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Pathology Review
Chapter 3: Breast Pathology

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8. **According to the current staging system, which of the following cases qualifies for pN1?**

   a. 1 node positive for macrometastases (macromets), 2 nodes positive for micrometastases (micromets), 1 node positive for ITC.

   b. 2 nodes positive for micromets, 1 node positive for ITC.

   c. 1 node positive for macromets, 1 node positive for micromets, 1 node positive for ITC.

   d. 1 node positive for macromets, 2 nodes positive for micromets, 1 node positive for ITC.

   e. 3 nodes positive for macromets, 1 node positive for ITC.

   Answer: all

10. **The most helpful immunohistochemical stain to distinguish between florid ductal hyperplasia of the usual type and atypical ductal hyperplasia (ADH) is:**

    a. Calponin.

    b. p63.

    c. GCDFP.

    d. CK5/6.

    e. ERBB2 (formerly HER2/neu).

    Answer: d

15. **The neoplastic cells in Paget disease are often positive for the following stains except:**

    a. EMA.

    b. PASD.

    c. HMB45.

    d. S100.

    e. ER.

    Answer: c

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27. What is the name of cytologically bland clear cells found in the epidermis of the nipple that are CK7 positive, CD138 negative, and ERBB2 positive?

a. Tavassoli cells.

b. The organ of Chivietz.

c. The organ of Zuckerkandl.

d. The organ of Corti.

e. Toker cells.

Answer: e

31. Classify stromal tumors of the breast.

• Stromal tumors of the breast can be classified as:

- Biphasic tumors:

  Fibroadenoma.

  Phyllodes tumor.

  Periductal stromal tumor.

- Pure stromal tumors according to tissue of origin (see table below):

Benign	Malignant
• Benign stromal spindle cell tumors (BSSCT): - BSSCT with predominant myofibroblastic differentiation: myofibroblastoma. - BSSCT with predominant fibroblastic differentiation: solitary fibrous tumor/ hemangiopericytoma. • Pseudoangiomatous stromal hyperplasia (PASH). • Nodular fasciitis. • Fibromatosis.	• Malignant stromal cell tumor with predominant myofibroblastic differentiation. • Malignant stromal cell tumor with predominant fibroblastic differentiation.
• Lipoma, spindle cell lipoma.	• Liposarcoma.
• Leiomyoma.	• Leiomyosarcoma.
• Neural origin: - Granular cell tumor. - Neurofibroma. - Schwannoma.	
• Vascular lesions: - Angiomas. - Angiomatosis.	• Angiosarcomas: primary, postradiation, post–radical mastectomy.

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50. List eight features that differentiate epithelial hyperplasia from ductal carcinoma in situ (DCIS).

Feature	Epithelial hyperplasia	Low grade DCIS
Intratubular lumens	• Irregular, slit-like, mainly peripheral.	• Regular, rounded, rigid.
Streaming	• Present.	• Absent.
Bridges	• Long axis of nuclei parallel to the bridge.	• Roman arches (long axis of nuclei perpendicular to the bridge).
Cell types	• Polymorphous (epithelial and myoepithelial).	• Monotonous (only epithelial cells).
Cell margin	• Indistinct.	• Well defined.
Nucleus	• Overlapping normochromatic nuclei with indistinct nucleoli.	• Evenly spaced nuclei with or without obviously malignant features (atypia, hyperchromasia, prominent nucleoli).
Apocrine metaplasia	• Can be focally present.	• Absent.
Necrosis	• Absent.	• Present/absent.

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57. Describe briefly the criteria used to grade IDC.

• The modified Bloom-Richardson system is widely used to grade IDC. It assigns points to three criteria, as follows:

Criterion	Points
Tumor tubule formation. — Tubules must have clear central lumina to be counted.	• 1 point: > 75% of tumor. • 2 points: 10–75% of tumor. • 3 points: < 10% of tumor.
Number of mitotic figures in the most active area. — Counting 10 HPFs (x40 objective comparable to a field diameter of 0.44 mm).	• 1 point: <=5 • 2 points: 6-11 • 3 points: > 11 If field diameter is 0.55 mm: • 1 point: <=8 • 2 points: 9-17 • 3 points: >17
Nuclear pleomorphism.	• 1 point: minimal nuclear variation in size and shape. • 2 points: moderate nuclear variation in size and shape. • 3 points: marked nuclear variation in size and shape (more than 3 times).

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• The IDC grade is based on the total points:

- Grade I: 3–5 points.
- Grade II: 6–7 points.
- Grade III: 8-9 points.

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59. List four histologic subtypes of invasive breast carcinoma that indicate a better prognosis than invasive ductal carcinoma NOS (not otherwise specified).

• Colloid/mucinous carcinoma.

• Papillary.

• Tubular.

• Medullary.

• Cribriform.

• Adeonoid cystic.

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64. What are the major molecular subtypes of breast cancer (invasive ductal carcinoma not otherwise specified)? Compare the subtypes for the following factors: genetic, biologic, immunoprofile, and clinical.

• Major molecular subtypes:

- Luminal A.
- Luminal B.
- Normal breast-like.
- ERBB2 (formerly HER2/neu).
- Basal-like.

***Note: some authors question the designation "normal breast-like," therefore only the other subtypes are compared in the table below.**

• Comparison of subtypes (see table below):

Factor	Luminal A	Luminal B	ERBB2	Basal-like
Genetic expression pattern.	• High expression of normal luminal profile (LMWCK) and hormone receptors. • ERBB2 expression negative.	• Expression of normal luminal profile (LMWCK), with weak to moderate expression of hormone receptors. • Variable ERBB2 expression.	• High expression of ERBB2 on chromosome 17. • Low expression of hormone receptors. • TP53 mutation common.	• High expression of basal epithelial profile (HMWCK). • Low expression of both hormone receptors and ERBB2. • TP53 mutation common.

Biologic features.	• ~ 50% • Slow growing, responds well to hormonal treatment.	• ~ 20% • Higher grade and higher proliferation index than luminal A.	• ~ 15% • High grade, high proliferation index, high node positive.	• ~ 15% • High proliferation index.
Immunoprofile:				
ER/PR.	• ER/PR: positive.	• ER/PR: positive.	• ER/PR: negative.	• ER/PR: negative.
ERBB2.	• ERBB2: negative. • KI67<14%.	• ERBB2: variable (often positive, triple positive). • KI67>14%.	• ERBB2: positive.	• ERBB2: negative (triple negative).
Clinical features:				
Response to therapy.	• Good response to hormonal therapy.	• Response to hormonal therapy not as good as luminal A, but better response to chemotherapy.	• Responds to Herceptin and anthracycline-based chemotherapy.	• Responds to platinum based chemotherapy.
Prognosis.	• Prognosis: good.	• Prognosis: not as good as luminal A.	• Prognosis: poor.	• Prognosis: poor (except medullary carcinoma).

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65. What are the features of breast carcinoma associated with BRCA1?

- Poorly differentiated.
- Syncytial growth pattern.
- Pushing margins.
- Prominent stromal lymphocytic response.
- ER/PR negative.
- ERBB2 negative.
- High proliferating index (Ki67) and mitotic count.
- CK5/6+, EGFR+

***Note: 13% of tumors associated with BRCA1 are medullary carcinomas.**

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68. What are the implications of LCIS?

- 20–30% develop invasive carcinoma (diagnosis on core needle biopsy), after long-term follow-up of 30 years.
- This increased risk applies to both breasts (slightly greater on the side of the biopsy).
- The invasive carcinoma can be either ductal or lobular type.
- The relative risk increases from 4.9 after one biopsy to 16.1 after a second biopsy shows LCIS.

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From WHO

- If Classical LCIS on core
  - Close, long-term follow-up
  - Excision when pathologic-radiology discordance
- If Pleomrophic LCIS of Classical LCIS with comedo necrosis or bulky mass-forming LCIS
  -Excision with negative margin or mastectomy

71. What are the histologic (architectural) variants of ILC?

- Classic.
- Alveolar.
- Tubulolobular.
- Mixed.
- Solid.

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72. What are the cytologic variants of ILC?

- Pleomorphic.
- Signet ring.
- Histiocytoid.
- Apocrine.
- Mixed.

76. Classify papillary lesions of the breast.

- Papilloma (solitary and multiple papillomas)
- Papilloma with ADH or DCIS
- Papillary DCIS
- Encapsulated papillary carcinoma
- Solid papillary carcinoma
- Invasive papillary carcinoma

77. What are the features of an atypical papilloma, and how do you differentiate between an atypical papilloma and DCIS arising in a papilloma?

• An atypical papilloma is defined by:

- Proliferation of epithelial cells with loss of myoepithelial cells within a papilloma.

— and —

- Areas of solid, cribriform, or micropapillary proliferation of uniform, monotonous atypical cells, confined to less than 1/3 of the lesion.

— or —

- Proliferation of uniform cells, < 3 mm in size.

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• **DCIS arising in a papilloma is defined by:**

- Involvement of more than 30% but less than 90% of areas of solid, cribriform, or micropapillary proliferation of uniform, monotonous atypical cells.

— or —

- A proliferation of uniform cells ≥ 3 mm in size.

***Note: in DCIS, there is preservation of myoepithelial cells in the peripheral duct lining.**

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81. A breast IHC quality assurance program determines that the ER/PR stain in your lab is insensitive. What factors can affect the results of ER/PR testing? List six factors.

- Delay in fixation — specimens should be placed in 10% neutral buffered formalin within one hour of removal from the patient.
- Fixation time — minimum of 6 hours.
- Choice of antibody — 3 types commonly used: 6F11, SP1 and ID5; SP1 is said to be superior.
- Concentration of antibody in the reagent.
- Method of antigen retrieval.
- Expired reagents.

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84. What is the differential diagnosis of Paget disease?

- Bowen disease.
- Malignant melanoma in situ.
- Toker cell hyperplasia.

85. How would you differentiate Paget disease from the differentials listed in question 84?

IHC	Paget disease	Bowen disease	Melanoma in situ	Toker cell hyperplasia
Mucin	+/-	-	-	-
CK7	+	-	-	+/- (+ in 67%)
Cam5.2	+	-	-	+/-
EMA	+	-	-	-
HMWCK	-	+	-	-
HMB45	-	-	+	-
ERBB2	+	-	-	+/-