The Pathology of Cancer

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Citation: Ok CY, Woda B, Kurian E. The Pathology of Cancer. In: Pieters RS, Liebmann J, eds. *Cancer Concepts: A Guidebook for the Non-Oncologis*t. Worcester, MA: University of Massachusetts Medical School; 2017. doi: 10.7191/cancer_concepts.1023.

This project has been funded in whole or in part with federal funds from the National Library of Medicine, National Institutes of Health, under Contract No. HHSN276201100010C with the University of Massachusetts, Worcester.

Summary and Key Points

1. Pathology is the study and diagnosis of disease.
2. Cancer is generally defined as a malignant process of autonomous, unregulated cell proliferation with the ability to spread (metastasize) to distant sites.
3. Cancers are usually named based on the organ from which they arise; they are many diseases.
4. Cancer is the second leading cause of death in the United States surpassed only by cardiovascular disease.
5. Cancers frequently develop from precursor lesions.
6. Surgical pathologists use gross and microscopic study of tissue for classification and understanding the pathogenesis of disease.

Introduction

Pathology

The department of pathology is inclusive of clinical pathology (microbiology, blood bank, chemistry, and hematology), anatomic pathology (autopsy/forensics, cytopathology, and surgical pathology) and molecular pathology. Pathologists are responsible for choosing the methodology and overseeing the accuracy and precision of the testing results reported in lab reports and the stated normal and abnormal ranges. Any questions regarding how to obtain a sample, appropriate test to order, or interpretation of a test can be directed to a pathologist for guidance; since pathologists are considered the “doctor’s doctor.” Cytopathology is the subspecialty that reviews the cells in CSF, urines, pap smears, brushings and fine needle aspirations of lesions.

Cytopathologists can provide quick on-site immediate assessment for adequacy of sampling of fine needle aspiration biopsies, usually performed on an outpatient basis. A surgical pathologist examines and interprets biopsies, excisions of organs, and autopsies. Surgical pathologists can offer intra-operative frozen section diagnoses to guide surgical management.

Patients and physicians depend on pathologists to make the diagnosis of cancer and of the specific type of cancer. Pathologists are expert in pattern recognition and in the natural history of diseases, including cancers.

Cancer

Cancer is the second leading cause of death in the United States surpassed only by cardiovascular disease. Our understanding of how cancers begin and spread has undergone a significant change over the last half century. Historically, theories invoked to explain the cause of cancer included infectious diseases and nutritional deficiencies. While the development of some cancers can result from infections, we now appreciate that cancers occur as the result of DNA mutations in normal cells.

Basic Principles

In general, cancer cells are distinguished from normal cells by two fundamental properties. First, cancers possess abnormalities in the regulation of cell division and survival. Most cells in the human body are not actively dividing at any given moment. Entry into cell cycle is tightly controlled in normal cells. Many cancers, however, have alterations in one or more proteins that regulate mitotic activity. Normal cells also will undergo apoptosis – programmed cell death – as a result of a variety of conditions including extensive damage to the genome. Cancer cells, however, frequently have alterations in the genes that control apoptosis and, therefore, survive in conditions that would normally be lethal.

The second characteristic of cancer cells that distinguishes them from normal cells is the ability to metastasize. Metastasis refers to the cancer

cells acquired ability to break away from neighboring cells, traverse tissue boundaries, enter and travel through lymphatics and blood vessels, and then grow in foreign tissue environments.

It is important to appreciate that cancer is not one disease, but a category of many, which share abnormal cell features. The shared biologic characteristics of cancerous cells can be classified by their required cellular properties defined as follows[1]:

1. Ability for a cancer to generate mitogenic signals – this is the ability to initiate signal transduction pathways leading to mitosis
2. Resist exogenous growth-inhibitory signals
3. Genetic instability- refers to a set of events causing unscheduled alteration within the genome. These changes can be broadly divided into:
   a) Chromosomal level (i.e. chromosomal gains, loss, translocations, duplications etc.)
   b) At the nucleotide level (i.e. mutations in DNA repair pathway, mismatch repair pathway defects etc.)
4. Evade apoptosis and acquire unregulated proliferation (immortalized cells)
5. Angiogenesis (growth and proliferation of blood vessels)– required for nutritional support, waste removal and oxygenation to the cancer
6. Tissue invasion and metastasis through blood or lymphatics

Many cancers have a pattern of metastasis. For example tumors which commonly metastasize to the brain include breast cancer, melanoma, renal cell carcinoma (kidney cancer), and lung cancer. In contrast, cancers which commonly metastasize to the bone include kidney, thyroid, lung, prostate and breast.

Cell Cycle Regulation

Normal cells have regulated cell cycles composed of the following phases: quiescent phase [G0], growth phase [G1 S, G2] and mitotic phase [M]) with checkpoints and a regulated process of programed cell death (apoptosis).

The G1/S checkpoint is involved in most malignancies. This point is referred to as the *restriction point* and is a point of irreversible progression towards cell division. Cells will normally continue proliferation in early-mid G1, unless inhibited by inhibitory signals or growth factor deprivation. The retinoblastoma protein (RB) is a key regulator for irreversible initiation of cell division. Inactivation of the RB by phosphorylation allows the cell to continue to the S phase. In the event of DNA damage, the ATM (ataxia-telangiectasia mutated) signal transduction pathway may act to arrest replication (G1 or G2 phases) or prolong replication (G1, S, G2 phases) for repair of the DNA damage. The ATM pathway phosphorylates MDM2 bound to p53. The dissociated p53 is now able to stop cell cycle progression, synthesize repair enzymes and initiate apoptosis. Apoptosis is the process of programmed cell death during cell development or after cellular injury. Apoptosis can be readily identified on histologic sections by the following features: cell shrinkage, chromatin condensation, formation of cytoplasmic blebs, and phagocytizing macrophages. See Robbins and Cotran, pp 26-32 for additional details.- The Lamar Souter Library has Robbins & Cotran 9th edition, 2015 on the reference shelf; the page reference should be 32-60

Cells with irreparable DNA damage are flagged for apoptosis, thereby limiting the potential for uncontrolled cell proliferation. However, in most cancers there is one or more genetic alteration in this G1 checkpoint. More of these alterations are discussed in the Cancer Biology chapter.

Pathology: Defining Tumor, Neoplasm and Cancer

Tumor refers to “swelling” which may produce a mass. The cause of the mass may be benign or malignant. It is a generic term that may refer to a reactive inflammatory process, an infectious process, benign tissue mass or malignant growth of tissue. It is used interchangeably with neoplasm in the setting of an abnormal tissue growth (either benign or malignant).

Neoplasms are derived from a single clone of cells which grow in an uncoordinated manner. The term neoplasm refers to a clonal growth which can be either benign (non-invasive) or malignant (invasive/cancer). Neoplastic cells must undergo a number of genetic alterations in order to overcome the regulated cell growth maintained by normal cells.

Benign neoplasms are localized expansile masses composed of cells with unregulated cell growth that, with rare exceptions, **do not invade tissues and do not metastasize**. They often are surrounded by a fibrous capsule and usually easy to surgically resect.

Malignant neoplasms are masses of unregulated cell growth which are

locally invasive and can metastasize. Due to their invasive, irregular border they can be difficult to surgically resect. The word “cancer”, is derived from the Latin word for crab or “karkinos” because of the observed finger-like invasion.

Pathologic examination is performed after a biopsy or surgical removal is performed. The evaluation of the cells allows the pathologist to determine whether a neoplasm is benign or malignant. Multiple features must be evaluated by the pathologist in order to distinguish a benign neoplasm from a malignant neoplasm. When a neoplasm is determined malignant, the neoplastic borders are assessed for evidence of infiltration and into normal tissue. A well differentiated malignancy has features like the tissue of origin. However, poorly differentiated malignancies do not appear anything like components of the precursor organ, thereby making determination of tumor origin more challenging. A low grade (grade 1) indicates a well-differentiated malignancy, whereas a high grade (grade 3) indicates a poorly differentiated malignancy. The grade of the malignancy (differentiation) is a key component of a pathologic assessment.

Nomenclature

Cancers are named according to their tissue origin and to describe features of the appearance of the malignancy. Medical terminology is composed predominantly of Latin prefixes and suffixes which can be pieced together to give a description of a neoplasm. A few of the common prefixes can be found in the glossary section.

For example, the prefix (adeno-) means glands and the suffix (– oma) means tumor, so an adenoma translates to a benign growth of glands (Figure 1).

In contrast, an adenocarcinoma (adeno meaning glands and carcin meaning cancer and oma meaning tumor) is a cancerous growth of glands (Figure 2).

A tumor (-oma) generally suggests a benign growth process, however there are exceptions to this rule. For example: Melanoma is a malignant neoplasm derived from melanocytes (melan-) residing in the basal layer of epithelium.

Lymphoma is a malignant neoplasm derived from lymphocytes (lymph-).

Sarcoma– malignant tumor of mesodermal origin (i.e. connective tissue) (sarc-, means flesh).

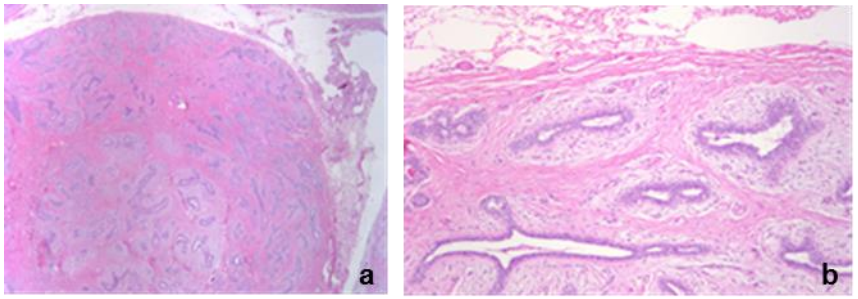
During embryologic development, pluripotential cells become committed into 3 primary lineages: endoderm, mesoderm and ectoderm; these continue to differentiate into organs. The endoderm (inner layer) gives rise to the digestive tract, respiratory tract, and glands (pancreas and liver etc). Mesoderm (middle or mesenchymal layer) differentiates into muscles, kidneys, genitals, inner linings (pleura, peritoneum), circulatory system, and bones/cartilage. Finally, the ectoderm (outer layer) develops into skin and its related structures as well as the central nervous system.

In routine pathologic classification, cancers are named according to the organ/cell from which they originate. Neoplasms can be subdivided based into embryologic cell type categories:

Carcinomas arise from epithelium, both ectoderm and endoderm.

Benign epithelial neoplasms include papillomas and adenomas (Figure 1)

Note: The pictures that follow are all hematoxylin and eosin (H&E) stained paraffin embedded sections of tissue. Nuclei are typically blue and cytoplasm, muscle, etc. pink. Fat appears as circular white spaces as shown in Figure 2a & b.



Figures 1a, b. This is a fibroadenoma of the breast composed of a benign proliferation of glands within fibrous breast tissue as the name implies. This adenoma is by definition well-circumscribed with a fibrous capsule (see left side, low magnification), and lacks features of malignancy (right side, higher magnification). Images courtesy of University of Massachusetts Medical School, Department of Pathology.

Malignant epithelial neoplasms are termed carcinomas, i.e. adenocarcinoma (Figure 2), squamous cell carcinoma, basal cell carcinoma, small cell carcinoma etc.

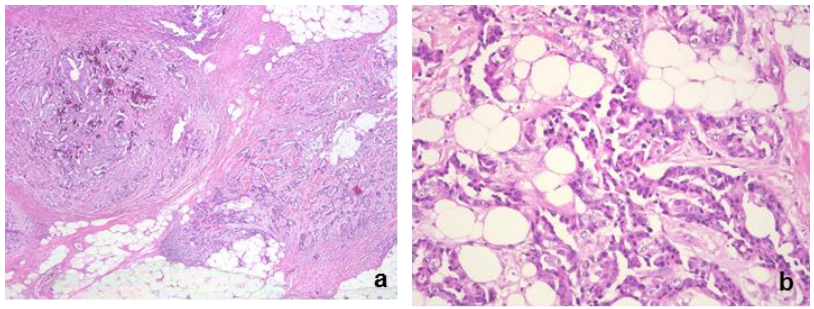


Figure 2a, b. Breast Adenocarcinoma. (a) This is an invasive ductal adenocarcinoma of the breast (low magnification). (b) Invasion is seen by the tumor infiltration of the adjacent benign fat (higher magnification). (Compare normal glands of the fibroadenoma in Figure 1 to the disorganized cancerous glands). Images courtesy of University of Massachusetts Medical School, Department of Pathology.

Sarcomas- derive from mesenchymal tissue: This is includes connective tissue. Examples of malignancies include:

Osteosarcoma	Bone
Chondrosarcoma	Cartilage
Fibrosarcoma (Figure 3a,b)	Connective tissue
Leiomyosarcoma	Smooth muscle
Rhabdomyosarcoma	Striated muscle
Angiosarcoma	Blood vessel

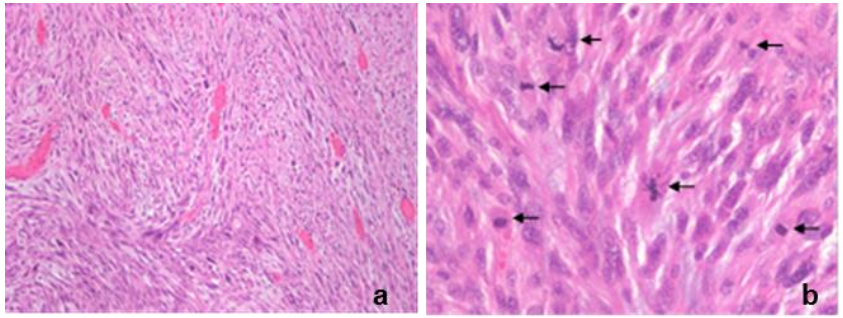


Figure 3a, b. (a) Fibrosarcoma (low magnification) is a malignant tumor of immature proliferating fibroblasts characterized by spindled-cells in fascicles. (b) Higher magnification shows multiple mitotic figures (arrows). Images courtesy of University of Massachusetts Medical School, Department of Pathology Department.

Hematopoietic cancers are also derived from mesenchymal tissue: Tumors of the blood or hematopoietic derivatives

Lymphoma: Refers to hematopoietic mass within the soft tissue, organs, or lymph nodes (Figure 4)

Leukemia: Refers to hematopoietic malignancies of blood or fluid spaces

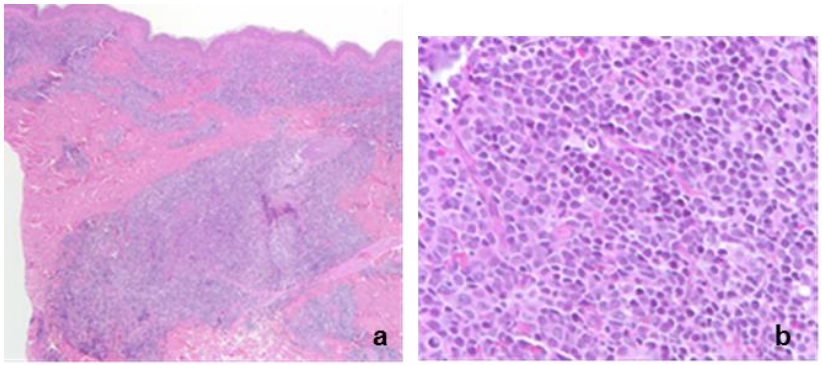


Figure 4a, b. Diffuse Large B cell lymphoma. (a) Low magnification of a skin biopsy shows malignant lymphocytes (blue) within the dermis (pink). (b) Higher magnification shows large crowded single lymphocytic cells with scant cytoplasm and high mitotic count. Images courtesy of University of Massachusetts Medical School, Department of Pathology.

Neural crest (ectoderm) derived cancers:

Tumors of the brain and spinal cord (Central Nervous System):

- Glioblastoma: High grade malignant brain tumor arising from astrocytes

Tumors of the melanocytes in the basal layer of the skin

- Benign melonocytic neoplasm (nevus): a mole or birthmark
- Malignant melanocytic neoplasm: Melanoma (Figure 5)

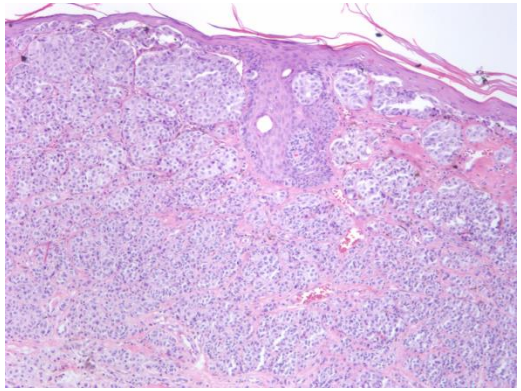
- 

Figure 5. Malignant melanoma. This shows nested proliferation of malignant melanoncytic cells in the dermis (low magnification). Image courtesy of University of Massachusetts Medical School, Department of Pathology Department.

Identifying Features of Malignancy

A neoplasm is considered to be malignant when pathologic examination shows characteristic features which include:

- Disordered growth pattern: Back-to-back glands or irregular arrangement of cells (Figure 6)

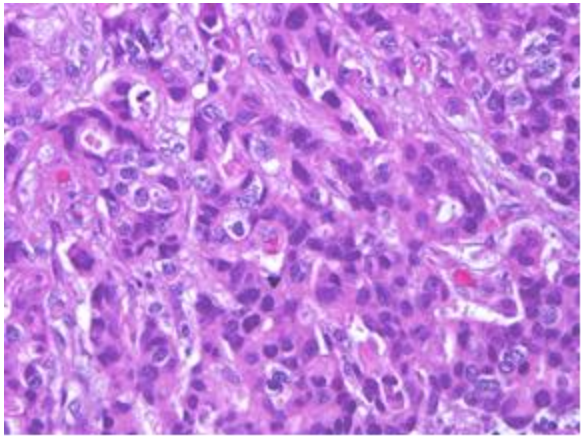


Figure 6. Adenocarcinoma with back-to-back glands (20x). Image courtesy of University of Massachusetts Medical School, Department of Pathology.

- Cellular atypia. Cells have increased nuclear size relative to cytoplasm (nuclear-to-cytoplasmic ratio or N:C ratio), prominent nucleoli or darker appearing nuclei due to increased DNA content (hyperchromatic), pleomorphism (variation in size and shape) (Figure 7).

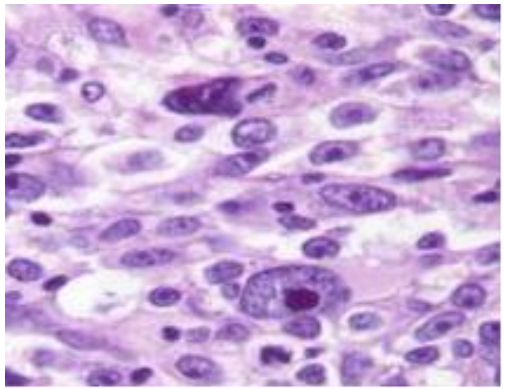


Figure 7. Pleomorphism is defined as variations in size and shape of cells (x40). Notice the increased nuclear –to –cytoplasmic ratio (N:C ratio), hyperchromatic nuclei and prominent nuclei of the malignant cells. Image courtesy of University of Massachusetts Medical School, Department of Pathology.

- Increased mitotic activity or atypical mitotic figures. While increased mitotic figures are not in itself indicative of malignancy, often with increased cell turn-over there are atypical mitotic figures (Figure 4) and/or necrosis (Figure 8).

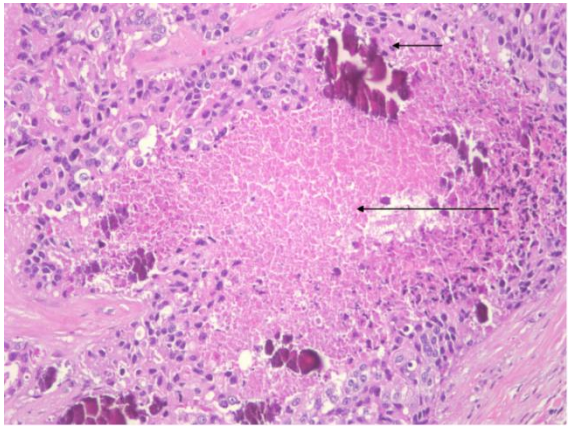


Figure 8. Breast carcinoma with necrosis (long arrow) and calcifications (short arrow). Image courtesy of University of Massachusetts Medical School, Department of Pathology.

- Demonstrates invasion: for example, invasion through basement membrane into submucosa or deeper in gastrointestinal sites (Figure 9), invasion of a capsule such as in endocrine organs (i.e. thyroid or adrenal) or evidence of infiltration of stroma or adipose tissue (Figures 2a, b; 9) or into lymphatics (Figure 10).

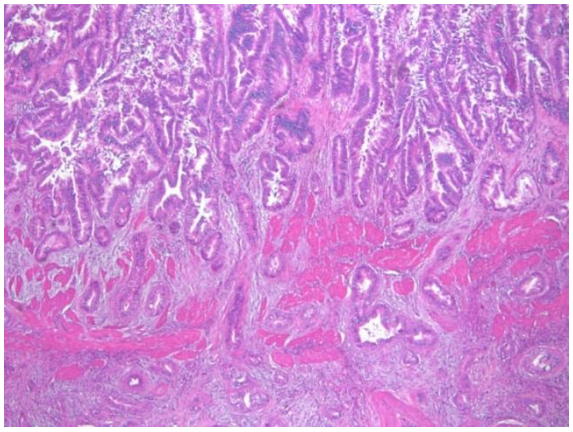


Figure 9. Gallbladder with invasive adenocarcinoma through the muscle and deep into the submucosa (4x). Image courtesy of University of Massachusetts Medical School, Department of Pathology.

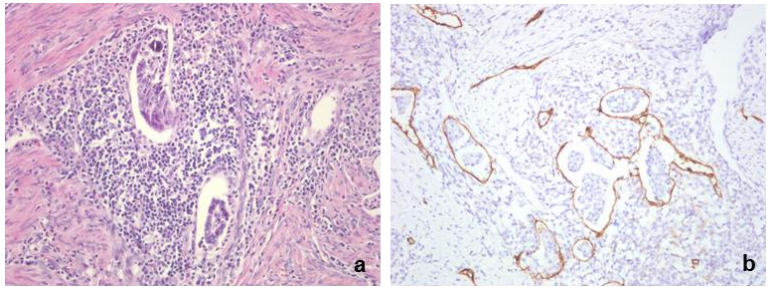


Figure 10a, b. **(a)** Lymphatic invasion (40x). **(b)** The picture on the right uses a special stain to highlight the lymphatic channels and clearly shows that malignant glands are within the lumens (40x). University of Massachusetts Medical School, Department of Pathology.

- Loss of polarity – for example, in reference to columnar neoplasms, the nucleus is at the base on top of the basement membrane (Figure 11a). In a malignant process the cells begin to crowd and lose this orderly process, so that nuclei can be seen stratified towards the apical surface (Figure 11b).

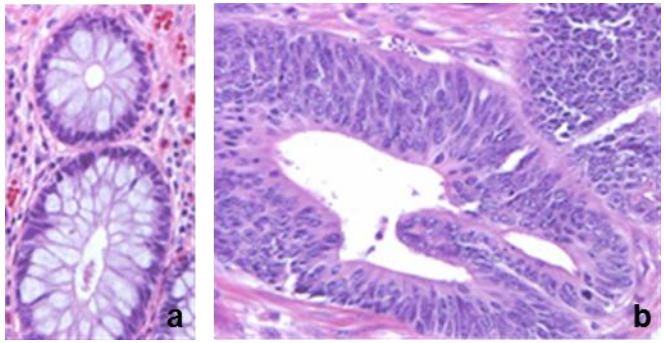


Figure 11 a, b. Loss of polarity. Compare basally located nuclei with apical mucin in normal glandular epithelium **(a)** to nuclear stratification in malignant gland **(b)** (x40). University of Massachusetts Medical School, Department of Pathology.

Precursors of Cancer

Cancers frequently develop from precursor lesions. It is the early detection of these precursor lesions which is the basis for screening tests (i.e. pap

smears for cervical cancer, colonoscopy for colon cancer etc.).

Metaplasia

Metaplasia is the replacement of one type of epithelium by another. This process is thought to be a response to chronic irritation. In most cases metaplasia is a reactive response and considered benign. In smokers with chronic smoke irritation, the ciliated epithelium within the respiratory airway may undergo squamous metaplasia with loss of cilia necessary to evacuate accumulating mucus. In contrast, chronic acid reflux irritation at the gastro-esophageal junction (GE junction) can induce the flat esophageal squamous mucosa to undergo metaplastic change and become gland-forming intestinal mucosa. This gland formation is known as Barrett's esophagus (Figure 12a and b) and is a known precursor for the development of esophageal adenocarcinoma in the distal esophagus.

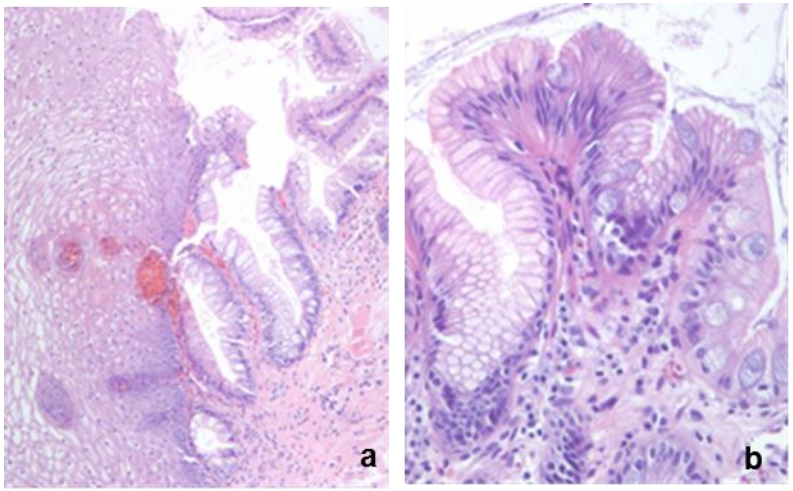


Figure 12a, b. Barrett's metaplasia. **(a)** This is a biopsy of the gastro-esophageal junction (GE junction) showing esophageal squamous epithelium (left) and metaplastic Barrett's esophagus (right) (10x). **(b)** Compare the normal pink columnar gastric mucosa (right) the adjacent Barrett's esophagus which shows a bluish tint and prominent mucinous vacuoles reminiscent of colonic glandular epithelium (20x).

Dysplasia

This is the abnormal growth of cells. In contrast to hyperplasia which is the overgrowth of normal cells, dysplastic cells tend to have variation in both size and shape (pleomorphism), shows cellular crowding, atypia and, over time, may progresses to cancer. This progression to cancer may be over the course of many years.

Dysplasia can be considered low grade or high grade depending on nuclear features. Low grade dysplasia indicates that there are atypical cells that involve only the area closest to the basement membrane. In some locations such as the cervix, low grade dysplasia may regress back to normal. Alternatively, in most organs this may remain low grade dysplasia or progress to high grade dysplasia. High grade dysplasia usually has large cells crowding and stratifying toward the apical surface away from the basement membrane. High grade dysplasia is always worrisome for impending progression to cancer and requires clinical management (Figure 13a and b).

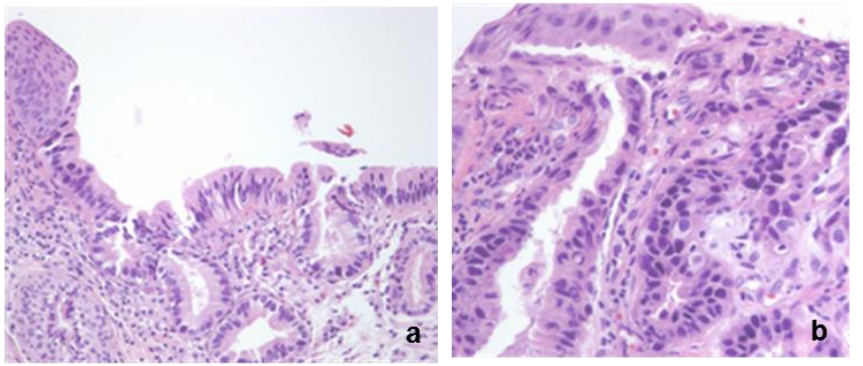


Figure 13a, b. This is another biopsy of the GE junction (a) (10x). The esophageal squamous mucosa is on the right transitioning into low grade dysplasia in this patient that has Barrett's esophagus (not illustrated in this image). **(b)** These glands demonstrate high grade dysplasia. Note how the crowded cells are stratified rather than remaining near the basement membrane, the nuclei appear hyperchromatic (darker) with nuclear enlargement (20x). Compare to Figure 14.

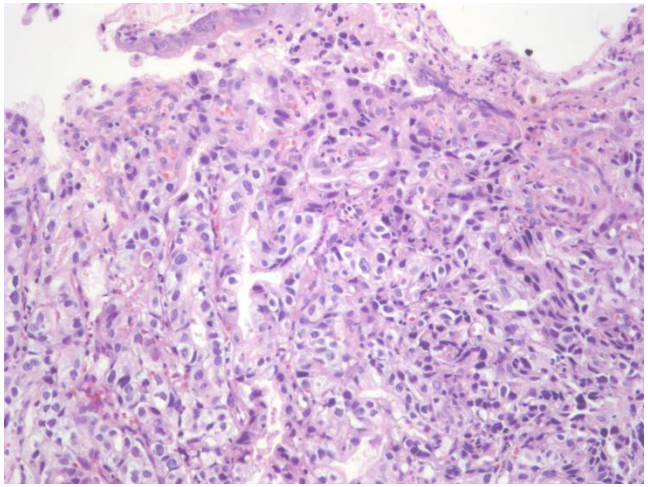


Figure 14: Invasive esophageal adenocarcinoma with surface ulceration. University of Massachusetts Medical School, Department of Pathology.

Carcinoma-in-situ

In-situ is a Latin phrase meaning “in position”. The use of this term means that the cells fulfill all other criteria for malignancy, ***except*** they have not invaded the basement membrane (yet). These cells can shed off the surface, and this fact can be exploited by simple screening tests such as urinalysis and cervical pap testing. These cells must involve the full thickness of the epithelium, and if left untreated may progress to invade through the basement membrane becoming invasive cancer (Figure 14). As this is considered a precursor to cancer, clinical treatment is required.

Conclusion

Pathology uses microscopy to diagnosis human diseases. In the case of cancer, cell morphology reflects underlying genetic damage to what was once a normal cell. As genetic alterations accumulate, cell morphology becomes increasingly bizarre. The changes described in this chapter – alterations in polarity or nucleus to cytoplasmic ratio, emergence of prominent nucleoli, increased mitotic figures, and pleomorphism – all are ultimately due to mutations. Additional cell abnormalities lead to the ability of a neoplasm to invade tissues or metastasize to distant locations. Pathologic review of tissue specimens is able to distinguish between aberrant growth of tissue confined to appropriate anatomic boundaries in the region of the organ of origin and metastatic spread. Increasingly pathologists are also using molecular studies of tissue to help guide diagnosis of cancer. Ultimately a pathologist uses her tools to translate the underlying genetic damage of cells into a clinical diagnosis.

Thought Questions

1. A 47 year old woman has suspicious calcifications found in her left breast on mammogram. A biopsy of the area shows ductal carcinoma in situ. What can you tell her about how this differs from invasive ductal carcinoma? If untreated, will it become an invasive cancer?

Expert Answer

2. Understanding the pathogenesis of cancers has lead to better detection methods such as pap smear screening with HPV testing. Consider how we have applied this information to prevent cervical cancer. Can this technology be applied to other cancers, and why?

Expert Answer

Glossary

Angiogenesis- Formation of new blood vessels

Apoptosis- genetically determined programmed cell death

Barrett's esophagus- Intestinal metaplasia of the distal esophagus

Grade (of a malignancy)– Numerical assessment for differentiation; three tiers: low grade (grade 1 of 3) appears similar to normal, moderate grade (grade 2 of 3) and high grade (grade 3 of 3).

Hyperplasia- Increase in number of normal cells in a tissue

Metastases- Tumors growing in an organ remote from the primary tumor

MDM2 – a protein which, when bound to p53 down regulates the p53 tumor suppressor function, thereby permitting cell division

Pathology- The study of disease

Prefixes:

Adeno- glands

Astro- deriving from astrocytes, non neurons in centrala nervous tissue

Chondro- cartilage

Glio- arising from glial cells, also non-neuron cells in central nervous system

Leio- smooth muscle

Myo- muscle

Osteo- bones

Rhabdo-derived from skeletal muscle

Sarc- "flesh", refers to soft tissue

Stroma- Connective tissue framework of an anatomic structure, usually an organ

Tumor- Swelling (not necessarily neoplastic)

Well differentiated- Resembles normal tissue

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