How Do Pathologists Make a Diagnosis

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A pathologist provides care to which of the following patients?

A. 52-year-old female with an abnormal mammogram who has a biopsy performed
B. 21-year-old male requiring many units of blood after a motor vehicle accident
C. 72-year-old male with a fungal infection in his lung
D. A neonate who is being tested for Down’s Syndrome
E. 14-year-old female with low blood count following the beginning of menarche
Objectives

• Describe the scope of practice for pathology and laboratory medicine
• Discuss the value of pathology in providing best patient care
• Describe the process and quality systems used to ensure accurate results
• Understand the pathologic features neoplasms
• Describe the “team” of medical professionals
Scope of Practice for Pathology and Laboratory Medicine
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52-year-old female with an abnormal mammogram who has a biopsy performed

- A biopsy of tissue is sent to the laboratory
- Specimen is processed
- Tissue is thinly cut and put on a glass slide
21-year-old male requiring many units of blood after a motor vehicle accident

• Patients requiring large amounts of blood activates the Massive Transfusion Protocol
• Pathologist works with clinicians to ensure appropriate blood products to stabilize patient
• Review relevant laboratory studies to guide therapy
72-year-old male with a fungal infection in his lung

- A sputum sample is sent to the microbiology laboratory
- Specimen cultured on growth medium with proper nutrients
- A slide is prepared when the fungus grows
A neonate who is being testing for Down’s Syndrome

• A blood sample is sent to the laboratory and white bloods cells are removed
• The DNA (genetic material) is removed and tested
Karyotype showing the Philadelphia chromosome.
46,XX,t(9;22)(q34.1;q11.2)
14-year-old female with low blood count following the beginning of menarche

• A tube of blood is sent to the lab for a complete blood count

• Results indicate a microcytic anemia and a peripheral blood smear is made
Laboratory Medicine Impacts
Nearly Everyone

70% to 80% of medical decisions have a laboratory component
Tree of Medicine

THE TREE OF MEDICINE

- Dermatology
- Ophthalmology
- Psychiatry
- Anesthesiology
- Dentistry
- Radiology
- Gynecology
- Obestrics
- Obstetrics
- Neurology
- Surgery
- Pediatrics
- Internal Medicine
- Systemic Pathology
- General Pathology
- Anatomy
- Immunology
- Genetics
- Embryology
- Pharmacology
- Physiology
- Microbiology
- Histology
- Cell Biology
- Chemistry
- Physics
Laboratory Medicine

Anatomic Pathology
- Tissue specimens

Clinical Pathology
- Fluid specimens
Laboratory Medicine

Anatomic Pathology

Tissue specimens (Surgical)
- Breast
- GI
- Skin

Cellular specimens (Cytopathology)
- Pap Test
- Fine needle aspiration
- Urine

Autopsy
- Natural causes
- Accidental
- Homicide

Clinical Pathology
Value of Pathology to Patient Care
Value in Patient Care

Value = \frac{Benefit}{Cost}
Value of Laboratory Medicine in Patient Care

- **An accurate result**, from an
- **Appropriate test(s)**, provided at the
- **Right time**, on the
- **Right specimen**, from the
- **Right patient**, with result interpretation based on
- **Correct reference data**, and at the
- **Right and reasonable price**

Value = \[ \frac{\text{Benefit}}{\text{Cost}} \]
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• Describe the “team” of medical professionals
Your UVMMC Laboratory

- Approximately 2.7 million clinical laboratory tests are performed each year
  - Approximately 1 million specimen tubes are processed for these 2.7 million test
- 200,000 phlebotomy visits
- 22,000 phone calls to our customer service center
- Courier service collecting samples from 240 locations
- 37,350 tissue samples
  - These 37,350 tissue samples required 224,912 glass slides be prepared and reviewed
- 32,106 Pap tests
- 5,799 cytology (non-pap) cases
- 114 medical autopsy examinations
- 542 Medical Examiner autopsies
Experts in Pathology

- **Clinical Pathology**
  - Transfusion medicine and histocompatibility
  - Hematopathology and coagulation
  - Flow cytometry
  - Cytogenetics
  - Molecular pathology
  - Chemistry and toxicology
  - Urinalysis
  - Immunopathology
  - Microbiology
  - Point-of-care testing
  - Phlebotomy

- **Anatomic Pathology**
  - Surgical pathology
    - Multiple organ systems
  - Cytopathology
  - Autopsy pathology
  - Forensic pathology
  - Histology and immunohistochemistry
  - Reproductive medicine
  - Biorepository
  - Electron microscopy
UVMMC Blog Site

https://medcenterblog.uvmhealth.org
Regulatory Agencies

• The College of American Pathologists
• American Association of Blood Banking
• American Society for Histocompatibility and Immunogenetics
• Food and Drug Administration
• Foundation for Accreditation of Cellular Therapy
• New York State Department of Health
• The Joint Commission
• Center for Medicare & Medicaid Services
• American College of Surgeons
• National Radiation Council
• Cytotechnology Programs Review Committee
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Vitamin CDE

• Vascular
• Infectious / Inflammatory
• Traumatic / Toxic
• Autoimmune
• Metabolic
• Iatrogenic / Idiopathic
• Neoplastic

• Congenital
• Degenerative
• Endocrine
Figure 1.2

Leading Causes of Death in US, 1975 vs 2011
Percent of All Causes of Death

1975

- Other Causes: 22.0%
- Pneumonia and Influenza: 2.9%
- Accidents: 5.4%
- Chronic Lung Disease: 2.3%
- Cerebrovascular Diseases: 10.3%
- Heart Disease: 37.8%
- All Malignant Cancers: 19.2%

2011

- Other Causes: 35.4%
- Pneumonia and Influenza: 2.1%
- Accidents: 5.0%
- Chronic Lung Disease: 5.7%
- Cerebrovascular Diseases: 5.1%
- Heart Disease: 23.7%
- All Malignant Cancers: 22.9%

Source: US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention.
Neoplasm

• **New growth**
  – Abnormal mass of tissue
  – Growth exceeds surrounding normal tissue
  – Uncoordinated compared to surround normal tissues
  – Persists in the excessive manner after cessation of stimuli which the change
    • Non-reversible
Neoplasm

• **New growth**

• Clonal
  – Population of cells arising from a single cell which incurred genetic change (stimuli)

• Derangement of normal growth control mechanisms

• Balance of cell death and cell division is abnormal
Definitions

• Neoplasm
  – Benign
  – Malignant
  – Uncertain potential
Neoplasm - Benign vs. Malignant

**Benign**
- Remains local
- Does NOT invade adjacent tissues
- Cannot spread
- Cured by removal
- Patient generally survives

**Malignant**
- Invades and destroys adjacent structures
- Can spread to other sites
- May or may not be treatable
- Often causes death (if left untreated)

**Uncertain Malignant Potential**
- Unpredictable behavior
- Cannot be classified by histologic features
- Treatment may vary
Uterus

Benign Neoplasm

Malignant Neoplasm

BENIGN (Leiomyoma)
- Small
- Well demarcated
- Slow growing
- Noninvasive
- Nonmetastatic
- Well differentiated

MALIGNANT (Leiomyosarcoma)
- Large
- Poorly demarcated
- Rapidly growing with hemorrhage and necrosis
- locally invasive
- Metastatic
- Poorly differentiated
Uterus

Benign Neoplasm-Leiomyoma(s)
Breast Tissue - Benign vs. Malignant

Benign - Fibroadenoma

Malignant - Invasive adenocarcinoma
Cancer

• The commonly used term for **malignant** neoplasms

• Fits the definition well
  – **Caner** is Latin for crab
  – “Adheres to any part it seizes upon in an obstinate manner”
    • ? Definition for children?
Cancer Latin for Crab

Adheres to any part it seizes upon in an obstinate manner
Additional Terms Applied to **Malignant** Neoplasms
Terms for **Malignant** Neoplasms

- In-situ vs. Invasive
- Primary vs. Metastatic
Malignant Neoplasm

• **In-situ**
  – Does **not** invade the basement membrane
  – Considered pre-invasive cancer
  – **No** capability to metastasize

• **Invasive**
  – Tumor cells **breach the basement membrane**
  – Grows **into** surrounding tissue
  – Now tumor cells have access to vasculature
    • Ability to **metastasize**
In-situ vs. Invasive Malignant Neoplasm

Normal Cervix

Carcinoma in-situ

Invasive carcinoma
Access to Vessels

• **Carcinoma in-situ**
  – Not invasive
  – Cannot access the vasculature
  – Cannot spread

• Once a tumor is *invasive*
  – Access to vessels
  – Metastatic spread
Primary vs. Metastatic

• **Primary**
  – Tumor arising at the site of origin
    • Carcinoma of the breast arising in the breast

• **Metastatic**
  – Spread of tumor to distant sites
    • Lymphatic
    • Hematogenous
    • Seeding body cavity
  – Invasive *carcinoma* of the breast spreading to lung

• **Direct extension**
  – Neoplasm invades into adjacent organ
    • Prostate *carcinoma* invading into adjacent bladder
What the Mind Does Not Know
The Eyes Cannot See
Pathologic Features of Neoplasms
Gross Features

• Does not mean “icky”
• Features we can see with our naked eye
• Very important
  – First assessment of the specimen to determine benign or malignant
• Can provide information about adjacent tissues
  – Associated pathologies
Gross Features

- Must evaluate
  1. Circumscription of neoplasm
  2. Necrosis within the neoplasm
     - Cystic change
     - Ulceration
  3. Texture and character of neoplasm
  4. Number of neoplasms
     - Metastatic disease
     - Synchronous neoplasms
       - Occurring at the same time
Gross Features

• **Circumscription** of **Benign** Neoplasm
  – Smooth
  – Circumscribed
  – May have a capsule
  – Can be lobulated

• Low-grade malignancies can have these features
  – DOES **NOT** INVADE INTO SURROUNDING TISSUE
Gross Features

• Circumscription of **Malignant** Neoplasms
  – Irregular borders
  – Finger like projections
  – Remember Cancer=Crab
    • Latin for...
  – Often destroys adjacent tissue
Neoplasm Circumscription

- Benign
- Malignant
Circumscription of Benign Neoplasm

Liver section with single subcapsular neoplasm.

Smooth, circumscribed border.

Diagnosis: Hepatic adenoma
Circumscription of Malignant Neoplasm

Lung with single, large neoplasm.

Irregular circumscription arising from airway

Diagnosis: Invasive squamous cell carcinoma of the lung
Gross Features

• **Metastasis**
  – Defines malignancy in nearly 100% of neoplasms
  – Seeding of body cavities and surfaces
  – Lymphatic spread
  – Hematogenous spread

• Rare exception includes
  • Benign metastasizing leiomyoma

• ~30% of solid tumors (excluding skin cancer other than melanoma) will have metastasis at presentation
Metastatic Carcinoma to the Liver

Multiple irregular and focally necrotic nodules in the liver. Diagnosis is metastatic carcinoma.
Hematogenous Spread

Renal vein involvement by clear cell renal cell carcinoma of the kidney

Where might the tumor travel?
Gross Features

• Must evaluate
  1. Circumscription
     • Smooth (circumscribed)
     • Irregular (invasive)
  2. Necrosis/Ulceration
     • Very concerning when associated with a neoplasm
  3. Metastasis
     • Seeding a body cavity
     • Lymphatic spread
     • Hematogenous spread
Histologic Features
Histologic Features

• Features appreciated in tissue sections
  – Biopsy or resection specimens
  – Tissue is fixed in formalin, paraffin embedded, 5 micron section cut, and H&E stains are performed

• Look for architectural and cytologic features to confirm the diagnosis
  – Low to medium power for architecture
  – Medium to high power for cytologic features

• Compare to surrounding, NON-neoplastic tissues
Histologic Features- Low Power

- Invasion
- Loss of normal architecture
- Necrosis
- New structures
- Angiogenesis
- Inflammation
Breast Tissue - Benign vs. Malignant

Benign - Fibroadenoma

Malignant - Invasive adenocarcinoma

Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition. Copyright © 2009 by Saunders, an imprint of Elsevier, Inc. All rights reserved.
Histologic Evaluation of

Smooth border - Benign

Irregular border of invasion - Malignant
Squamous Cell Carcinoma with Desmoplastic Stroma

Normal Esophagus with normal stroma

Desmoplastic Stromal response

Invasive squamous cell carcinoma
Adipose tissue

NORMAL Breast

Interlobular fibrosis

Benign lobules

Terminal duct
Adenocarcinoma, invasive ductal, no special type

Loss of normal breast architecture

Desmoplastic stromal response

Normal
Papillary Structures

Papillary Serous Carcinoma of the Ovary
Cribiform

Rigid neolumen (glandular) formation perforated like a colander
Cytologic Features
Cytologic Features

• Study of **cells**
  – Exfoliative cytology
    • Sputum
    • CSF
    • Urine
    • Pap Test
  – Fine Needle Aspirations (FNA)

• Cells are directly smeared onto slide or processed by thin layer technology
Cytologic Features

- Pleomorphism
- Increased nuclear-to-cytoplasmic ratio
- Irregular nuclear membranes
- Chromatin clumping
- Hyperchromasia
Abnormal Mitoses

Atypical Appearing Tripolar mitotic figure
Differentiation in Squamous Cell Carcinoma

Well-differentiated squamous cell carcinoma

Keratin formation—“keratin pearls” and intracellular bridges
Adenocarcinoma in Ascites

Evidence for mucin in the cytoplasm Indicating glandular epithelium
Which histologic slide belongs to Gross A and which slide belongs to Gross B?
What is the correct slide-gross specimen combination?

A. Slide 1 with A & Slide 2 with B
B. Slide 1 with B & Slide 2 with A
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Diagnosing a Patient

It is a TEAM effort
Diagnosis
Treatment
Management
Breast Cancer Case Presentation

49-yr-old with newly palpable lump in the right breast
Core biopsy from right side at 11:30, 3 cm out

Normal

Invasive carcinoma

In-situ carcinoma (DCIS)
Estrogen receptor immunohistochemical stain... Result is positive in 80% of tumor nuclei
Her2/neu immunohistochemical stain...
Result is negative with weak, incomplete membranous (1+ pattern)

Example of a positive (3+ pattern) showing complete, thick staining of the cell membrane
Invasive carcinoma

In-situ carcinoma (DCIS)
<table>
<thead>
<tr>
<th>Tubule formation</th>
<th>Nuclear pleomorphism</th>
<th>Mitotic count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &gt; 75% tubules</td>
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<td>1 &lt; 9 mitoses/10HPF</td>
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<td>2 10%-75% tubules</td>
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<td>Histologic grade for invasive tumors (Well = 3,4,5; Moderate = 6,7; Poor = 8,9)</td>
<td></td>
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Blue in applied during our gross examination and processing

Tumor distance to margin
Lymphatic Drainage of the Breast

**Sentinel lymph node** is the first node in a regional lymphatic basin receiving lymph from primary tumor.
Scrape preparation prepared during surgery- “Intraoperative Consult”

Concerning cells
Lymph node metastasis
Synoptic Report for this Carcinoma

Laterality: Right
AJCC (7th edition): pT2, pN2a
Specimen: Total mastectomy; sentinel node biopsy; axillary dissection
Tumor Type: Invasive ductal
Tumor Size: 3.5 x 3.0 x 2.5 cm
Nottingham Combined Histologic Scores:
   Tubules: 3
   Nuclei: 3
   Mitoses: 3 (actual count 38/10 HPF with field diameter of 0.54 mm)
   Total: 9
Differentiation: Poor
Margins: Negative (closest margin 4.0 mm, anterior)
DCIS: Solid and Cribriform pattern, with necrosis, nuclear grade III
% DCIS: Less than 5%; DCIS also present outside main tumor mass
DCIS margins: Negative (closest margin 2.0 mm; anterior)
LVI: Not identified
Lymph nodes: 5/37 (positive/total count); largest metastasis 0.9 mm
ER/PR: ER positive (80%); PR positive (90%)
Her2: Negative/1+ by immunohistochemistry
Non-amplified by in situ hybridization; Her2:Chr17 ratio is 1.31
Who is going to care for this patient?
Team Effort

• Primary physician
  – Assess risk
  – Perform physical exam
    • Detect an abnormality

• Radiologist
  – Perform and review imaging
  – Perform biopsy

• Pathologist
  – Diagnose disease
  – Provide information to surgeon
Team Effort

• Surgeon
  – Counsel patient on treatment options
  – Consider other diagnostic tests
  – Perform cytoreductive surgery

• Pathology
  – Diagnose disease
  – Provide staging and prognostic information

• Medical and Radiation Oncologists
  – Counsel patient on treatment options
  – Consider other prognostic tests
  – Treat the disease
  – Manage the patient
Team Effort

• Nursing
  – Coordinate patient care
  – Follow-up on diagnostic and prognostic testing
  – Counsel patient

• Geneticist

• Nutritionist

• Primary physician
  – Continue to monitor and care for patient’s disease
  – Prevent further disease
  – Educate the patient and family
Thank you for attending Community Medical School