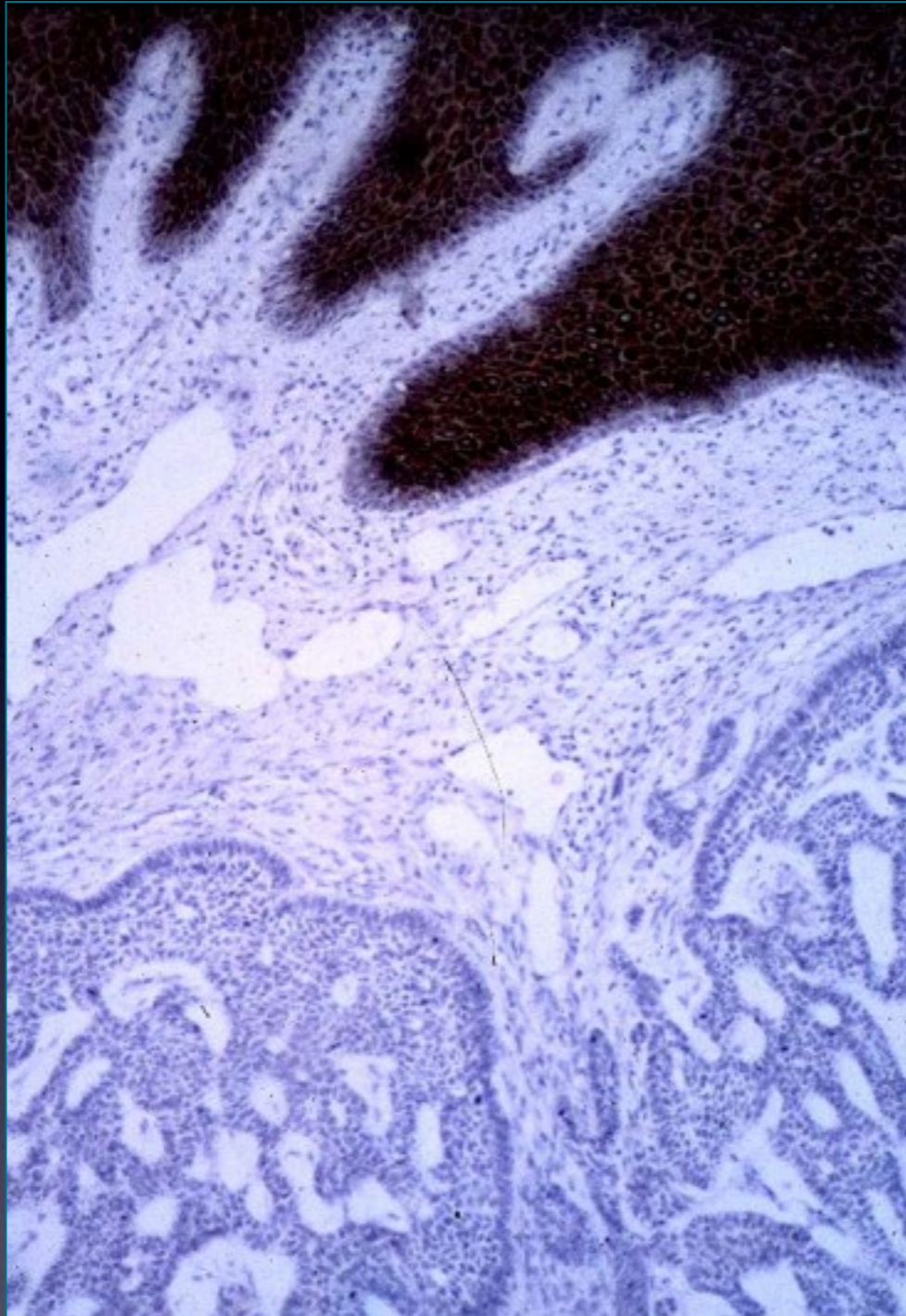
- *Epithelial Membrane Antigen*
 - Cell membranous glycoprotein that is observed in the majority of human epithelial cells
 - Expressed in a diffuse fashion by truly glandular or sebaceous neoplasms; if present at all in BCC, EMA is restricted to areas of divergent differentiation
- *Carcinoembryonic Antigen*
 - Cell surface glycoprotein that is produced by a wide variety of glandular and other epithelial cells, including normal sweat glands and sudoriferous neoplasms
 - Expressed in adenoid cystic carcinoma of the skin and other forms of adnexal neoplasia that may be confused with adenoid basal cell carcinoma, whereas all BCC variants except “eccrine epithelioma” are non-reactive for this marker



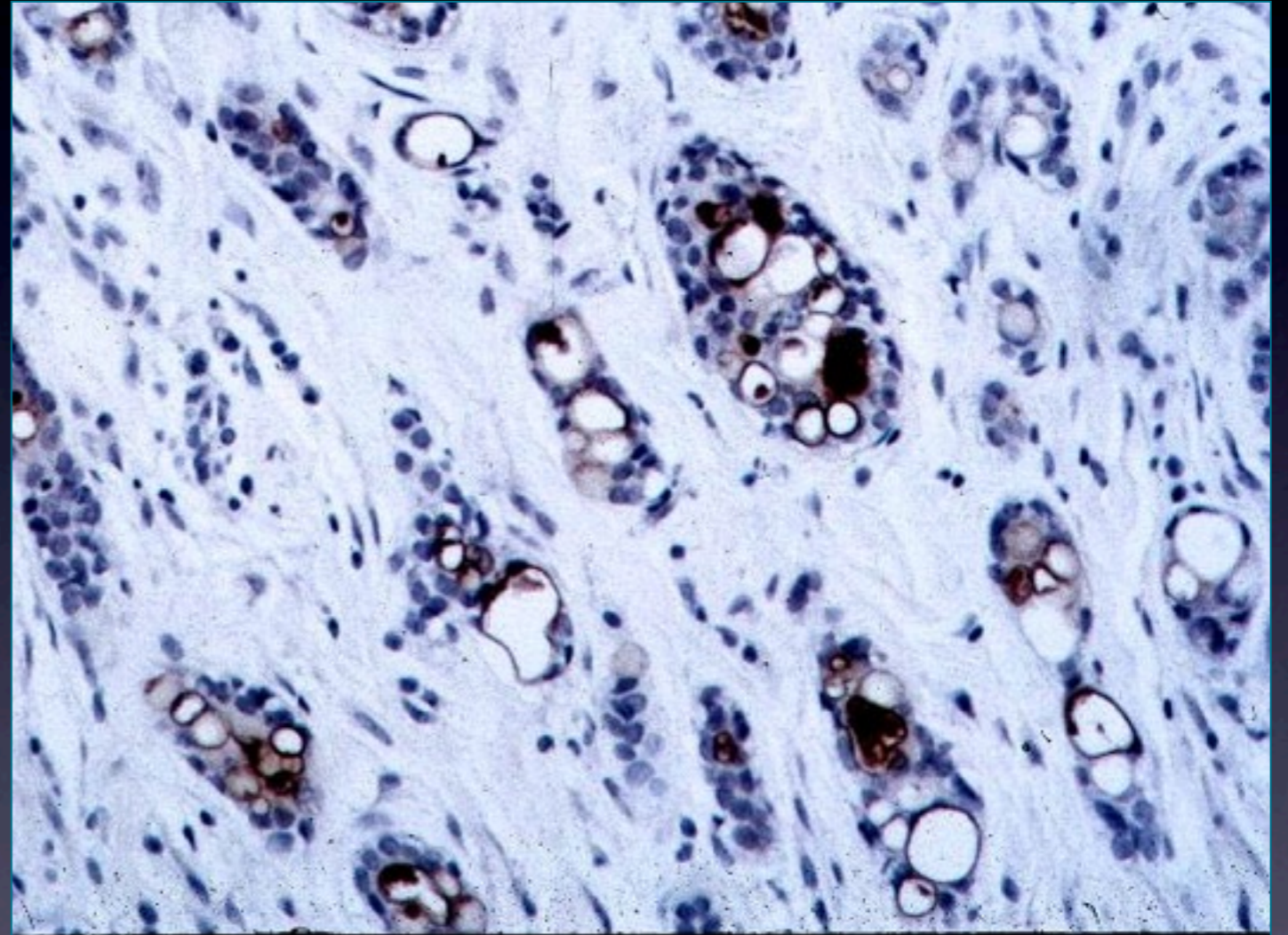
Adenoid BCC



Adenoid Cystic
Carcinoma of Skin



EMA- Adenoid BCC



CEA+ Adenoid Cystic CA of Skin

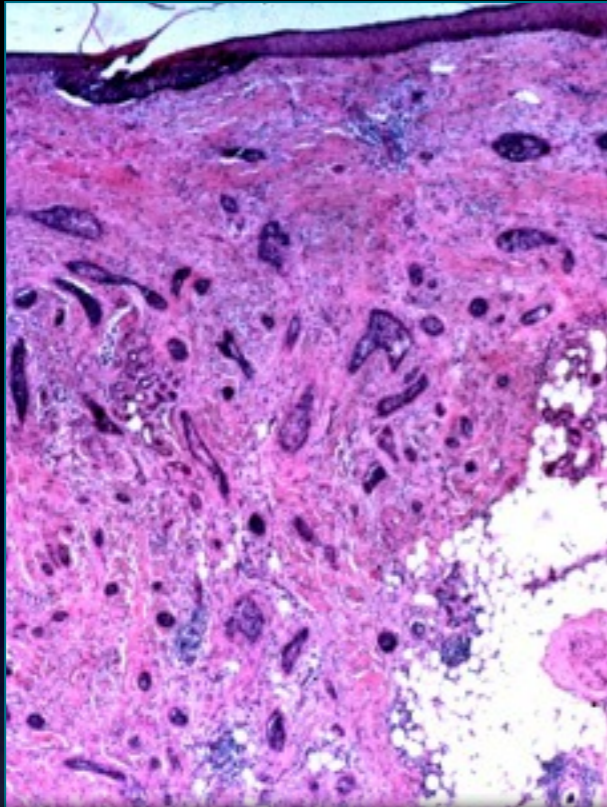
DDX OF MORPHEAFORM BCC AND DESMOPLASTIC TRICHOEPITHELIOMA

-Epithelial Membrane Antigen

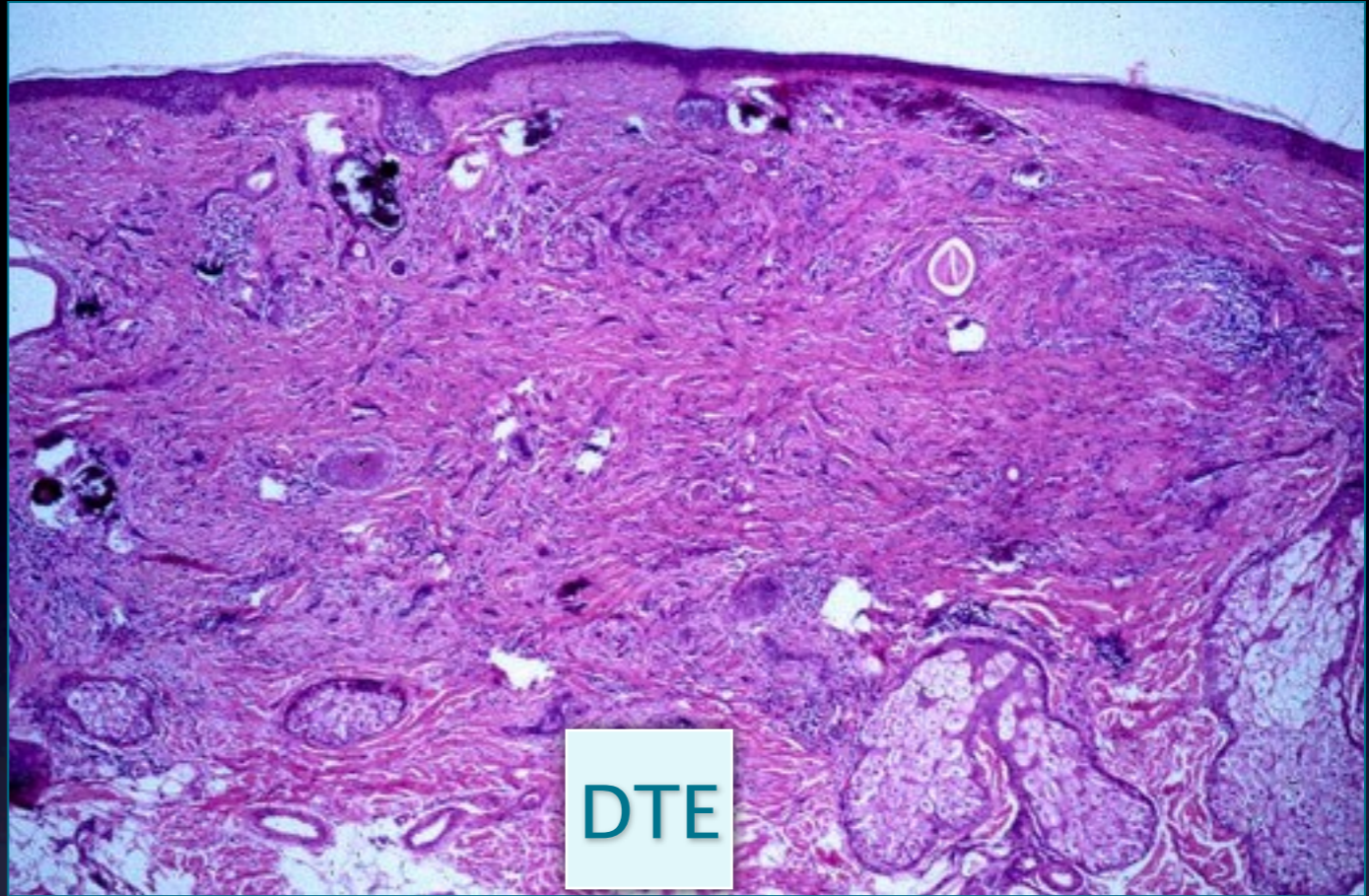
- Expressed by approximately 75% of desmoplastic trichoepitheliomas, but not by any BCC variant except for possibly focal reactivity in “eccrine epitheliomas”

Chromogranin

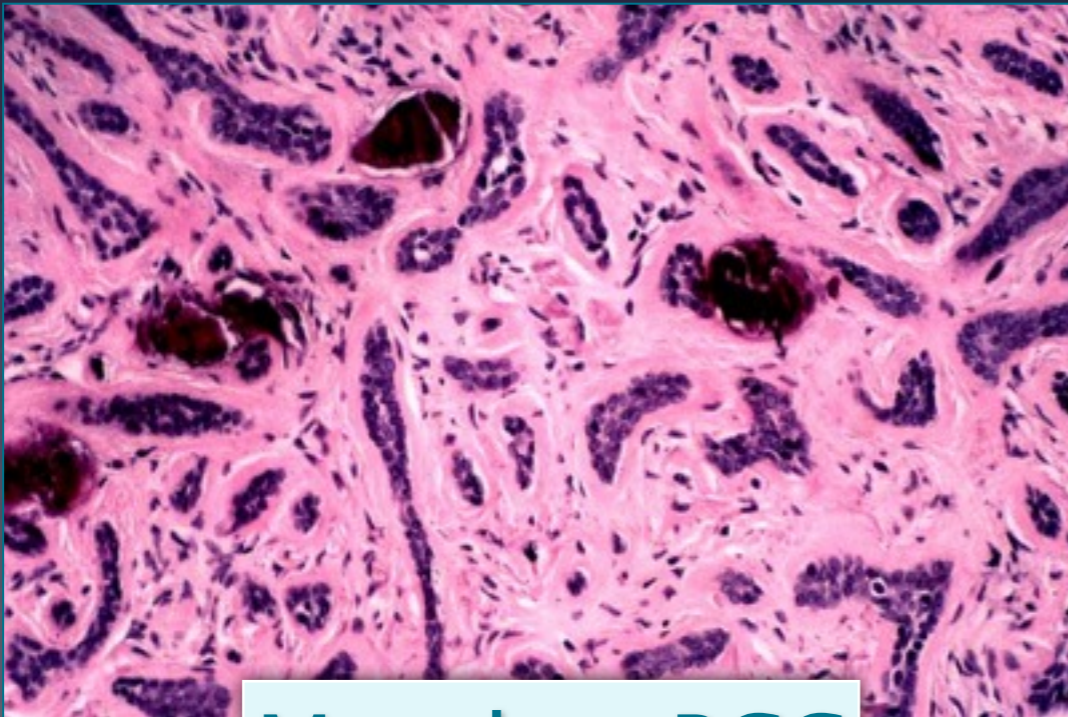
- Expressed in most DTEs but not most BCCs



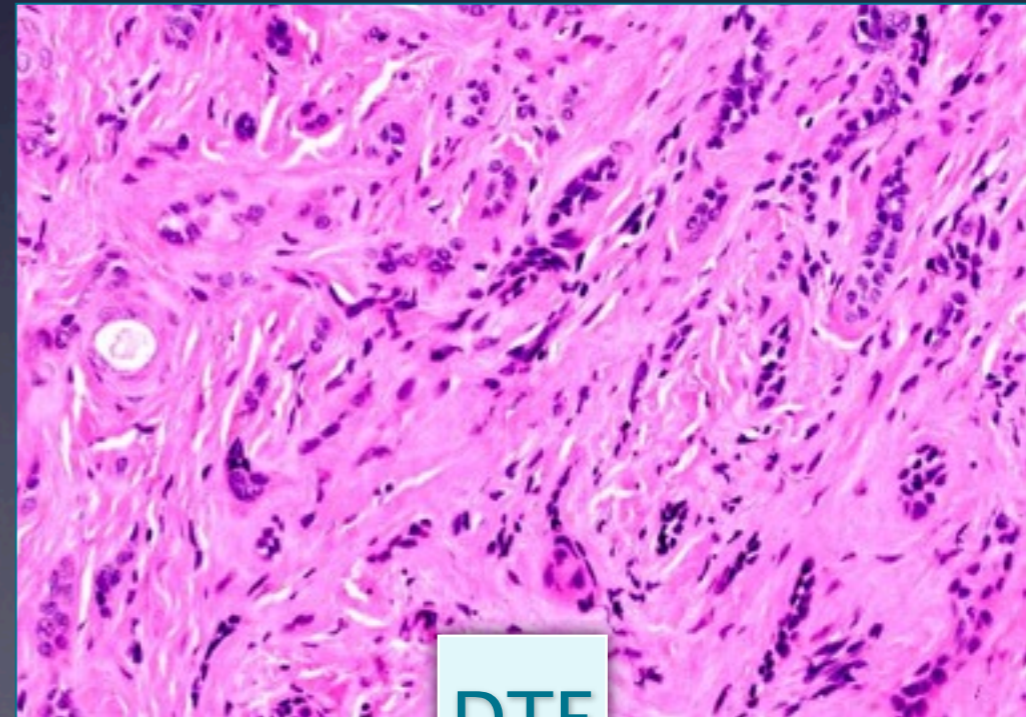
Morphea BCC



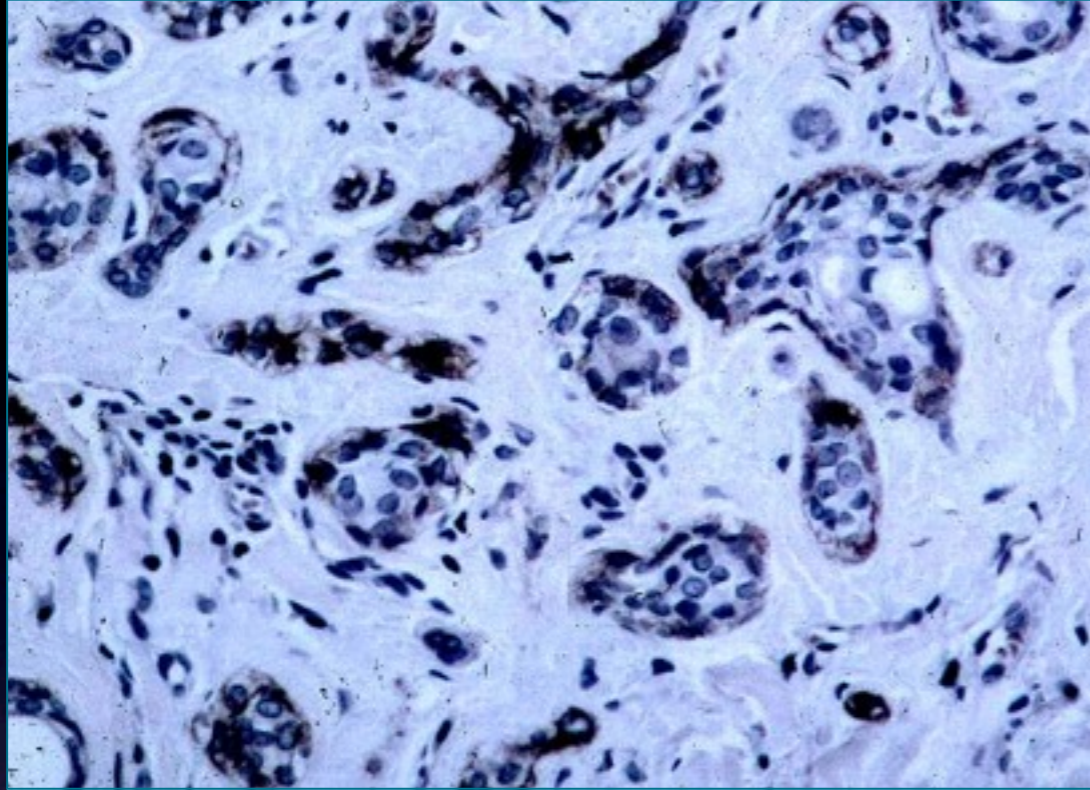
DTE



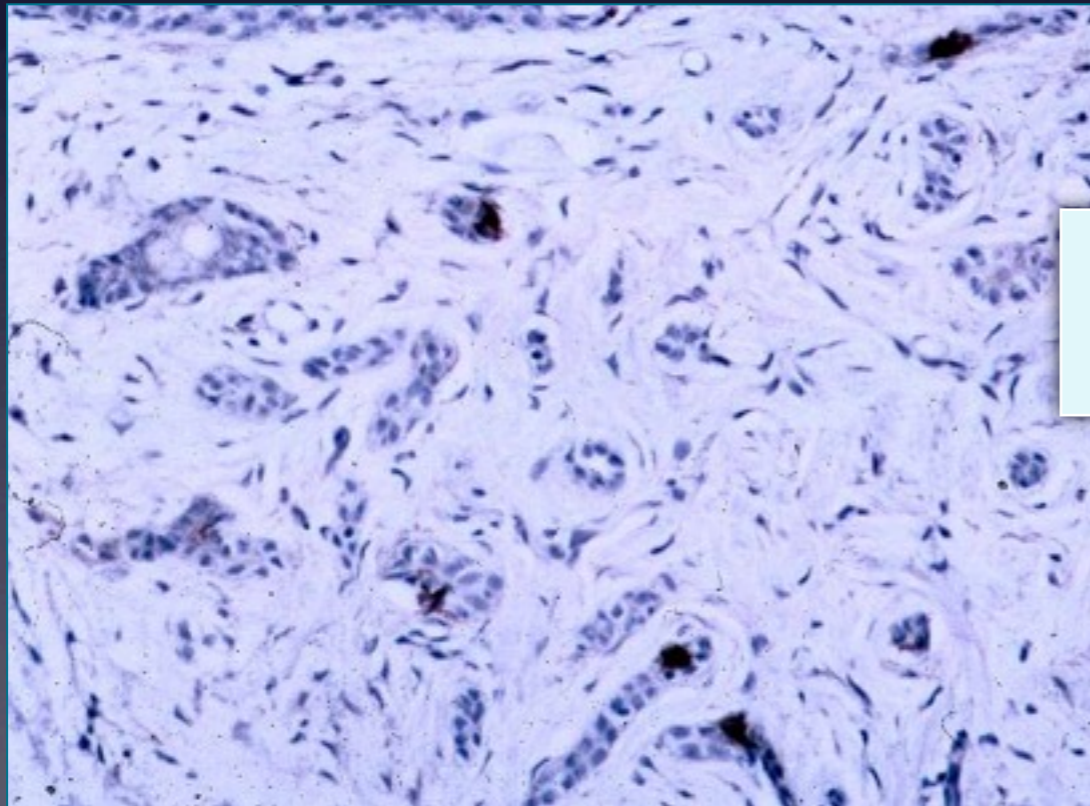
Morphea BCC



DTE



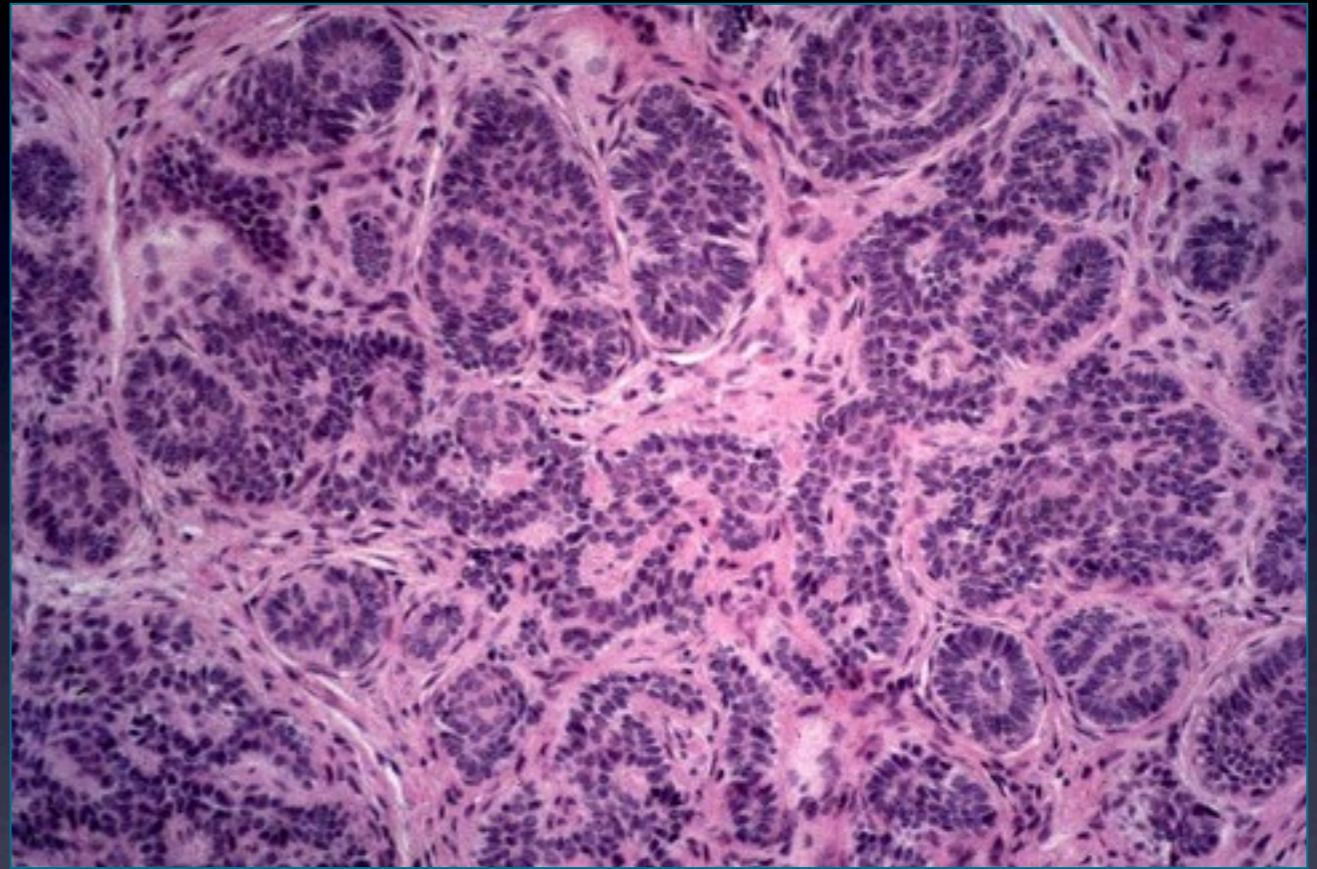
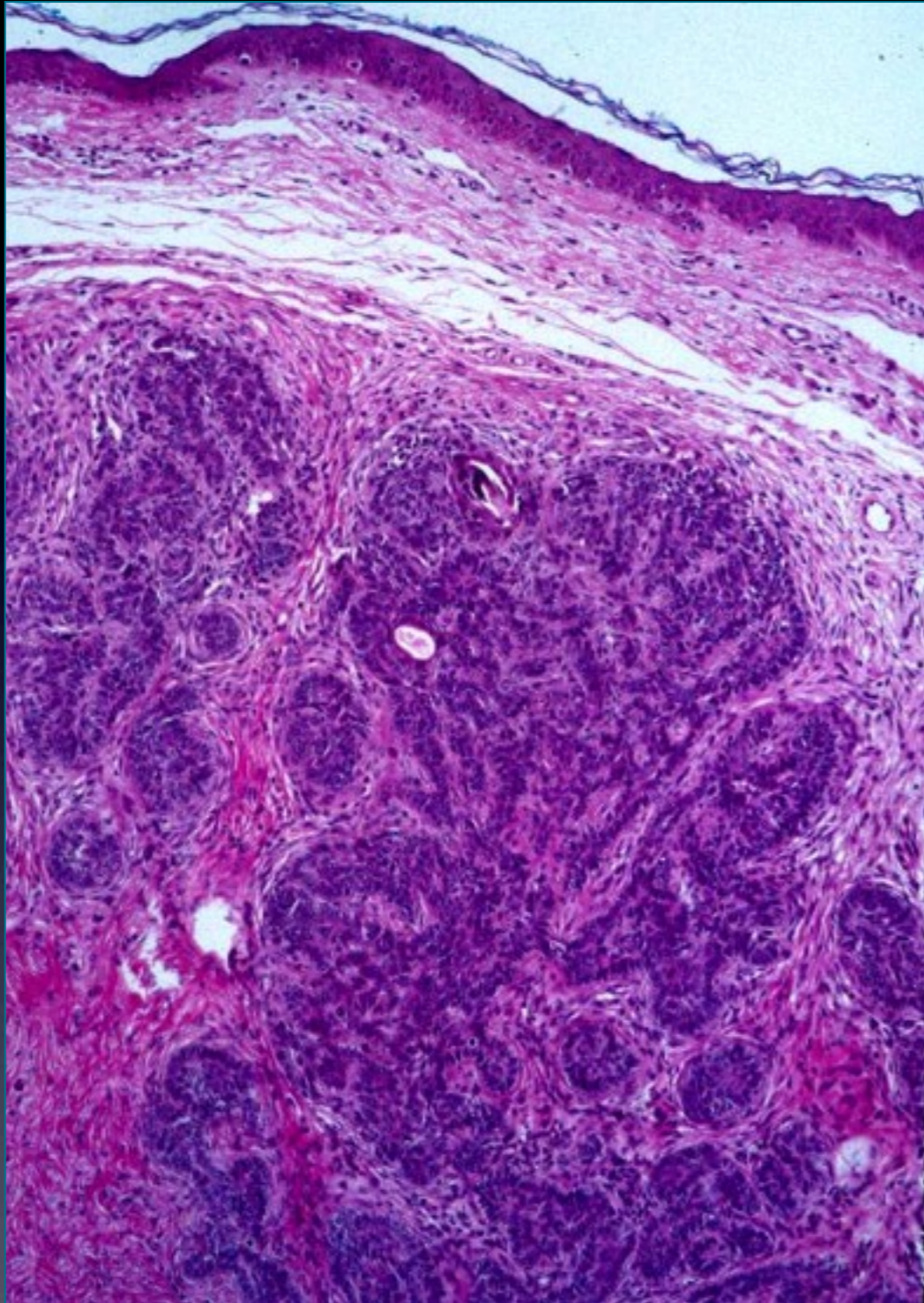
DTE-- Positive EMA



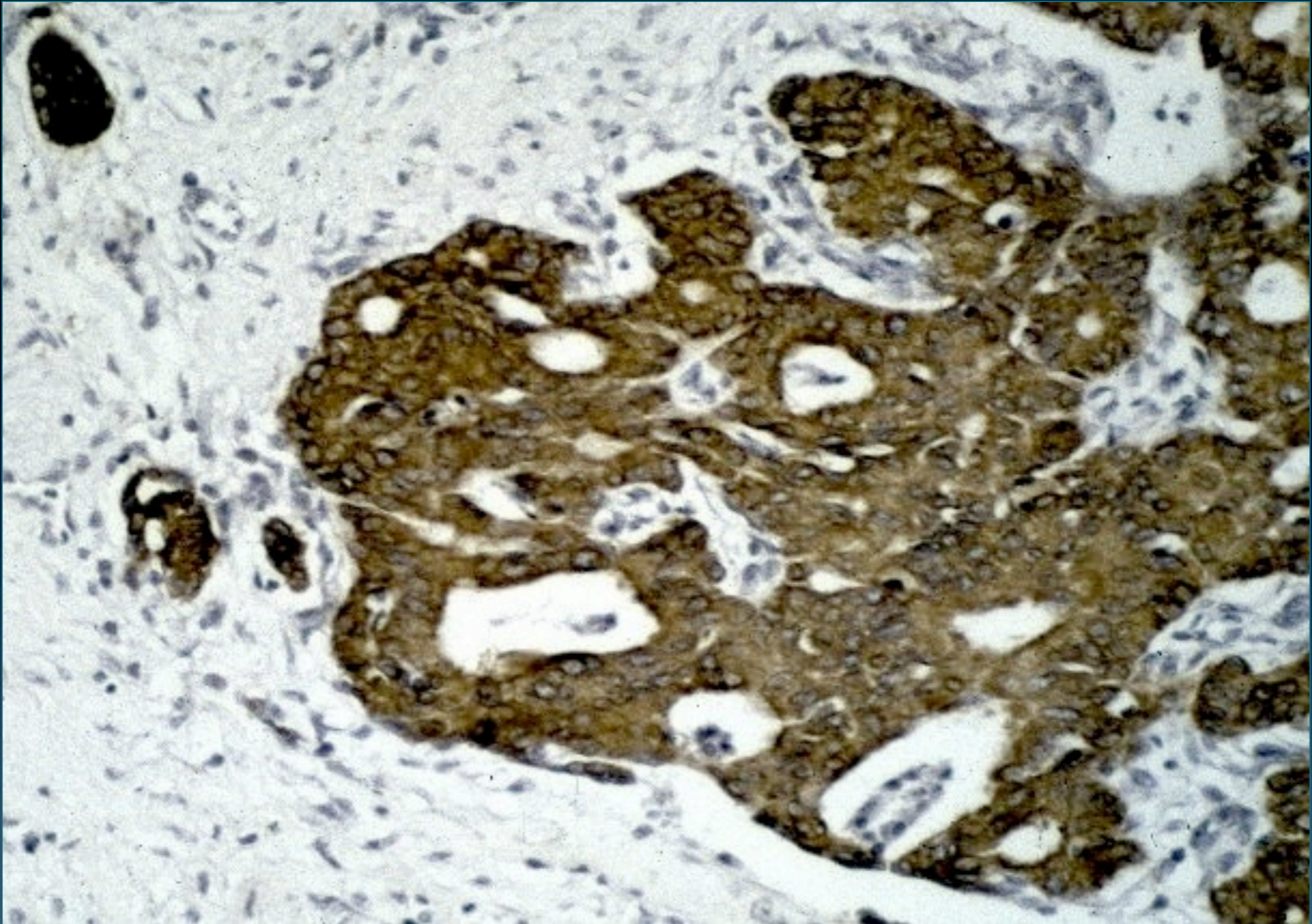
DTE-- Positive Chromogranin

IMMUNOHISTOLOGIC DDX OF BCC & CLASSICAL TRICHOEPITHELIOMA

- ***bcl-2* protein**
 - One report (Smoller BR, *et al.*: Br J Dermatol 1993; 131:28) found immunostains for *bcl-2* protein to be useful in separating BCC from classic trichoepithelioma
 - (Fitzpatrick M, *et al.*: Am J Clin Pathol 1995; 103: 508) has not borne out that contention; at present, morphology alone must be used to make the distinction between BCC and “usual” trichoepithelioma



“Trichoepithelioma”



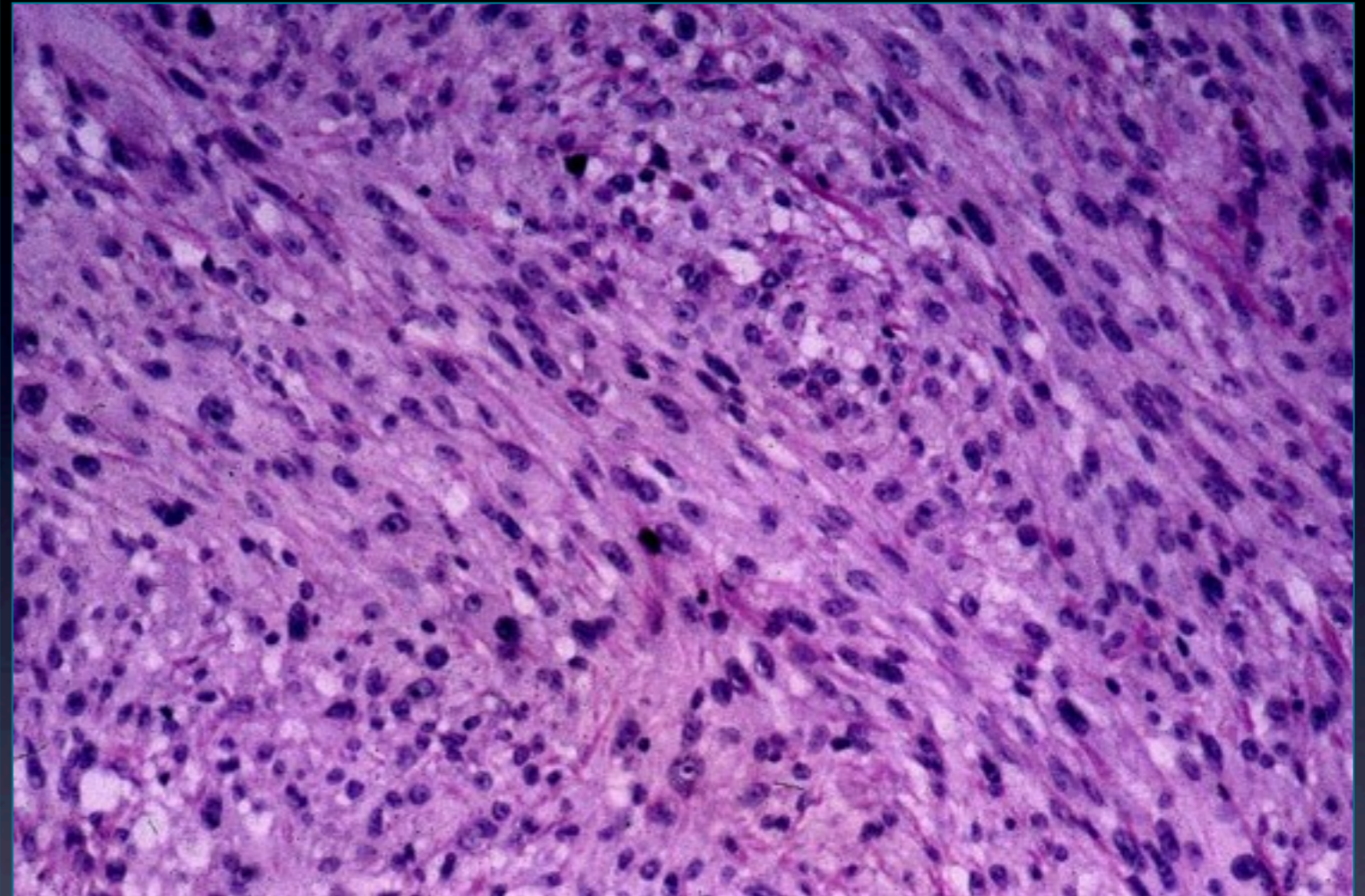
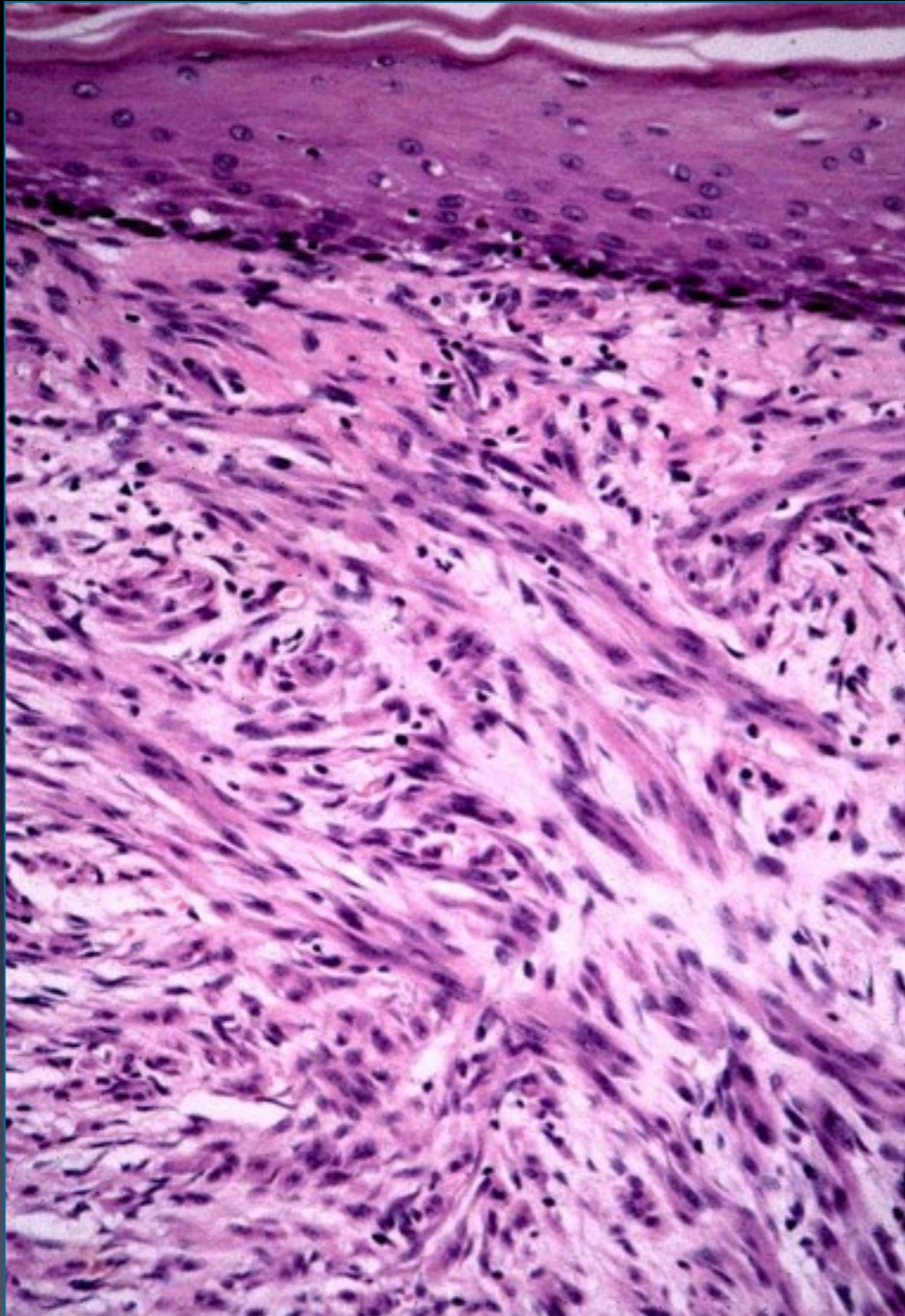
bcl-2 in BCC

TRICHOEPITHELIOMA (N=53)

	<i>Bcl-2</i>	<i>CD34</i>	<i>BER-EP4</i>
USABLE STAINS	43	41	47
POSITIVE	36	1 (desmoplastic)	30
NEGATIVE	7	41	17
COMMENTS	9 with peripheral accentuation pattern	15 with stroma surrounding tumor focally positive	---

DDX OF SARCOMATOID BCC/SCC FROM MESENCHYMAL NEOPLASMS

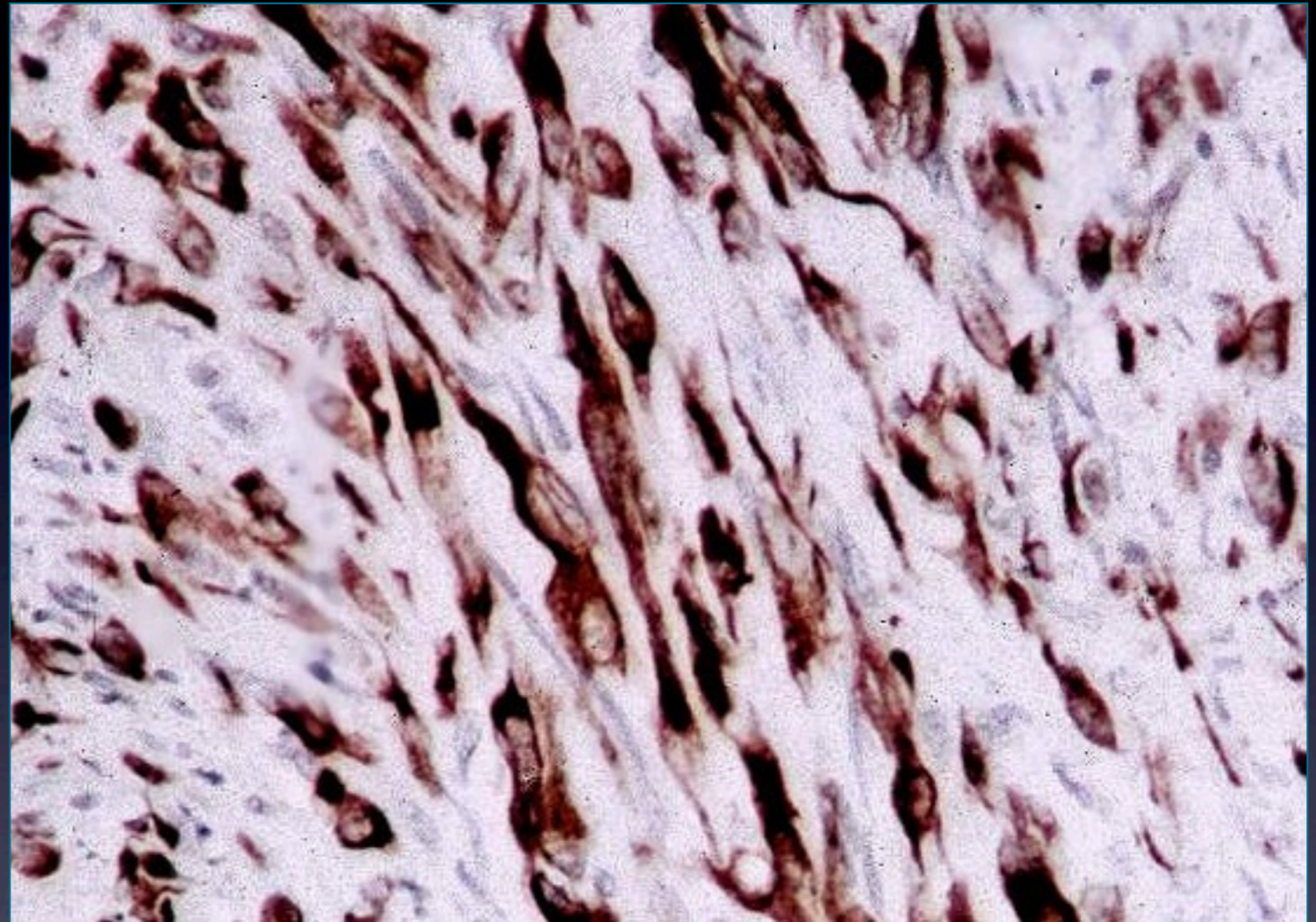
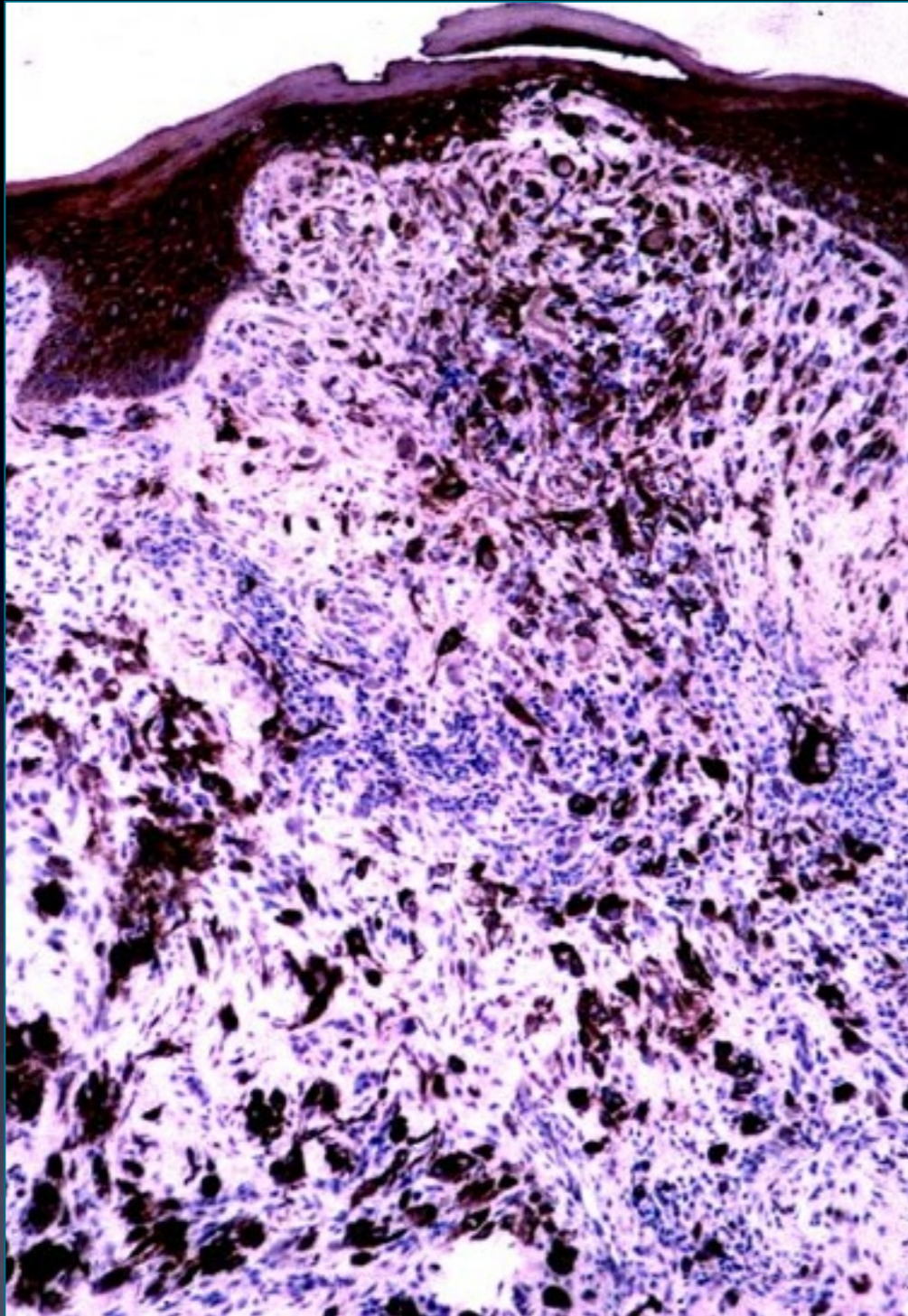
- *Keratin & Epithelial Membrane Antigen*
 - Reproducibly expressed multifocally in sarcomatoid carcinomas of the skin, but not in true cutaneous mesenchymal malignancies



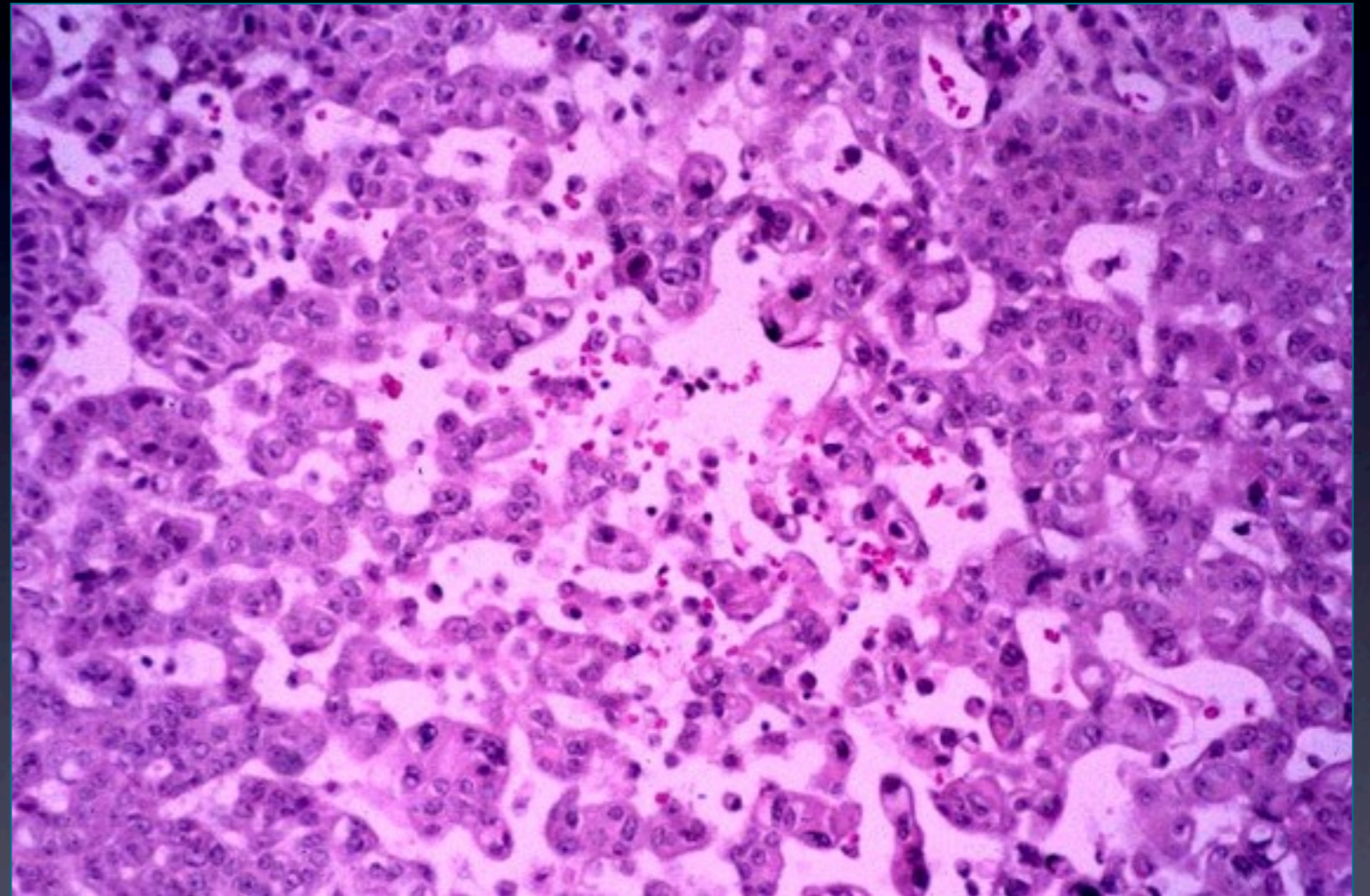
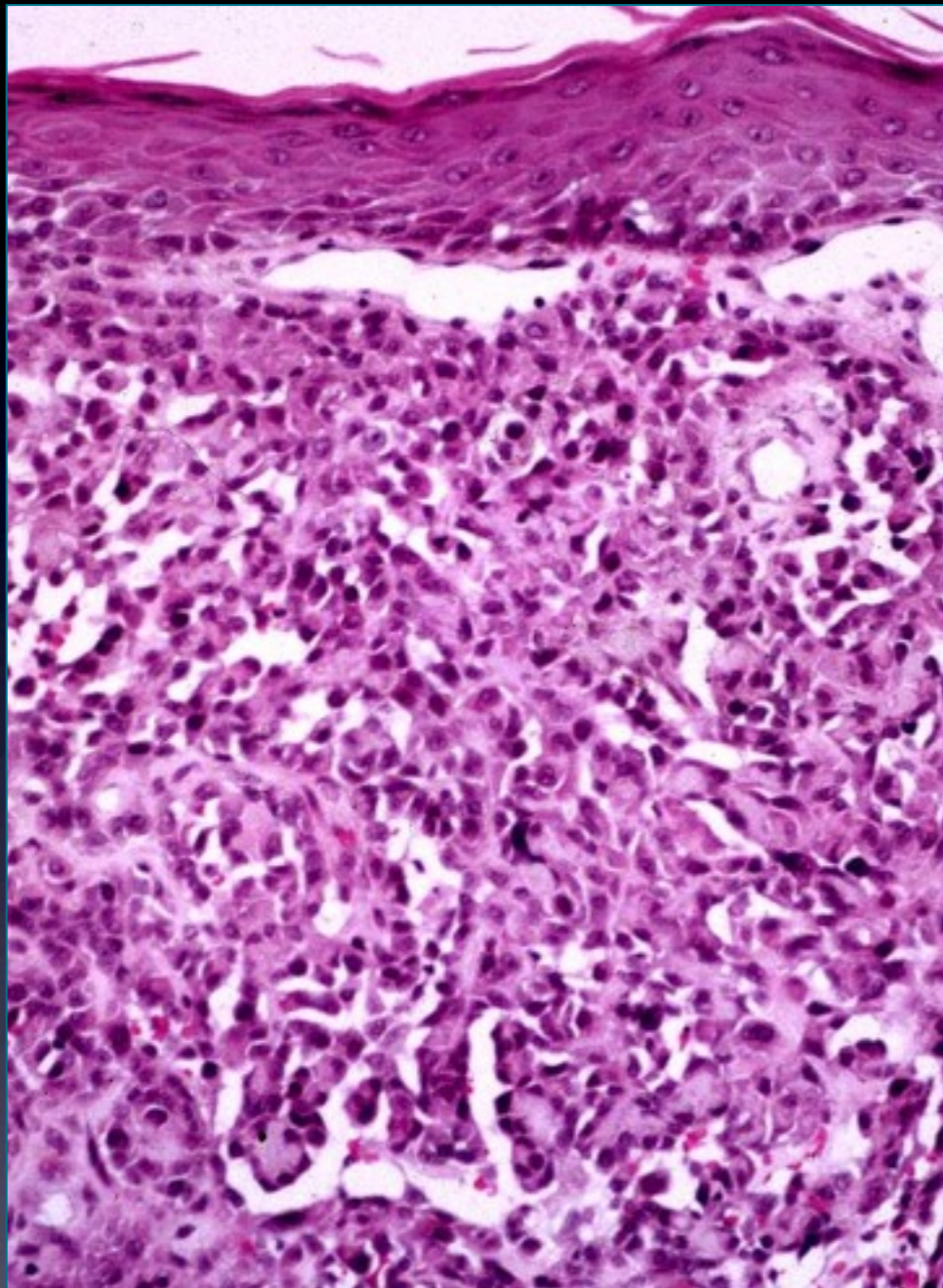
Sarcomatoid Carcinoma of Skin

DDX OF SARCOMATOID BCC & SCC OF THE SKIN

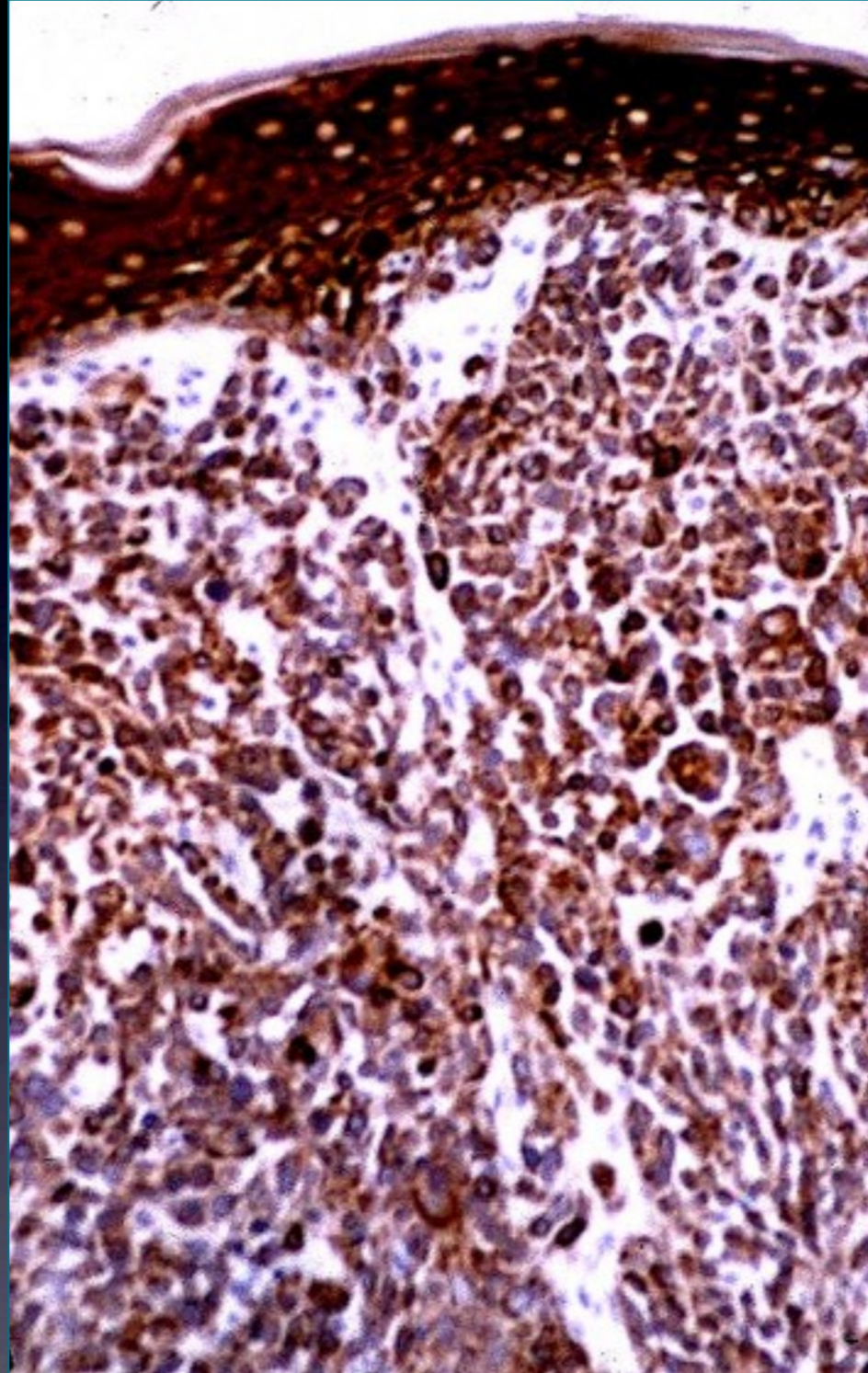
<u>TUMOR</u>	<u>KER</u>	<u>EMA</u>	<u>S100</u>	<u>VIM</u>
SCC	+	+/-	0	+/-
Melanoma	0	0	+	+
AFX & OTHER SARCOMAS	0	0	0	+



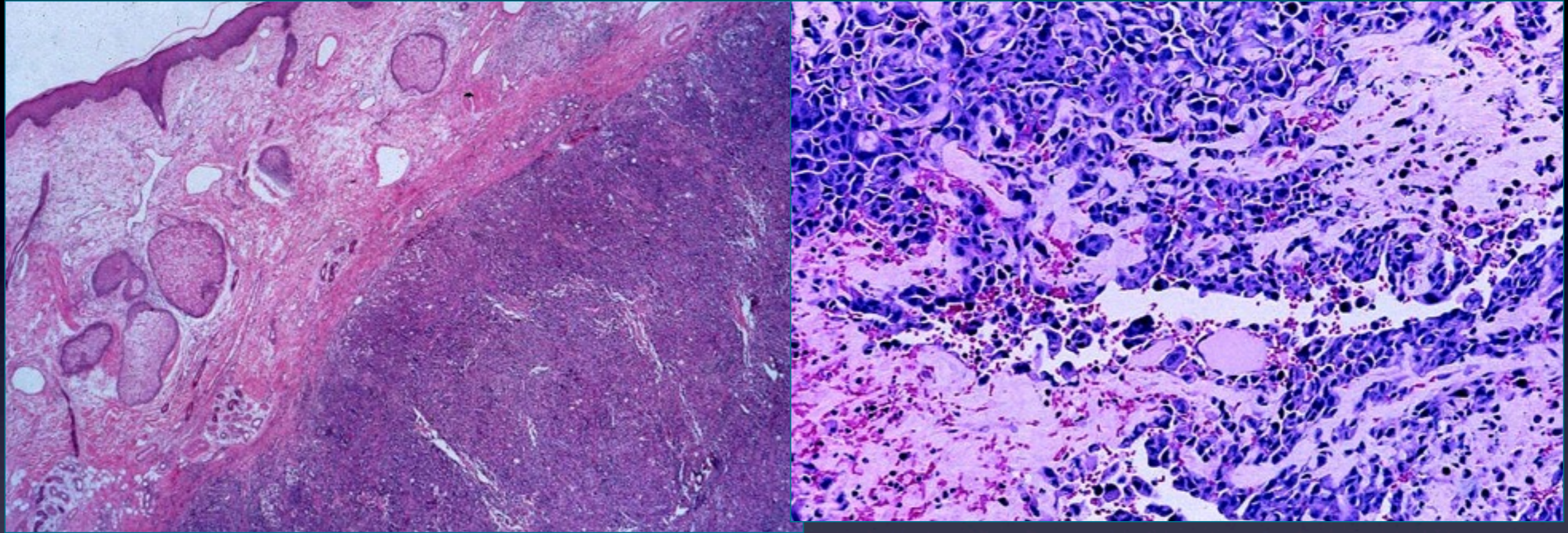
Keratin Positivity in Sarcomatoid Carcinoma of Skin



Angiosarcoma-like Squamous Cell Carcinoma of Skin



Cytokeratin + Pseudovascular Squamous Carcinoma of Skin



Epithelioid (Carcinoma-like) Angiosarcoma

IMMUNOHISTOLOGICAL QUIRKS OF EAS

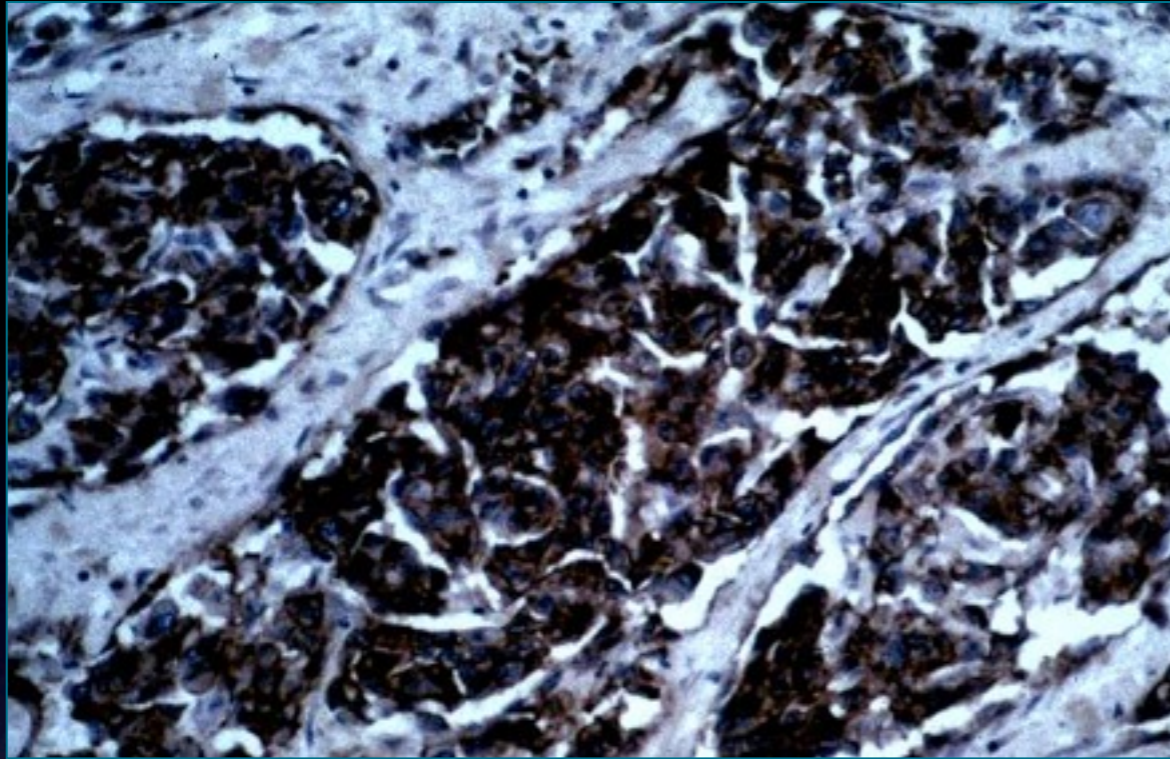
- Potential positivity for *keratin*
- Reactivity with *B72.3*

IMMUNOREACTIVITY FOR KERATIN IN EAS... WHY??

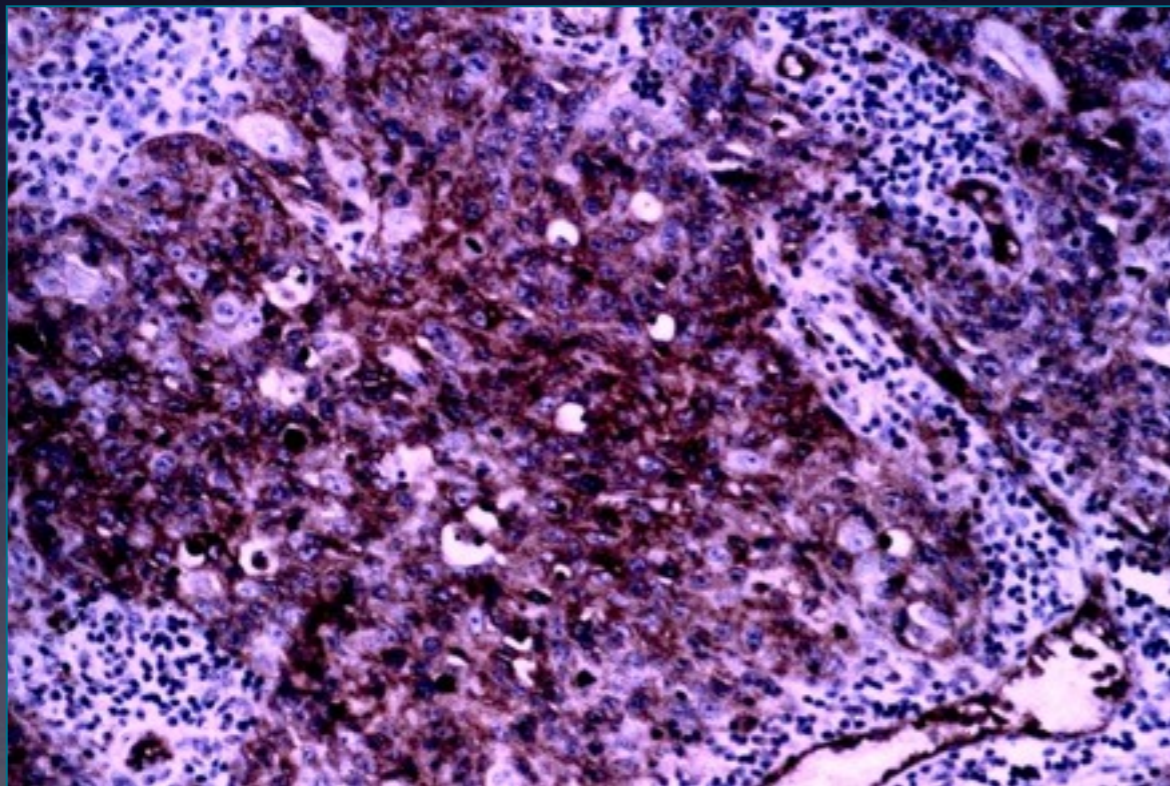
- Some reported cases of keratin+ EASDST represent simple technical artifacts due to faulty antibody titering;
HOWEVER,
- Other examples have had confirmation of keratin content by Western blot and/or mRNA hybridization....
- The latter probably reflects “atavistic” activation of the keratin gene complex in EASDST, which, among all soft tissue tumors, exhibits this aberrant trait most often for reasons that are currently unknown

HOW TO AVOID MISDIAGNOSIS OF EAS BECAUSE OF ABERRANT KERATIN REACTIVITY

- ***PANEL APPROACH!!!***
Epithelial membrane antigen -
Ulex europaeus I+
CD3 I+
CD34+
von Willebrand factor +/-



CD31 Positivity



CD34 Positivity

Epithelioid Angiosarcoma of the Skin

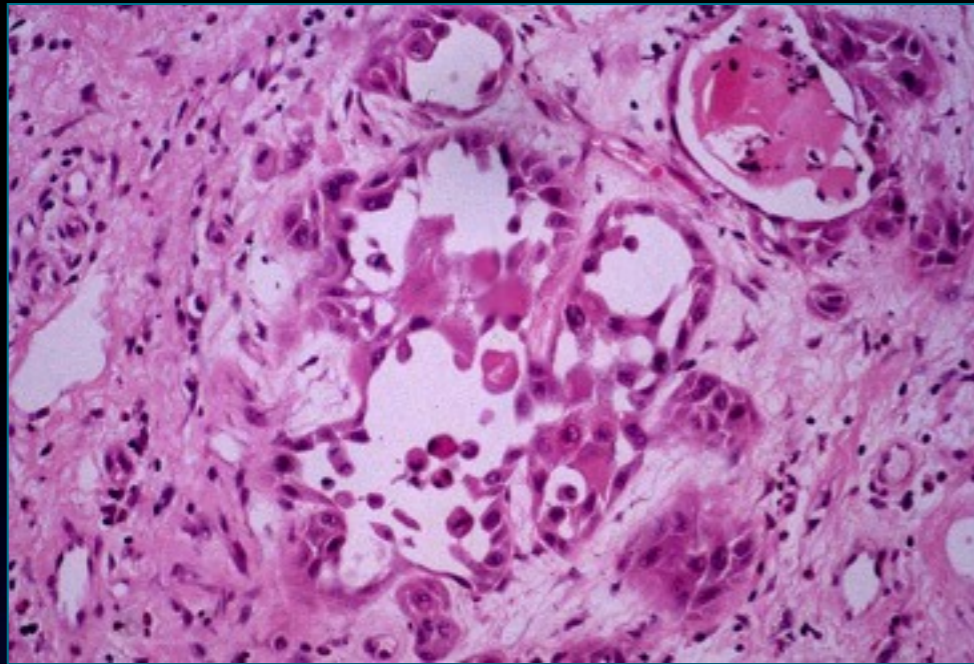
DDX OF ADENOID SCC AND SWEAT GLAND

- **CARCINOEMBRYONIC ANTIGEN**
 - Present in roughly 75% of sweat gland carcinoma variants but not in primary cutaneous SCC

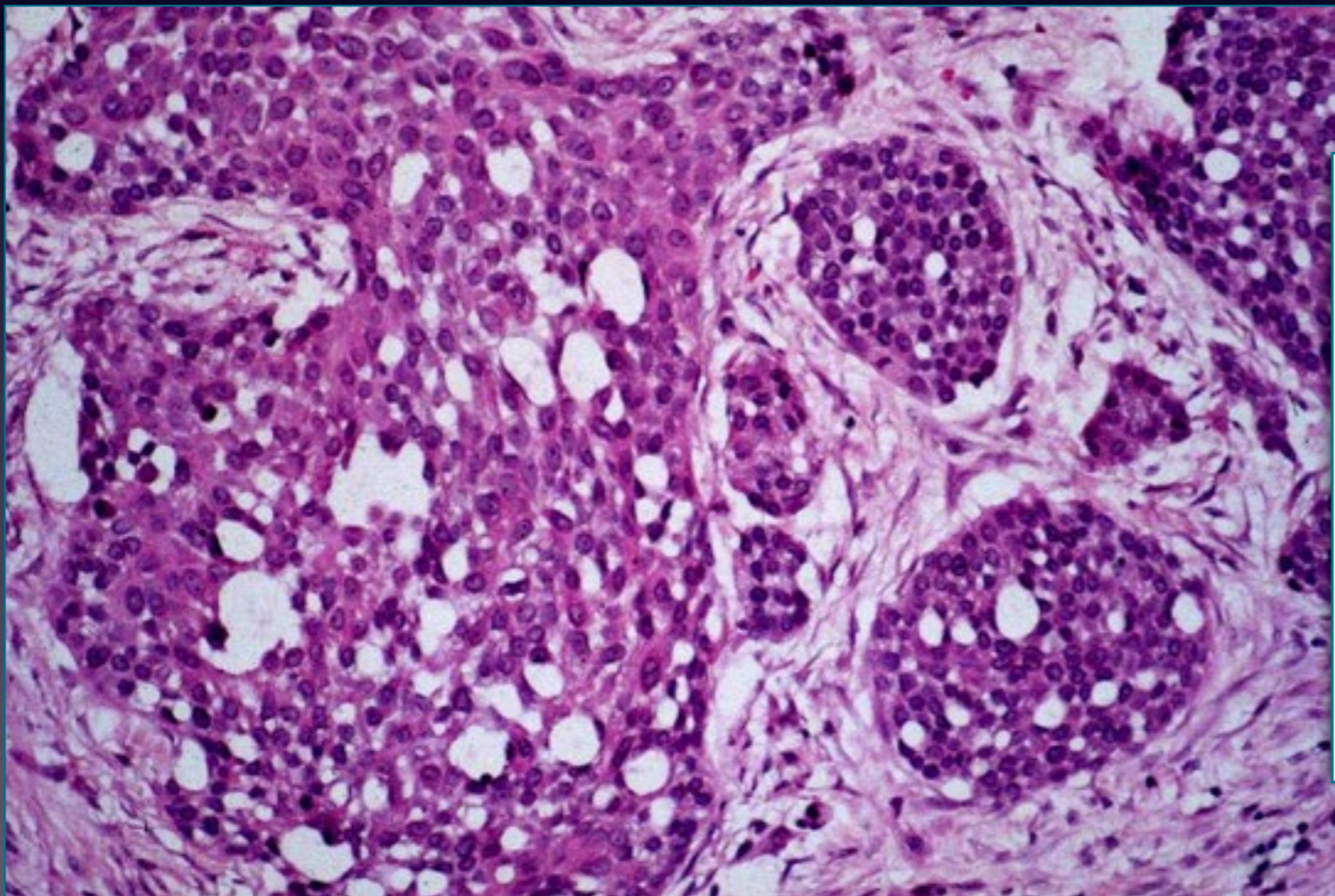
- **S100 PROTEIN**
 - Observed in approximately 60% of sudoriferous malignancies but not in SCC of the skin

CONJOINT EFFICACY OF CEA+S100---- 80-85%

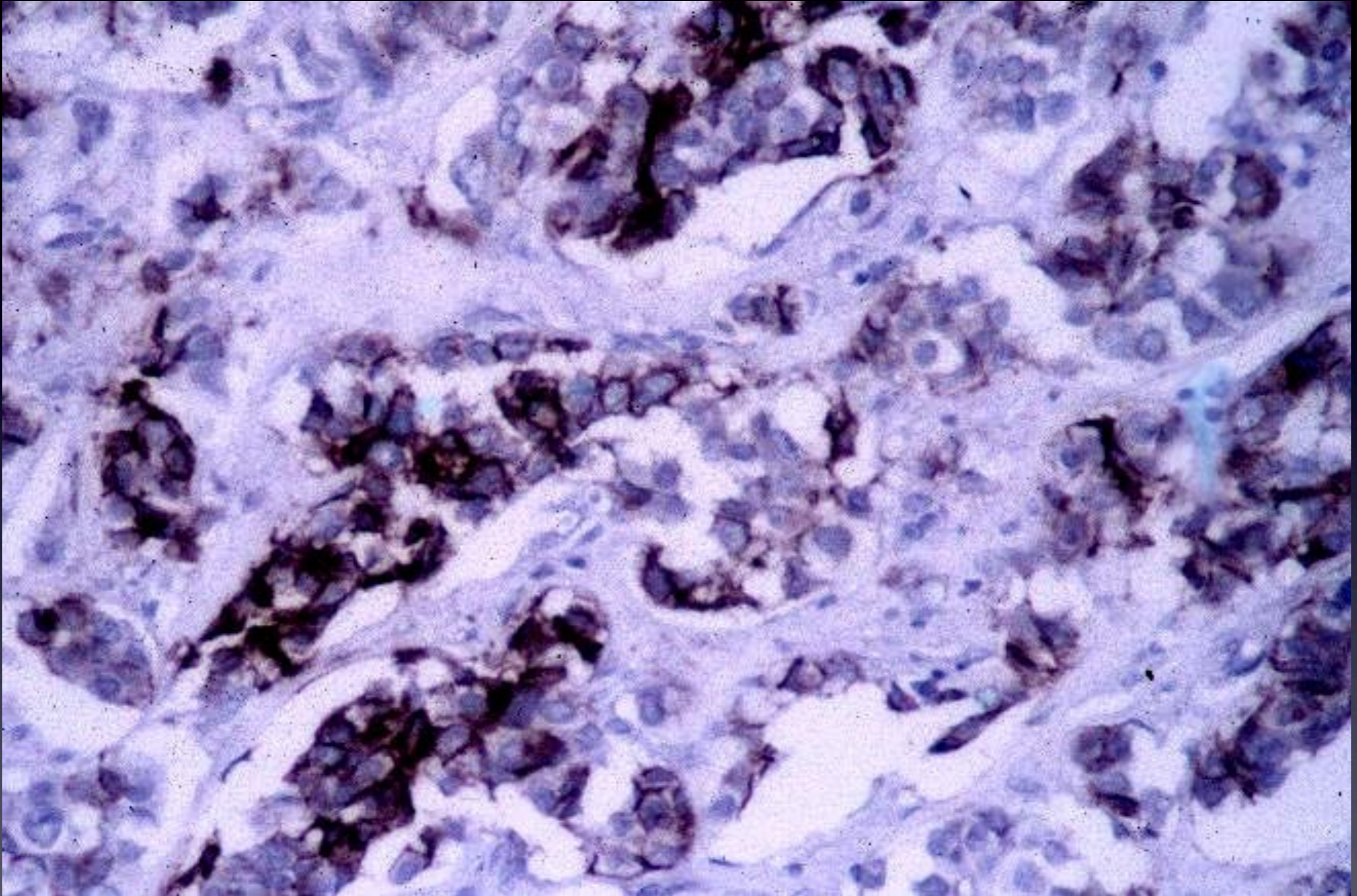
- **B72.3**
 - Discriminating power between SCC and SGC is still being studied



Adenoid (Pseudoglandular)
Squamous Cell Carcinoma



Sweat Gland Carcinoma
with
Squamous Metaplasia



B72.3+ Sweat Gland Carcinoma

MALIGNANT CLEAR CELL TUMORS OF THE SKIN: *Differential Diagnosis*

Clear cell (hydropic) BCC & SCC

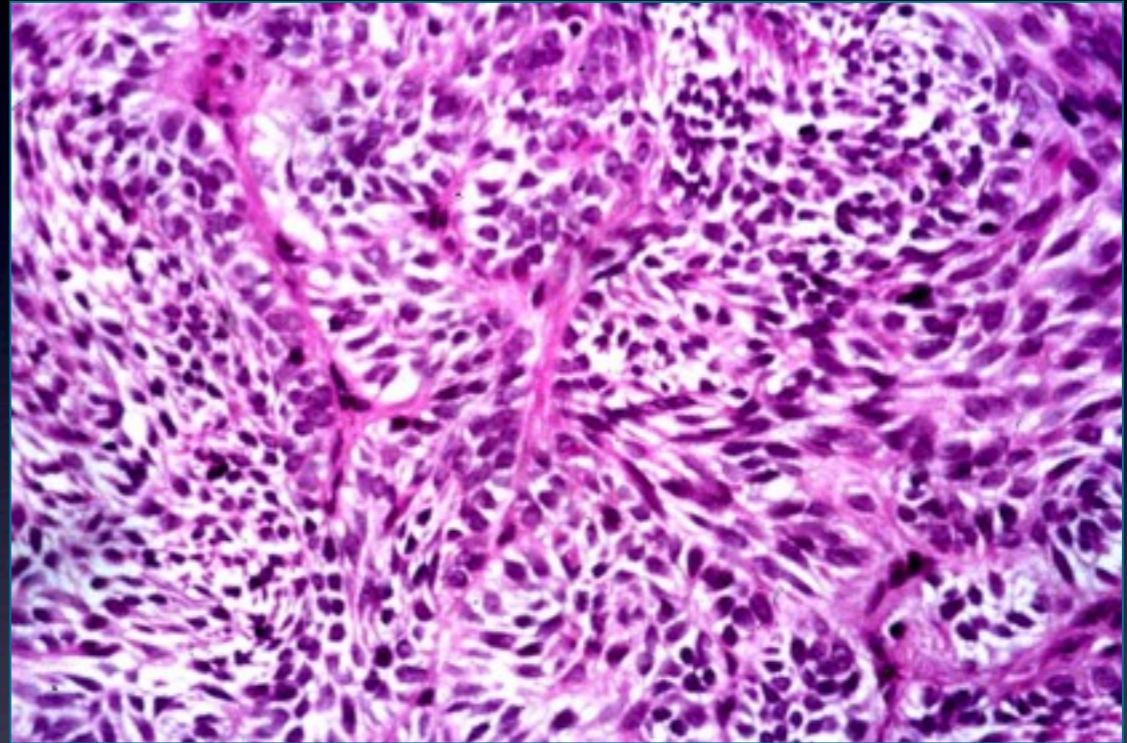
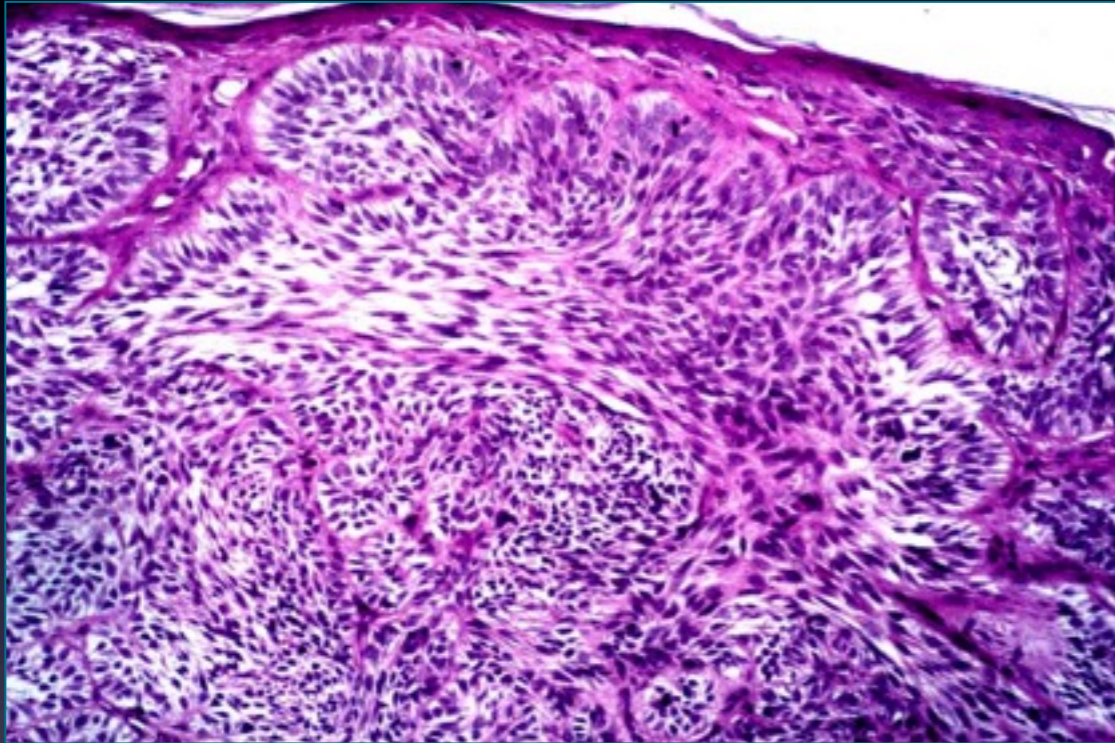
Clear cell eccrine adenocarcinoma

Sebaceous carcinoma

Tricholemmal carcinoma

Metastatic clear cell adenocarcinoma of
viscera

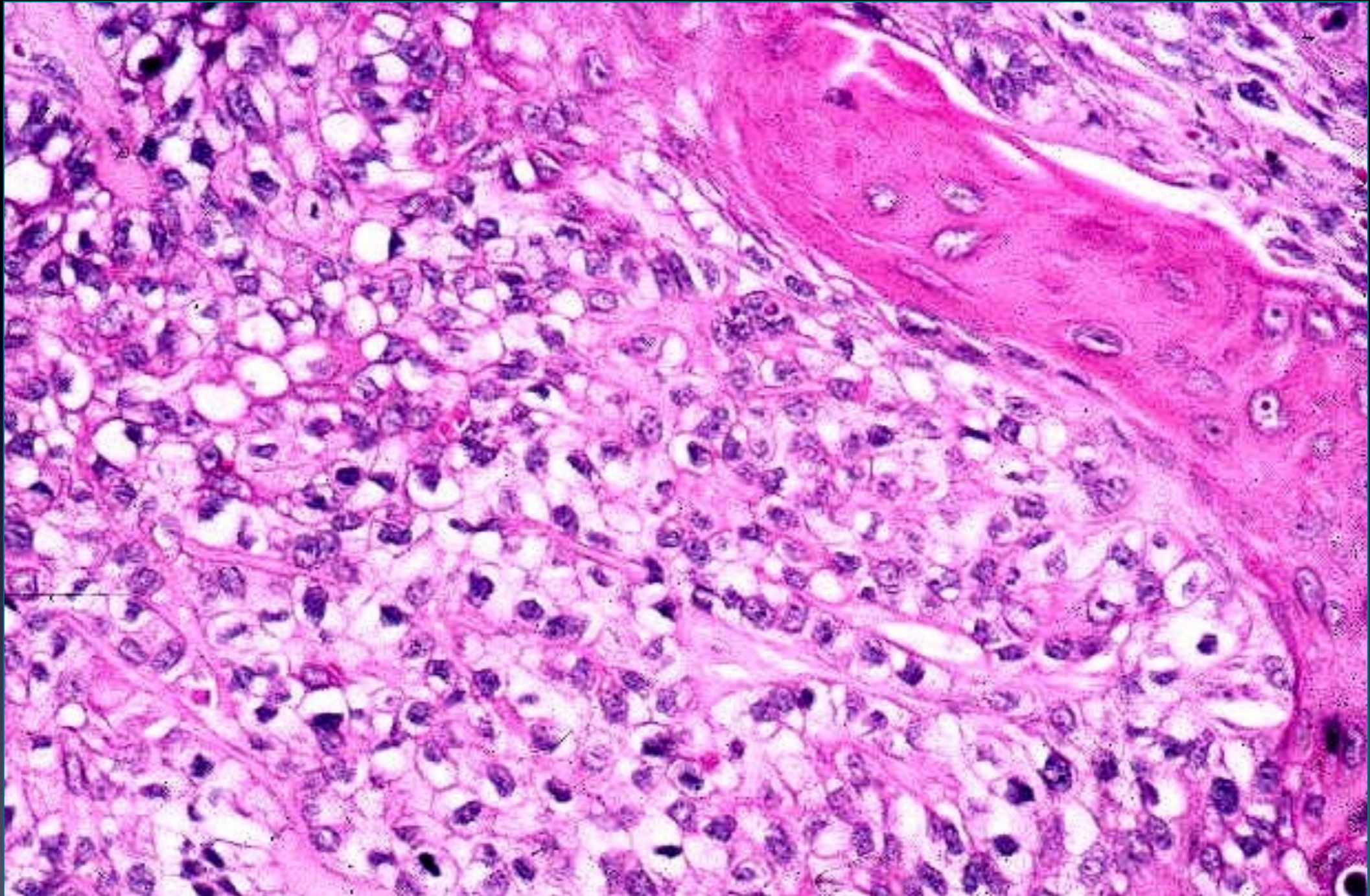
Clear (balloon) cell malignant melanoma



Clear Cell Basal Cell Carcinoma

CLEAR CELL BASAL CELL CARCINOMA: *Immunophenotype*

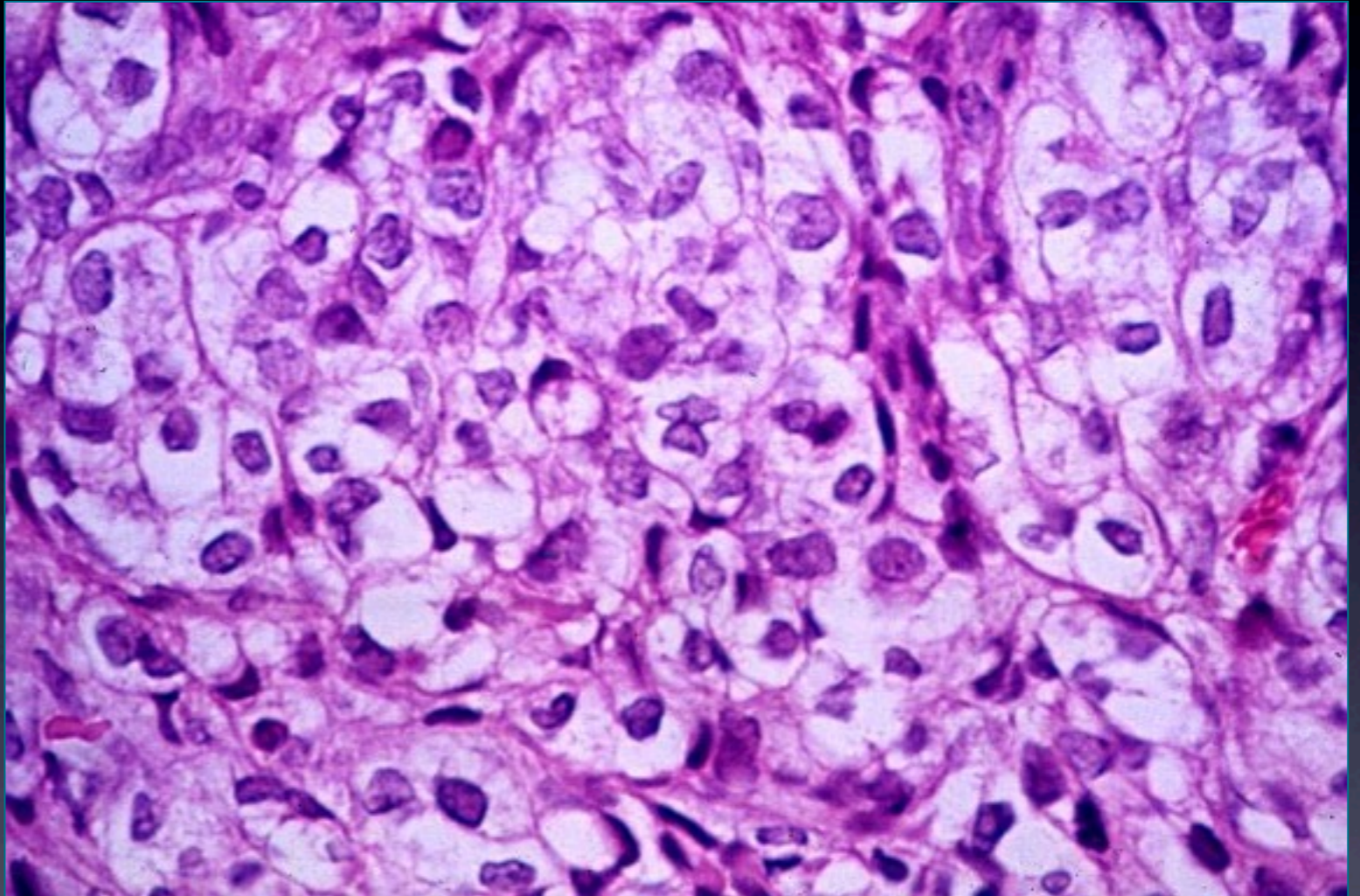
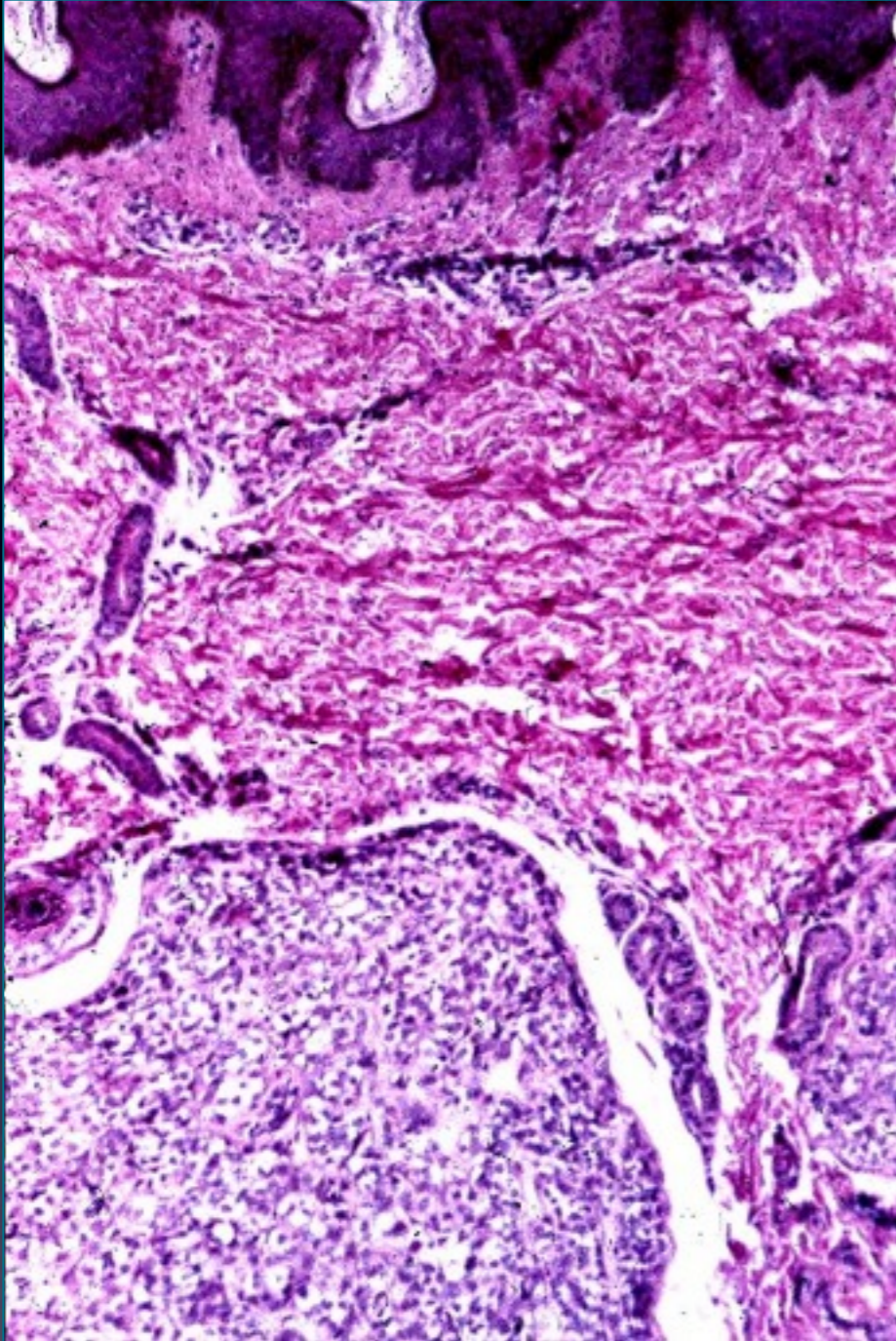
- Pan-Keratin +
- BER-EP4 +
- AE13/AE14 (-)
- EMA (-)
- CEA (-)



Clear Cell Squamous Cell Carcinoma

CLEAR CELL SQUAMOUS CELL CARCINOMA: *Immunophenotype*

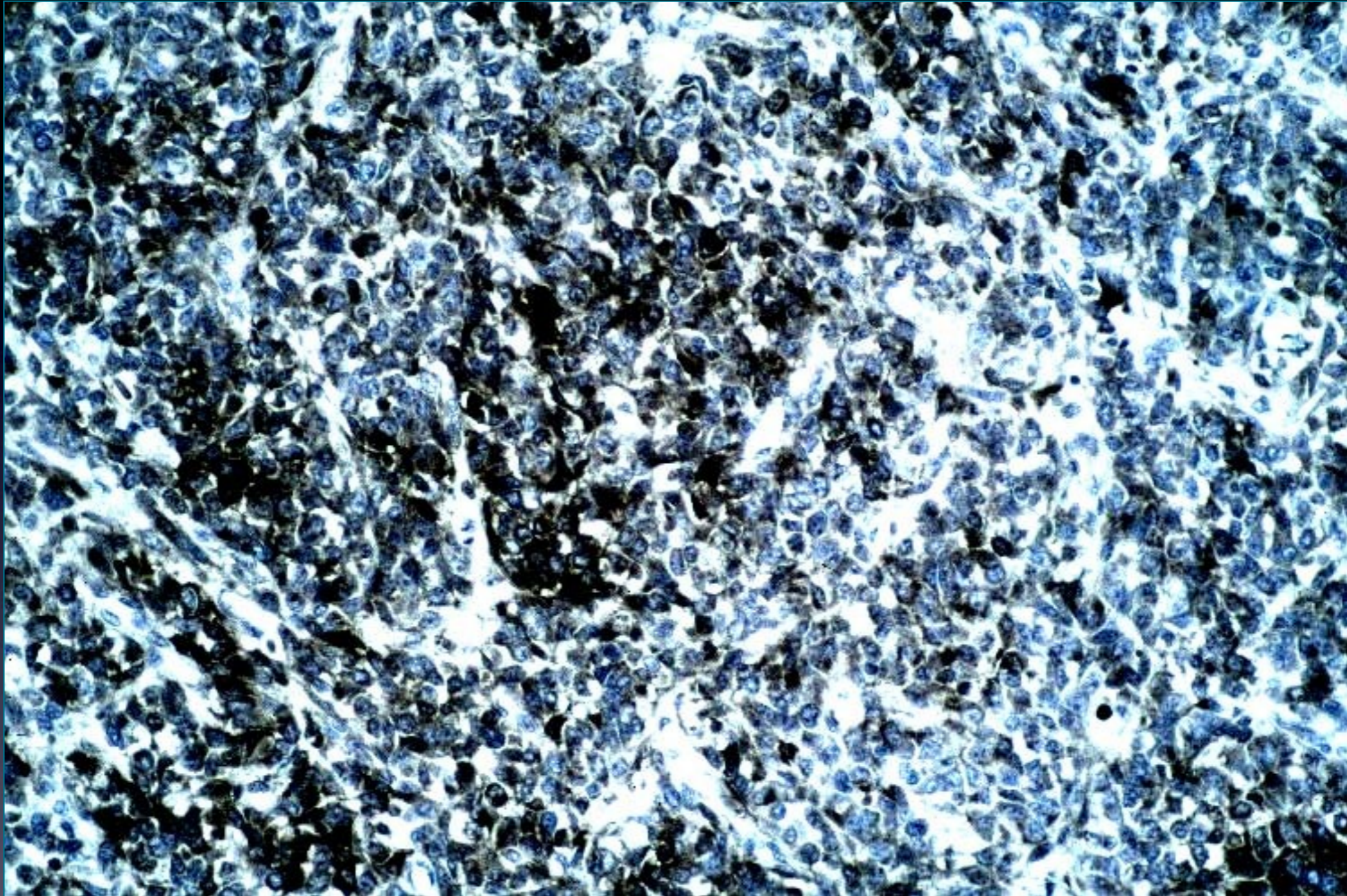
- Pan-Keratin +
- BER-EP4 (-)
- AE13/AE14 (-)
- EMA (+/-)
- CEA (-)
- S100 protein (-)



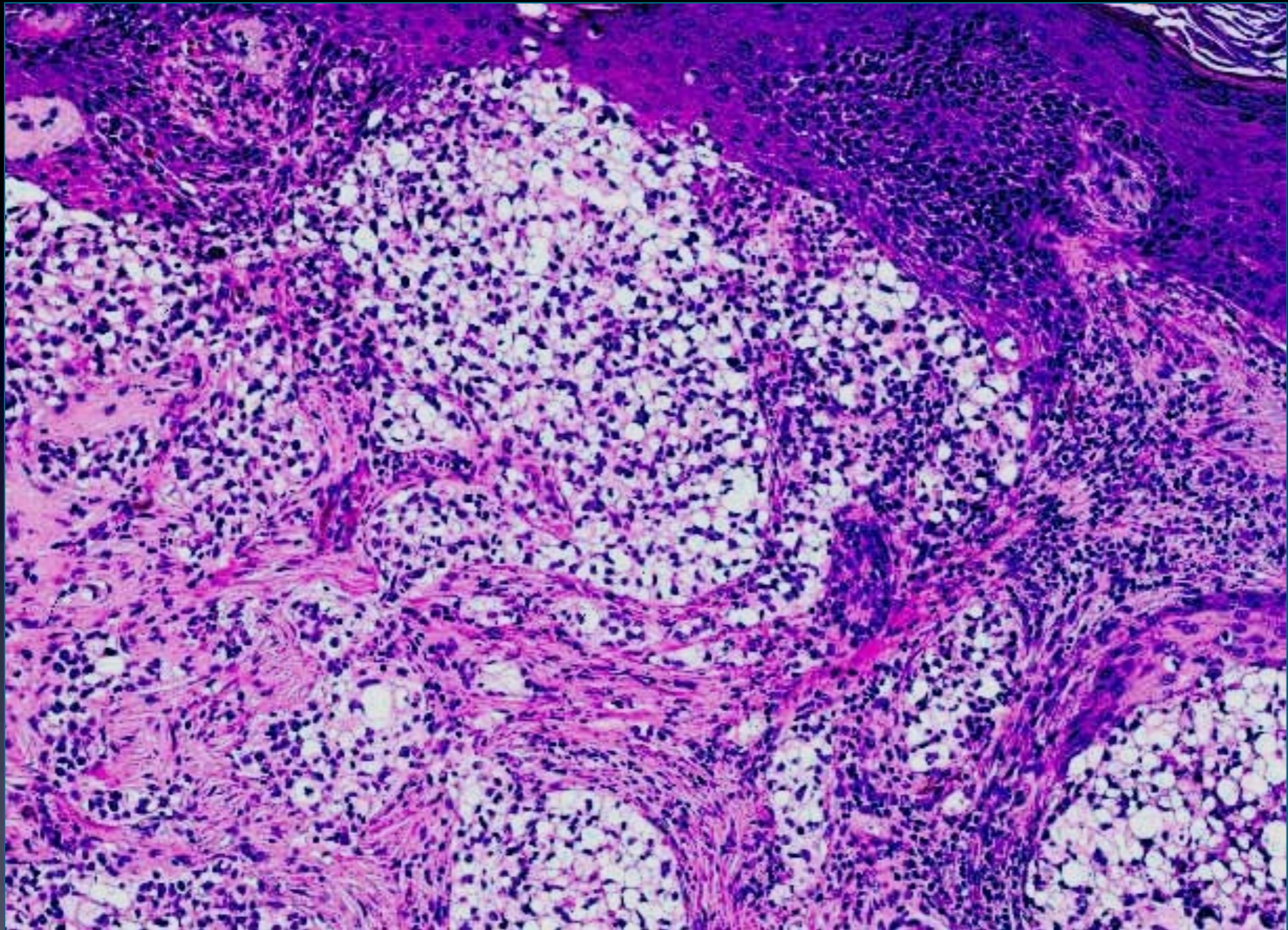
Clear Cell Eccrine Carcinoma

CLEAR CELL ECCRINE CARCINOMA: *Immunophenotype*

- Pan-Keratin +
- BER-EP4 (+/-)
- AEI3/AEI4 (-)
- EMA (+)
- CEA (+/-)
- S100 protein (+/-)



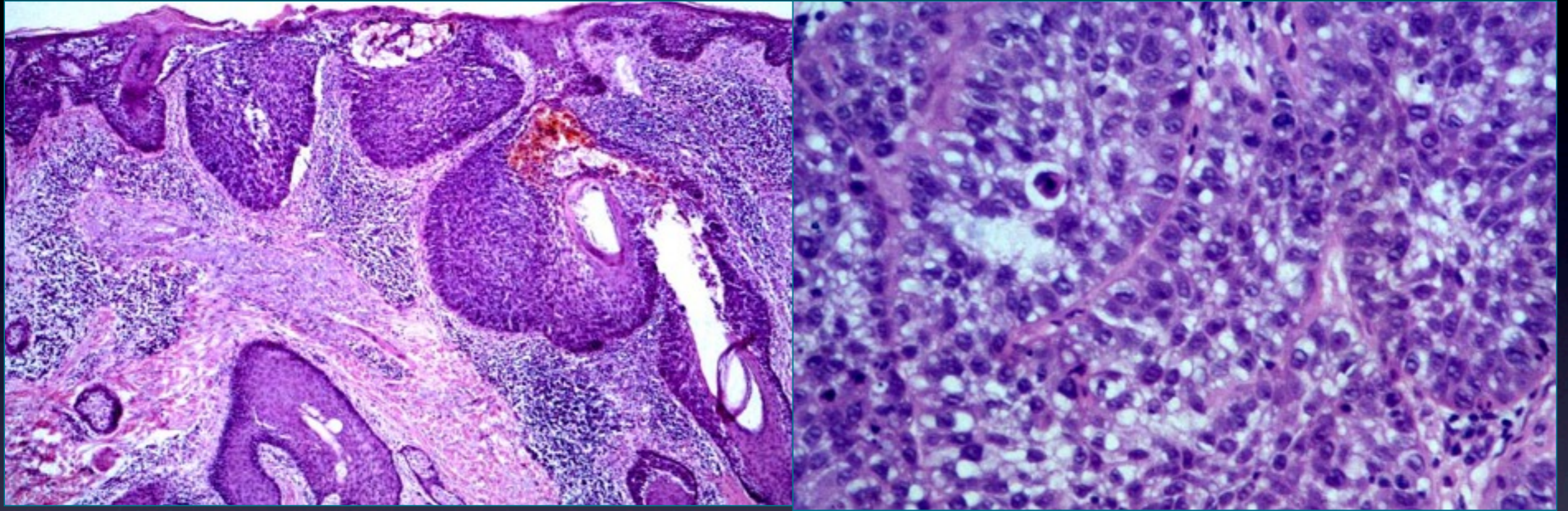
CEA+ Clear Cell Eccrine Carcinoma



Sebaceous Carcinoma

SEBACEOUS CARCINOMA: *Immunophenotype*

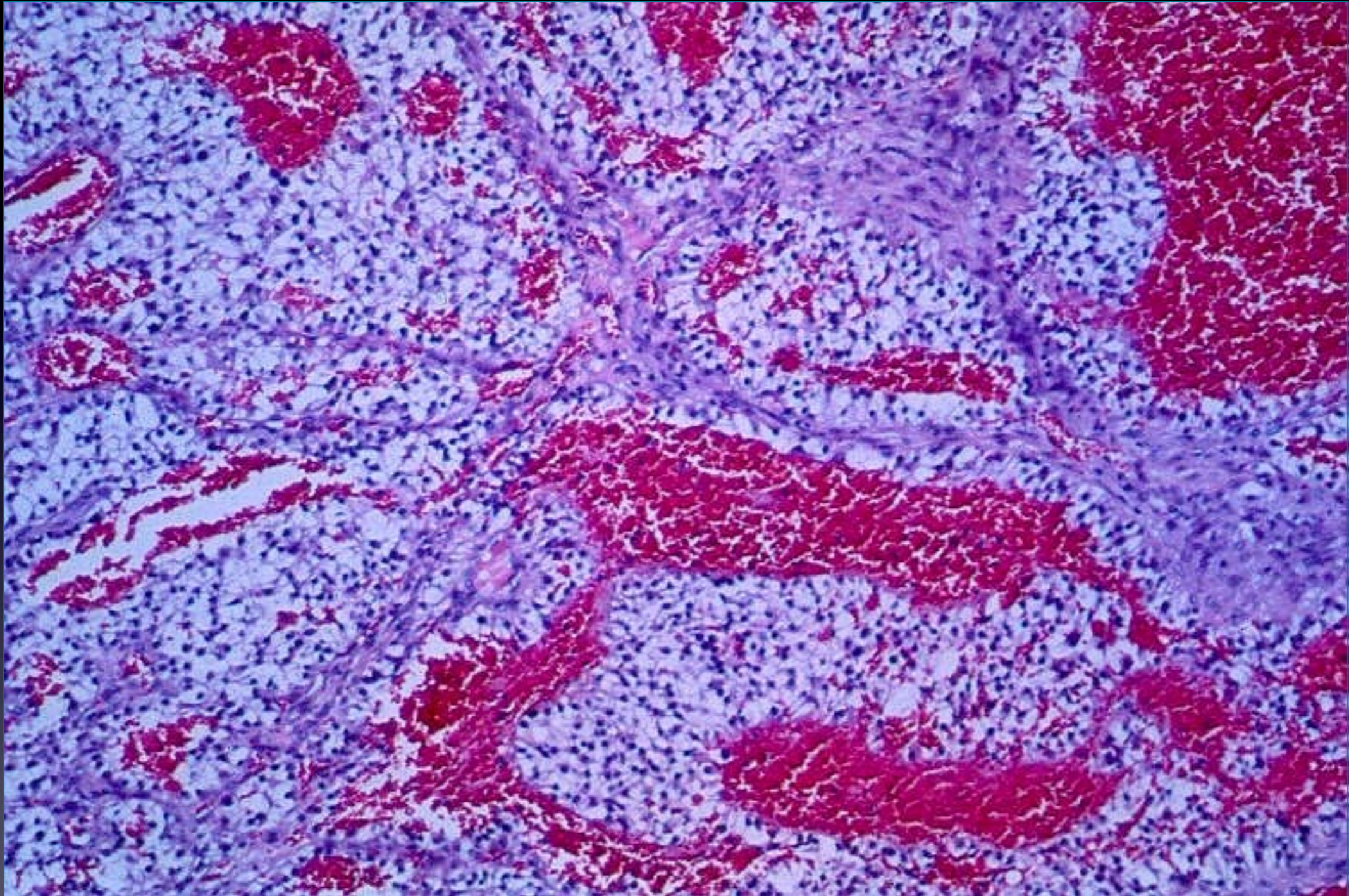
- Pan-Keratin +
- BER-EP4 (+/-)
- AEI3/AEI4 (-)
- EMA (+ *with multivacuolar cytoplasmic pattern*)
- CEA (-)
- S100 protein (-)



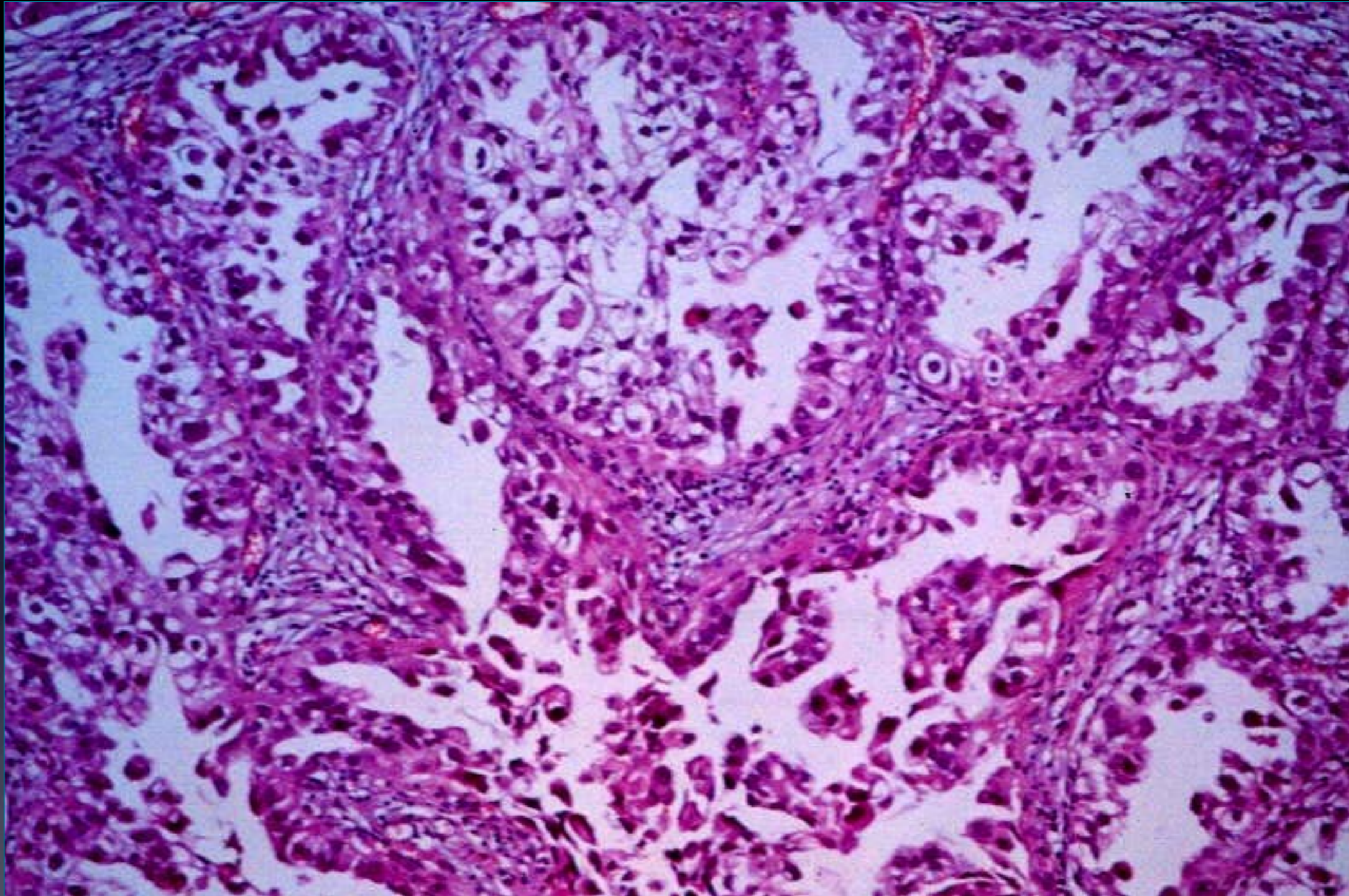
Trichilemmal Carcinoma

TRICHILEMMAL CARCINOMA: *Immunophenotype*

- Pan-Keratin +
- BER-EP4 (-)
- AE13/AE14 +
- EMA (+/-)
- CEA (-)
- S100 protein (-)



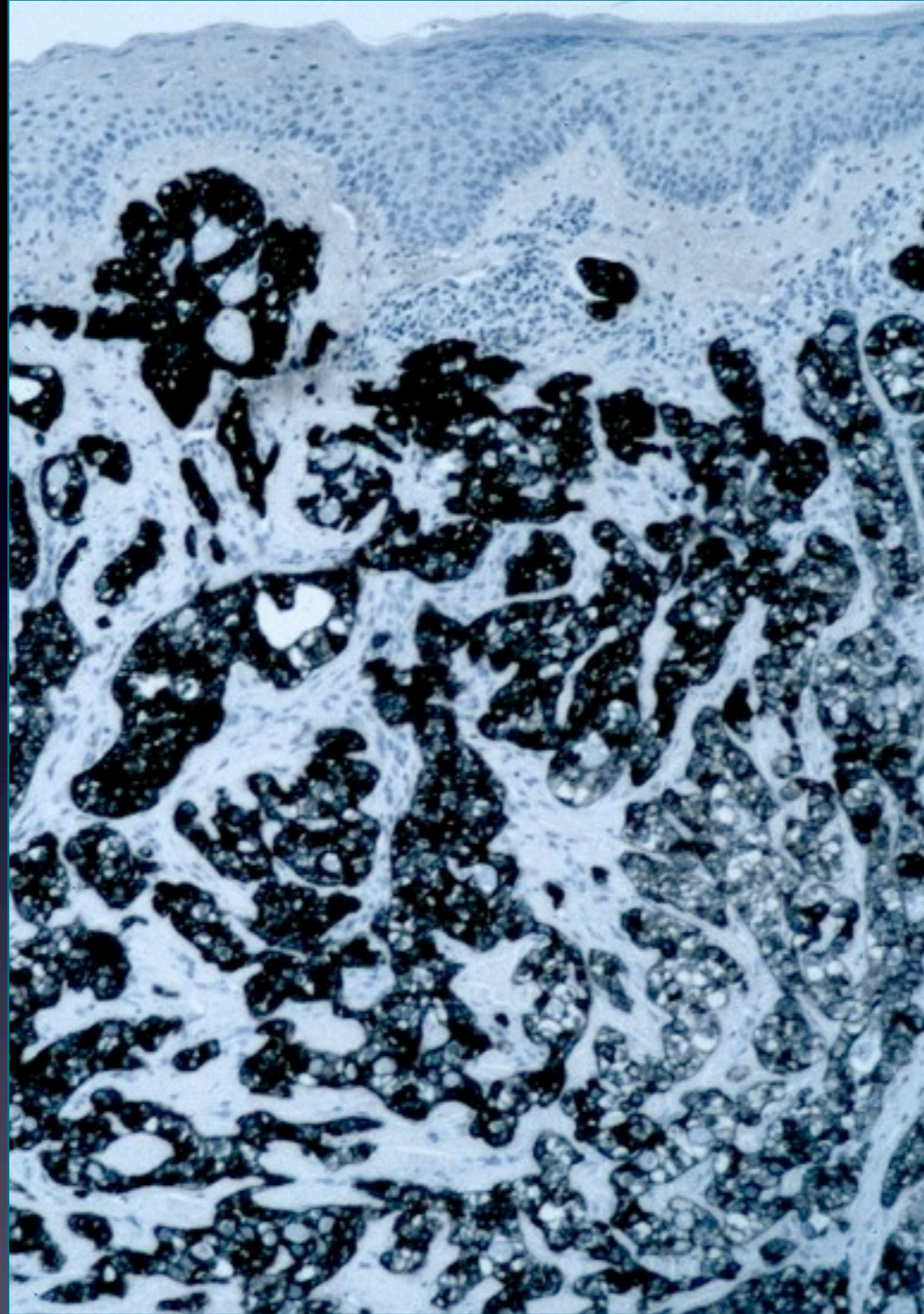
Metastatic Renal Cell Carcinoma



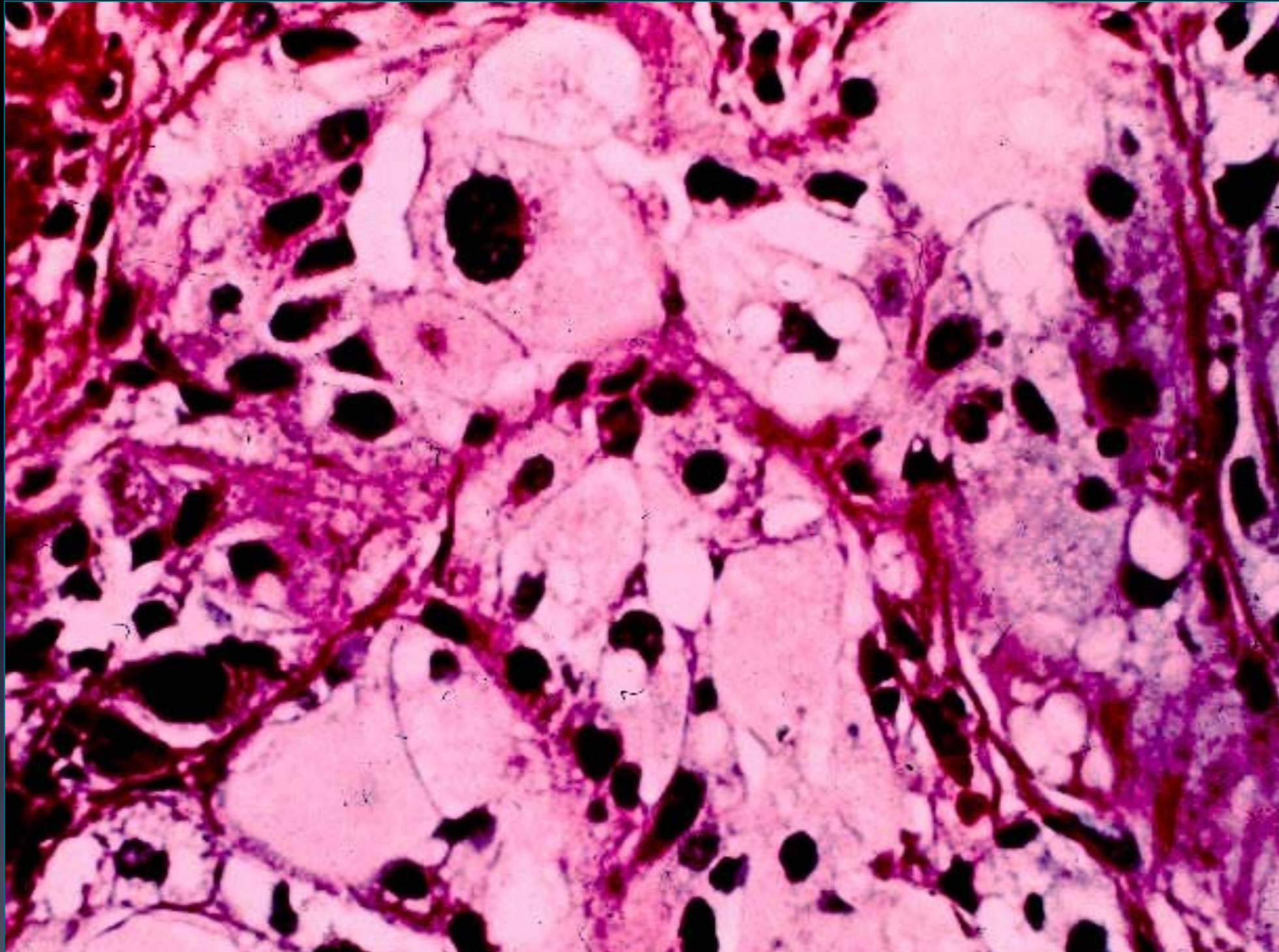
Metastatic Clear-Cell Carcinoma of Ovary

METASTATIC CLEAR CELL ADENOCARCINOMA: *Immunophenotype*

- Pan-Keratin +
- BER-EP4 (+/-)
- AE13/AE14 (-)
- EMA +
- CEA (+/-)
- S100 protein (+/-)
- *[CA-125 or PLAP may be +]*



CA-125+ Metastatic Clear Cell Ovarian Carcinoma



Balloon Cell Melanoma

CLEAR (BALLOON) CELL MELANOMA: *Immunophenotype*

- Pan-Keratin (-)
- BER-EP4 (-)
- AE13/AE14 (-)
- EMA (-)
- CEA (-)
- S100 protein +

Primer of Immunohistochemistry (Epithelial Markers)

Paul K. Shitabata, M.D.
Dermatopathology Institute
Torrance, CA