Classification of Tumors

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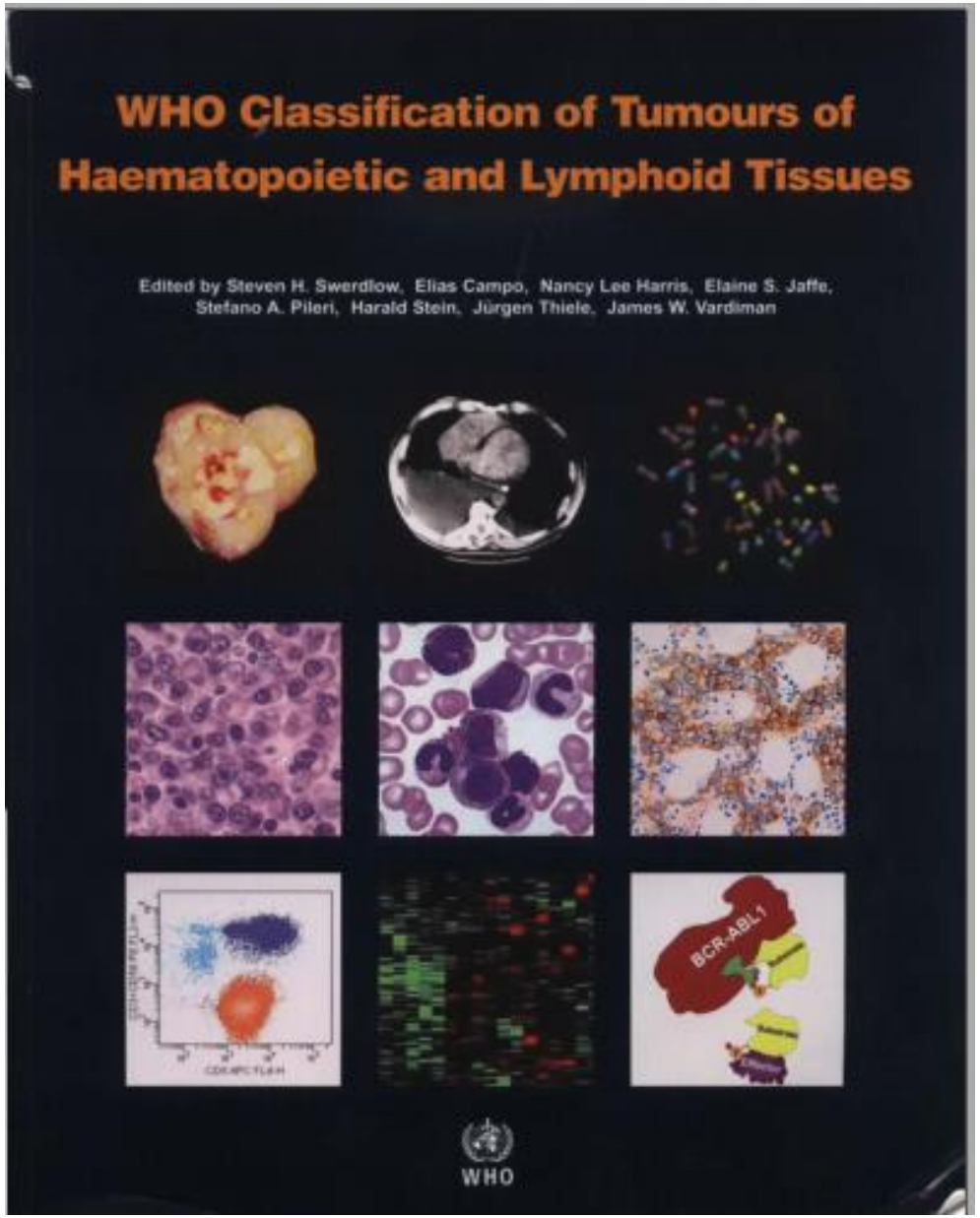

Blastic plasmacytoid dendritic cell neoplasm

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Definition

Blastic plasmacytoid dendritic cell (BPDC) neoplasm is a clinically aggressive tumour derived from the precursors of plasmacytoid dendritic cells (also known as professional type 1 interferon producing cells or plasmacytoid monocytes), with a high frequency of cutaneous and bone marrow (BM) involvement and leukaemic dissemination.

ICD-O code 9727/3

Synonyms

Blastic NK-cell lymphoma {1039}, agranular CD4+ natural killer cell leukaemia {277}, blastic natural killer leukaemia/lymphoma {576}, agranular CD4+CD56+ haematodermic neoplasm {1736}/tumour {920}.

Epidemiology

This is a rare form of haematologic neoplasm, without any known racial or ethnic predilection. It has a male/female ratio of

Sites of involvement

The disease tends to involve multiple sites, with a predilection for skin (almost 100% of cases), followed by BM and peripheral blood (PB)(60–90%), and lymph nodes (40–50%) {920, 1735}.

Clinical features

The patients usually present with asymptomatic solitary or multiple skin lesions that can be nodules, plaques, or bruise-like areas. Regional lymphadenopathy at presentation is common (20%); PB and BM involvement can be minimal at presentation, but invariably develops with progression of disease. Cytopenias (especially thrombocytopenia) can occur at diagnosis, and in a minority of cases can be severe, indicating BM failure {702, 920}. Following initial response to chemotherapy, relapses invariably occur, involving skin alone, or skin associated with other sites, including soft tissues and the central nervous system. In most cases a fulminant leukaemic phase ultimately leukaemia) with massive nodal or extranodal localization of plasmacytoid dendritic cells, in which the plasmacytoid dendritic cells are morphologically mature and CD56 negative {2335}.

Morphology

BPDC is usually characterized by a diffuse, monomorphous infiltrate of medium-sized blast cells with irregular nuclei, fine chromatin and one to several small nucleoli. The cytoplasm is usually scant and appears grey-blue and agranular on Giemsa stain. Mitoses are variable in number, but rarely prominent; angioinvasion and coagulative necrosis are absent. In cutaneous infiltrates, tumour cells predominantly occupy the dermis, sparing the epidermis, but eventually extending to subcutaneous fat. Lymph nodes are diffusely involved in the interfollicular areas and medulla, with a leukaemic pattern of infiltration.

Bone marrow biopsy may show either a mild interstitial infiltrate only detectable by

Objectives

- **Define the terms: neoplasm, tumor and oncology.**
- **Classify tumors into benign and malignant.**
- **Understand the concepts governing the classification of tumors and their nomenclature.**
- **Define hamartoma, teratoma, choristoma and heterotropic rest.**

General Definition

- ***Neoplasia*** **means "new growth,"**
- ***Neoplasm is often referred to as a tumor.***
- ***Oncology*** **(Greek *oncos* = tumor) is the study of tumors or neoplasms.**

Classification of Tumors

- ***Benign*** **when its microscopic and gross characteristics are considered relatively innocent, implying that it will remain localized, it cannot spread to other sites, and it is generally amenable to local surgical removal; the patient generally survives.**

- ***Malignant*** **implies that the lesion can invade and destroy adjacent structures and spread to distant sites (metastasize) to cause death.**

Similarity

- **All tumors, benign and malignant, have two basic components:**

1. **Clonal neoplastic cells that constitute their *parenchyma*.**

1. **Reactive *stroma* made up of connective tissue, blood vessels, and variable numbers of macrophages and lymphocytes.**

Important of Stroma

- **Although the neoplastic cells largely determine a tumor's behavior and pathologic consequences, their growth and evolution is critically dependent on their stroma.**
- **An adequate stromal blood supply is requisite for the tumor cells to live and divide.**

- **The nomenclature of tumors and their biologic behavior are based primarily on the parenchymal component.**

Benign Tumors

- **In general, benign tumors are designated by attaching the suffix -*oma* to the cell of origin.**

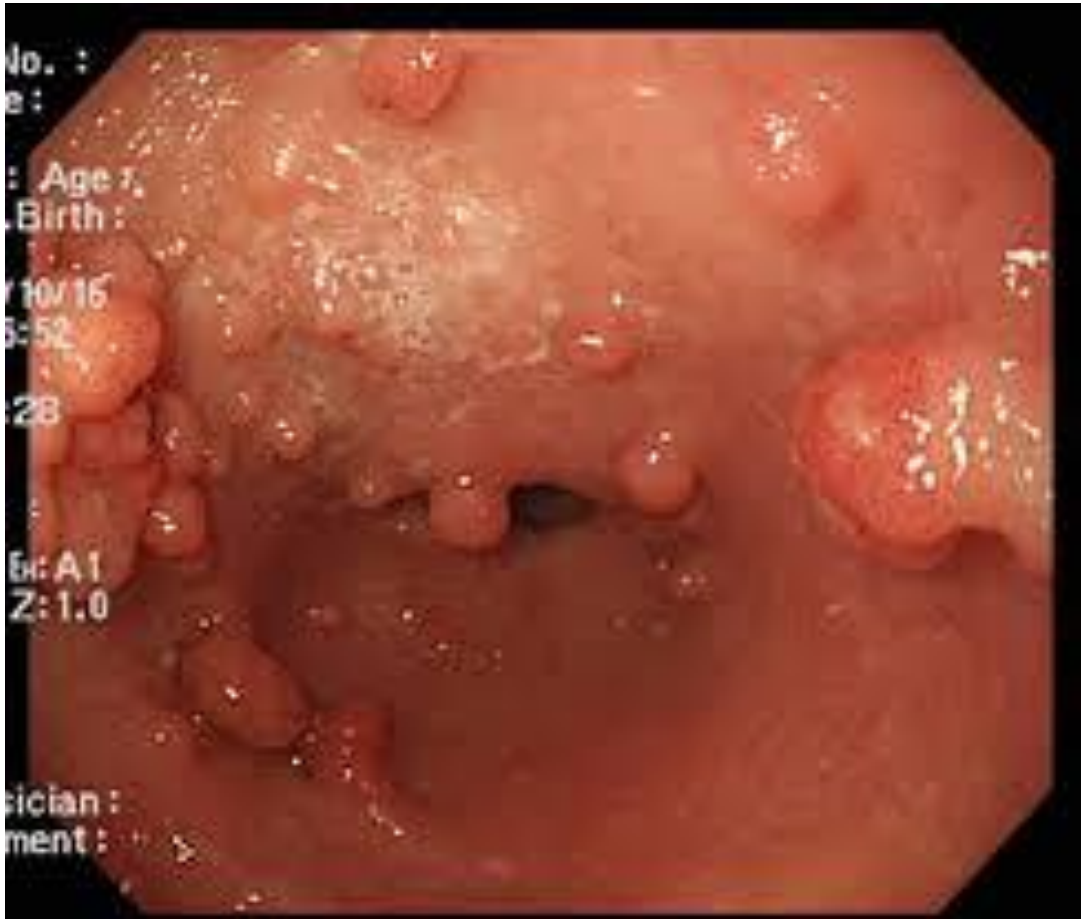
- **Tumors of mesenchymal cells generally follow this rule.**
- **For example, a benign tumor arising in fibrous tissue is called a *fibroma*, whereas a benign cartilaginous tumor is a *chondroma.***
- ***Adenoma* is applied to a benign epithelial neoplasm derived from glands, although they may or may not form glandular structures.**

Benign Tumors

- **Benign epithelial neoplasms producing microscopically or macroscopically visible finger-like or warty projections from epithelial surfaces are referred to as *papillomas*.**

- **Those that form large cystic masses, as in the ovary, are referred to as *cystadenomas*. Some tumors produce papillary patterns that protrude into cystic spaces and are called *papillary cystadenomas*.**
- ***Polyp*** is a mass that projects above a mucosal surface **produces a macroscopically visible projection above a mucosal surface .**

polyp



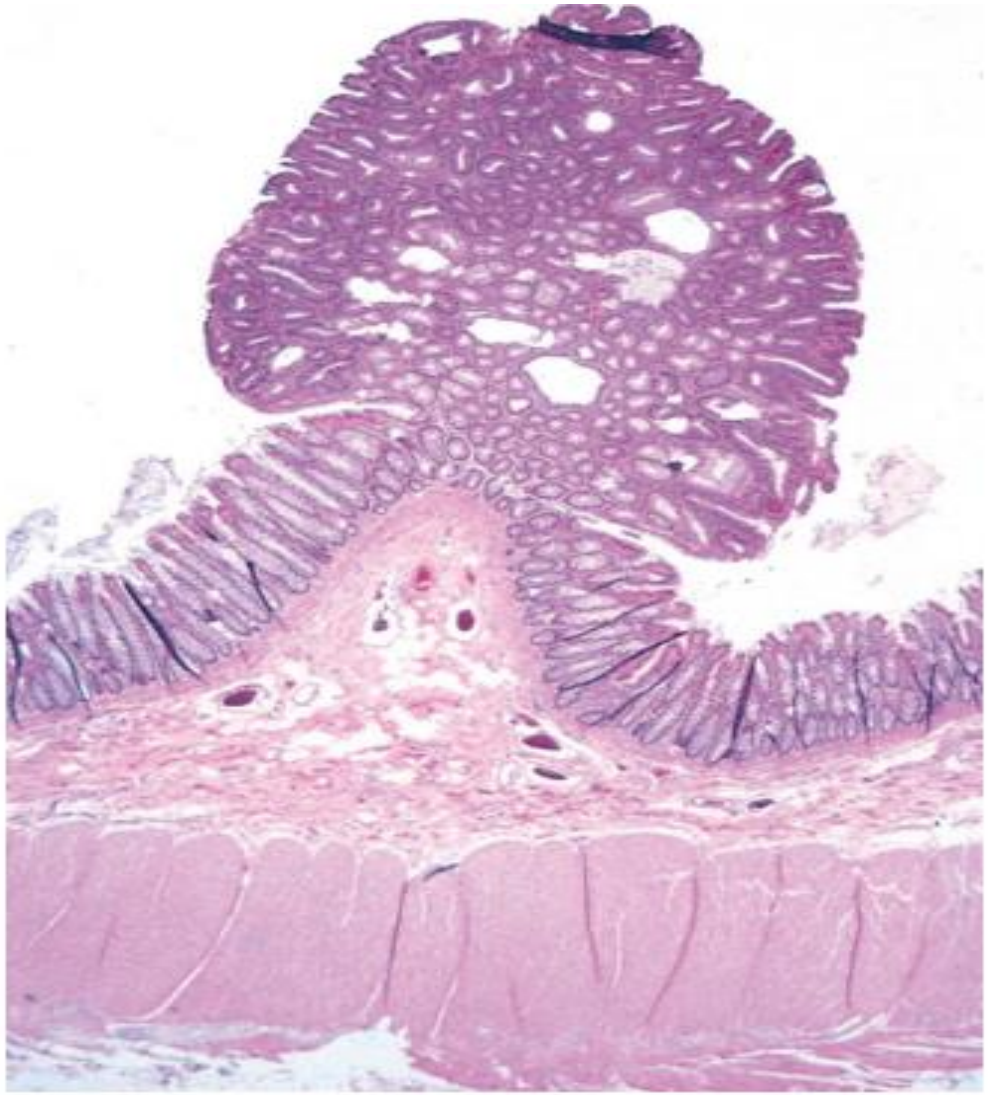


Figure 5–1 Colonic polyp. This glandular tumor (adenoma) is seen projecting into the colonic lumen. The polyp is attached to the mucosa by a distinct stalk.

Malignant Tumors

- ***Malignant tumors arising in mesenchymal tissue are usually called sarcomas .***

- **Malignant neoplasms of epithelial cell origin, derived from any of the three germ layers, are called *carcinomas*.**

- ***Squamous cell carcinoma* would denote a cancer in which the tumor cells resemble stratified squamous epithelium.**
- ***adenocarcinoma* denotes a lesion in which the neoplastic epithelial cells grow in glandular patterns.**

Malignant Tumors

- **Sometimes the tissue or organ of origin can be identified, as in the designation of renal cell adenocarcinoma. Not infrequently, however, a cancer is composed of undifferentiated cells of unknown tissue origin, and must be designated merely as an undifferentiated malignant tumor.**

Malignant Tumors

- **In many benign and malignant neoplasms, the parenchymal cells bear a close resemblance to each other, as though all were derived from a single cell. However,**

- **Divergent differentiation of a single neoplastic clone along two lineages creates what are called *mixed tumors*. The best example of this is the *mixed tumor of salivary gland origin*. These tumors contain epithelial components scattered within a myxoid stroma that sometimes contains islands of cartilage or bone . All these elements, it is believed, arise from a single clone capable of giving rise to epithelial and myoepithelial cells; thus, the preferred designation of these neoplasms is *pleomorphic adenoma*.**

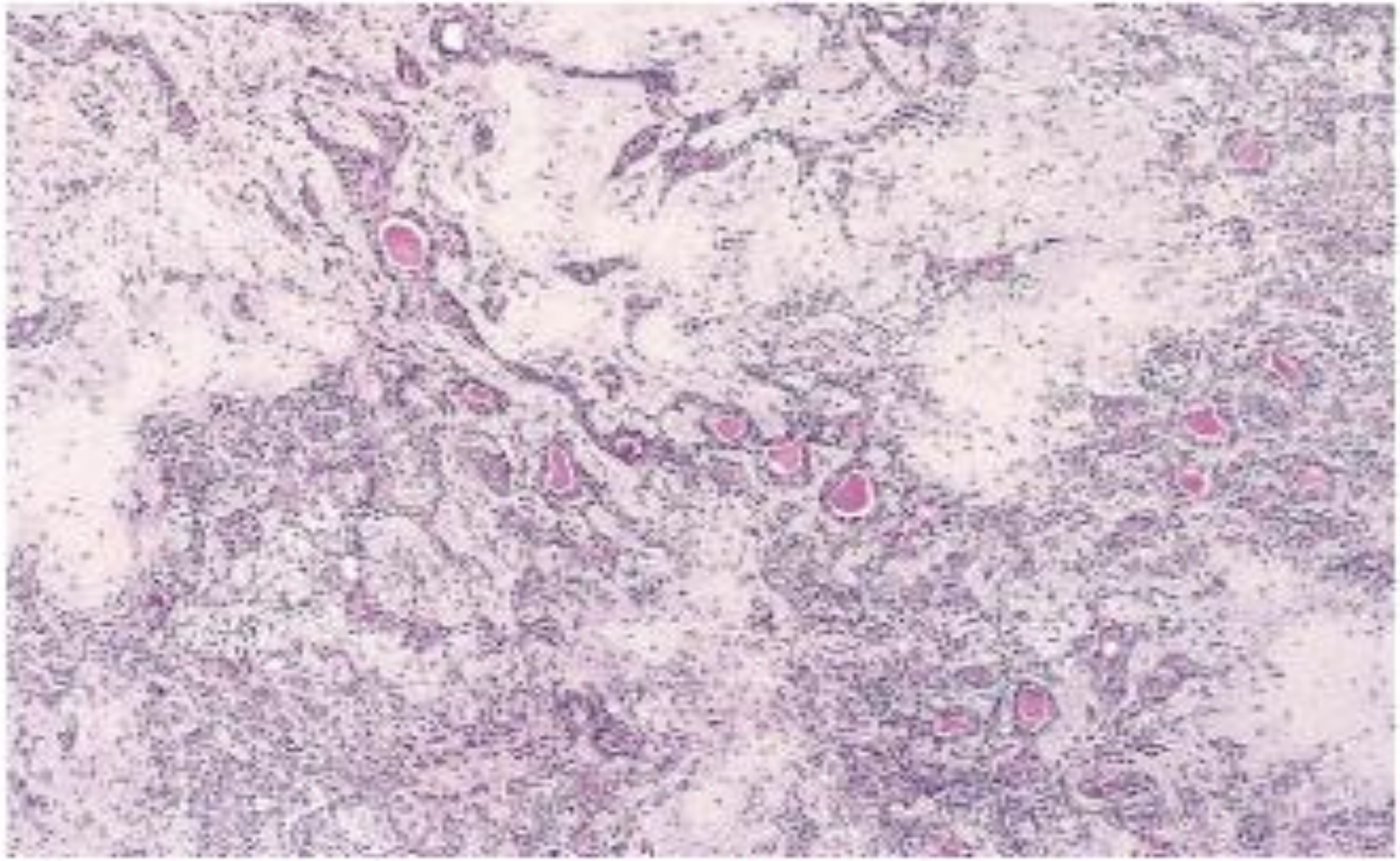
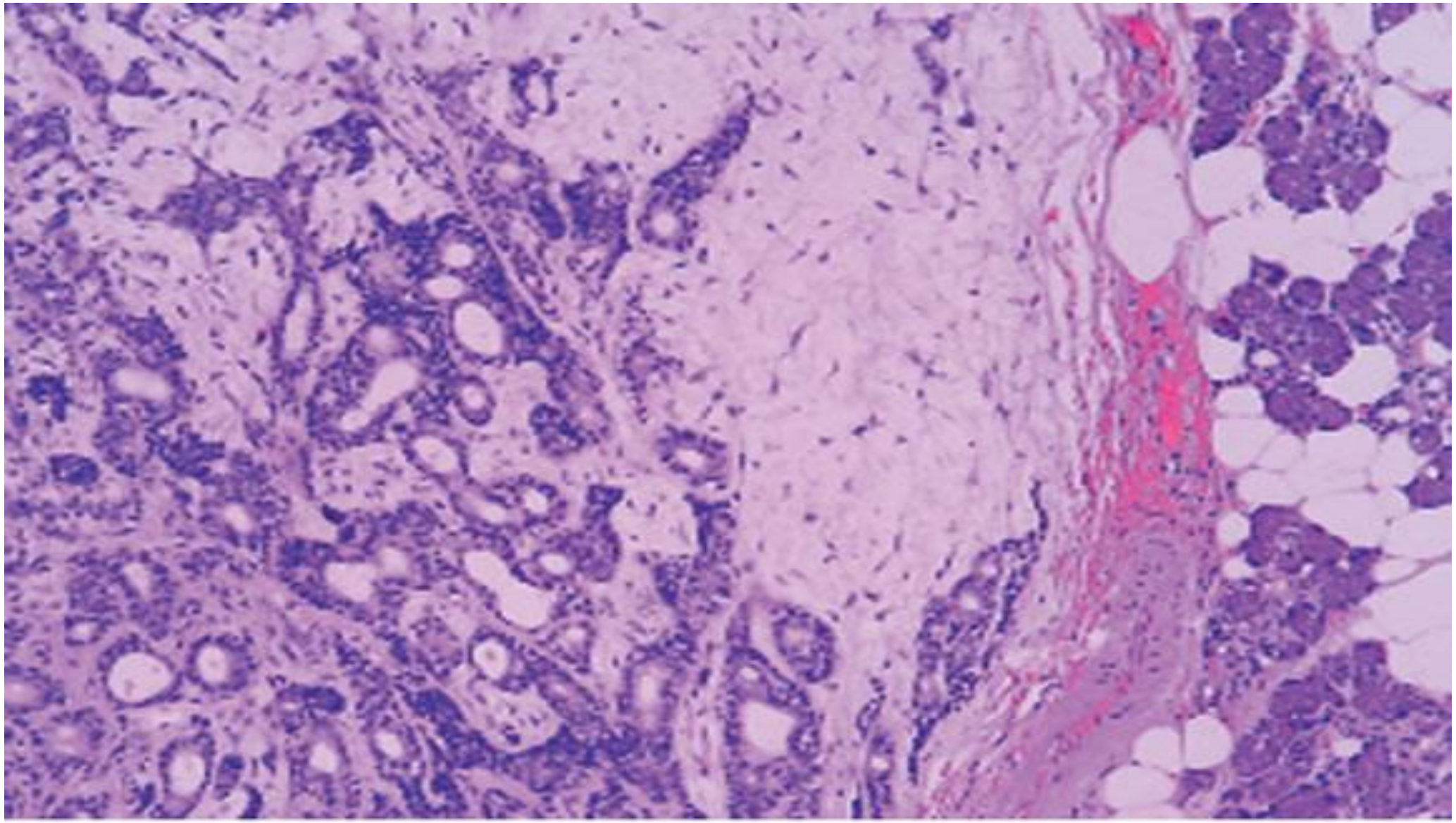


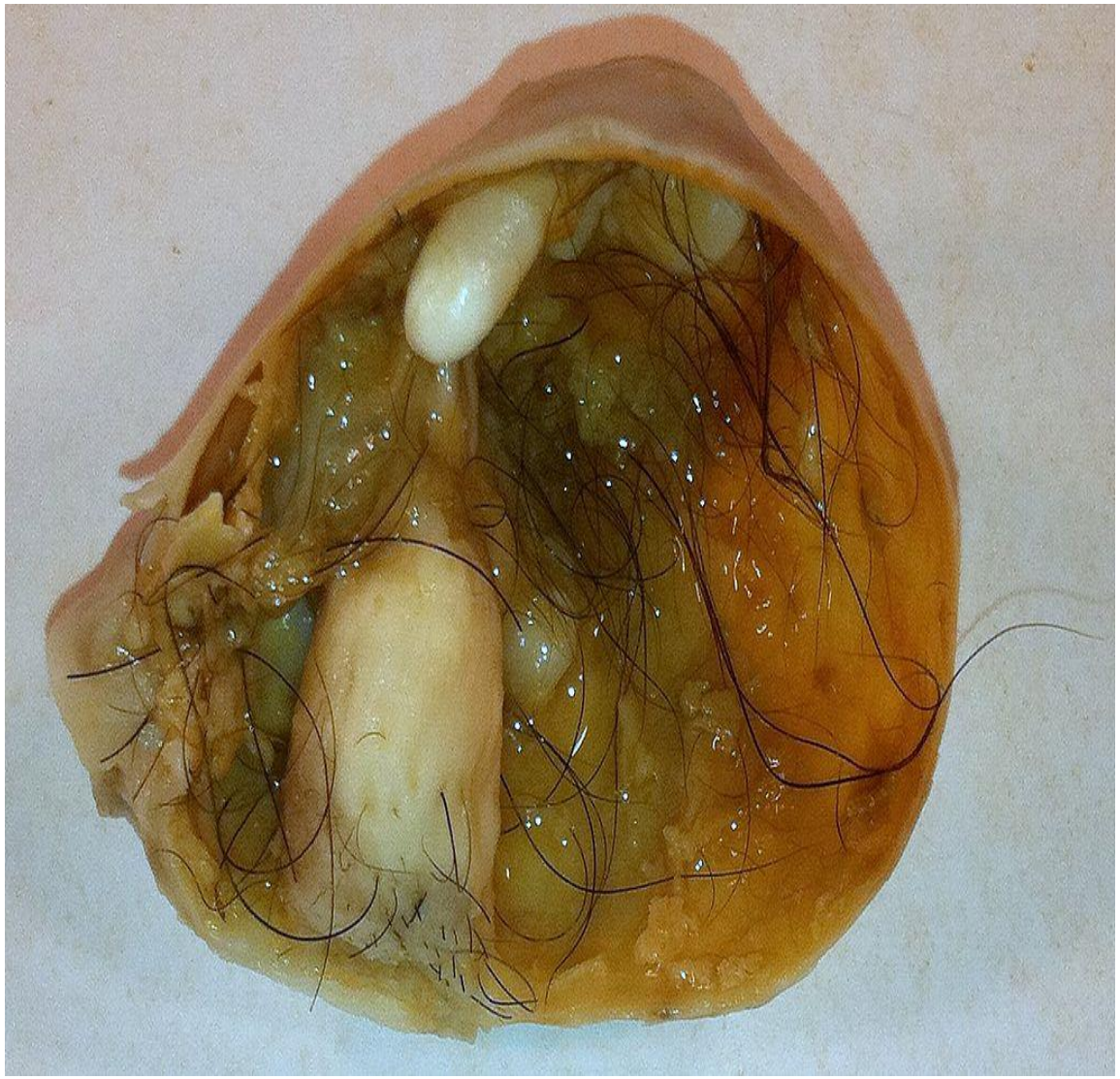
Figure 5–2 Mixed tumor of the parotid gland contains epithelial cells forming ducts and myxoid stroma that resembles cartilage.

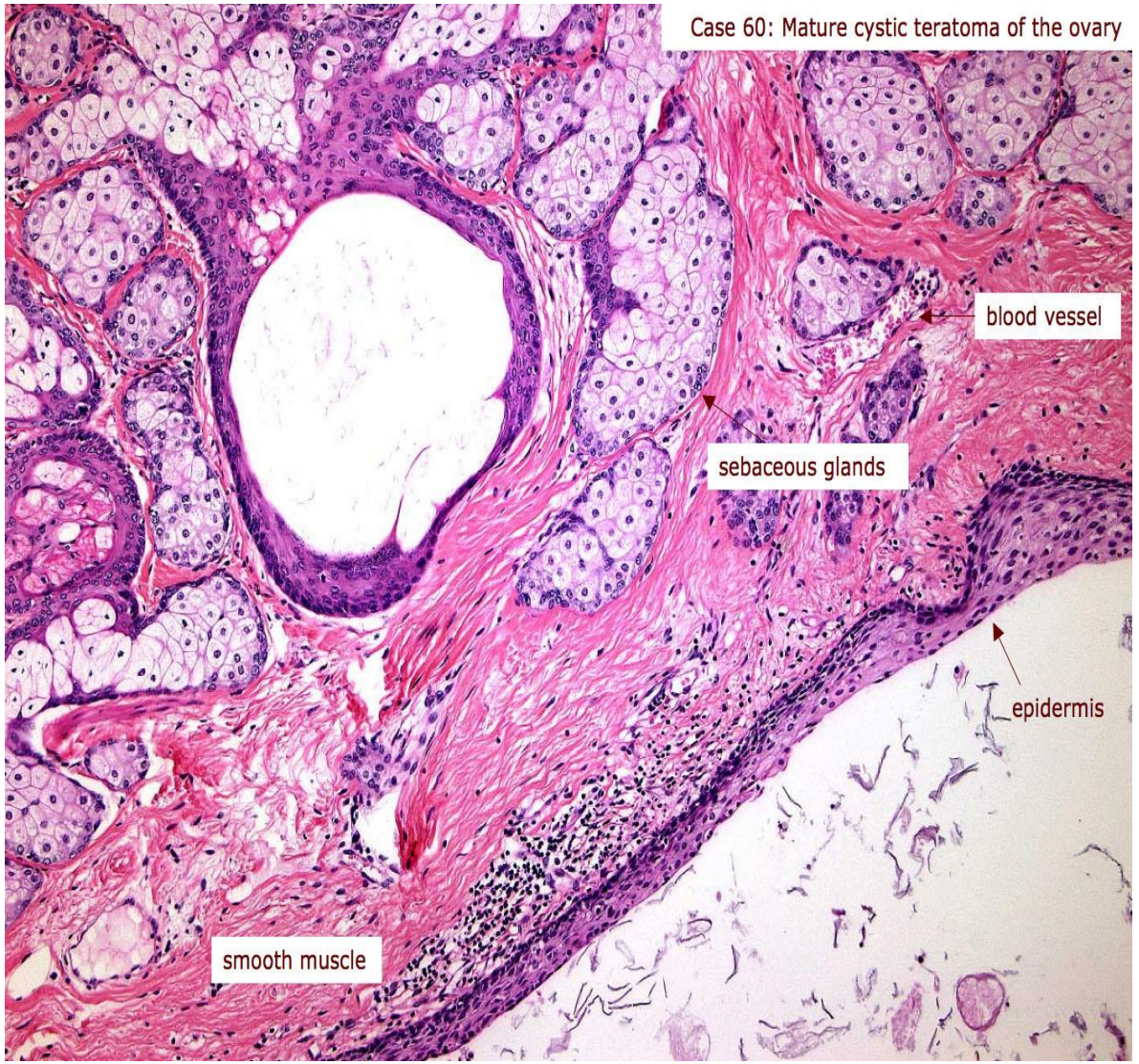
(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)



Teratoma

- ***Teratoma***, is a special type of mixed tumor that contains recognizable mature or immature cells or tissues representative of more than one germ cell layer and sometimes all three.
- Originate from **totipotential cells** such as those normally present in the ovary and testis and sometimes abnormally present in sequestered midline embryonic rests. Such cells have the capacity to differentiate into any of the cell types found in the adult body.
- When all the component parts are well differentiated, it is a *benign (mature) teratoma*; when less well differentiated, it is an immature, potentially or overtly, *malignant teratoma*.




Case 60: Mature cystic teratoma of the ovary
blood vessel
sebaceous glands
epidermis
smooth muscle

Critical Exceptions

- Benign-sounding designations such as **lymphoma, melanoma, mesothelioma, and seminoma** have been used for certain malignant neoplasms.

Critical Exceptions

- ***Hamartomas*** present as disorganized but benign-appearing masses composed of cells indigenous to the particular site. For example, pulmonary chondroid hamartoma contains islands of disorganized, but histologically normal cartilage, bronchi, and vessels.

- Traditionally been considered developmental malformations, but some genetic studies have shown the presence of acquired translocations, suggesting a neoplastic origin.

Critical Exceptions

- ***Choristoma*** is a congenital anomaly consisting of a heterotopic rest of cells. For example, a small nodule of well-developed and normally organized pancreatic tissue may be found in the submucosa of the stomach, duodenum, or small intestine. It has usual trivial significance.

Summary

- Although the terminology of neoplasms is regrettably not simple, a firm grasp of the nomenclature is important because it is **the language** by which the nature and significance of tumors are categorized.

- Remember the exceptions…

Table 5–1 Nomenclature of Tumors

Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma

Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Urothelial papilloma	Urothelial carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma
More Than One Neoplastic Cell Type—Mixed Tumors, Usually Derived from One Germ Cell Layer		
Salivary glands	Pleomorphic adenoma (mixed tumor of salivary gland)	Malignant mixed tumor of salivary gland
Renal anlage		Wilms tumor
More Than One Neoplastic Cell Type Derived from More Than One Germ Cell Layer—Teratogenous		
Totipotential cells in gonads or in embryonic rests	Mature teratoma, dermoid cyst	Immature teratoma, teratocarcinoma

Pathology

- **Fellowship of RCPA for Medical Graduates (apart from diplomas):**
  - **Anatomical Pathology: (SP/HP), (in NA other clinical pathology).**
  - **Chemical Pathology (BC, MC,…).**
  - **Clinical Pathology.**
  - **Forensic Pathology.**
  - **General Pathology.**
  - **Genetic Pathology.**
  - **Haematology.**
  - **Immunopathology.**
  - **Microbiology.**

Hematology & Immunology

- Clinical: Medicine or Pediatric.
- Pathology: NA or UK/AU, Residency, PhD.
- Research: transitional/basic…

KSF Pathology Programs

- Hematopathology & Blood Transfusion:

  - ❖ Bone Marrow report: Leukemia & some lymphoma and others.
  - ❖ Peripheral blood smear and other routine hematology lab (core lab): cytology & HE.
  - ❖ Coagulation tests and anti-coagulant clinic:
  - ❖ Transfusion Medicine & cellular therapy in future.
  - ❖Laboratory administration and quality management.

Properties of Benign and Malignant Neoplasm

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Objectives

- **Define the terms: differentiation and anaplasia.**
- **Identify the morphological changes that differentiate between benign and malignant tumors.**
- **Understand the terms metaplasia, dysplasia and carcinoma in situ.**
- **Compare between benign and malignant tumors in terms of differentiation, rate of growth, local invasion and metastases.**
- **List the pathways by which malignant tumors spread.**

How to differentiate

- ***There are four fundamental features by which benign and malignant tumors can be distinguished:***
  1. *Differentiation and anaplasia.*
  2. *Rate of growth.*
  3. *Local invasion.*
  4. *Metastasis*.

Differentiation and Anaplasia

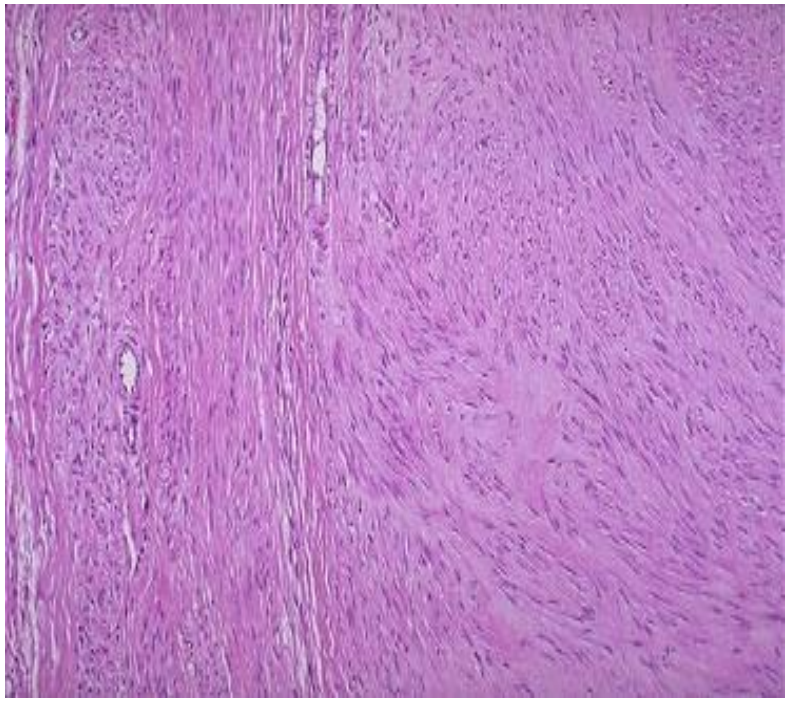
- Differentiation and anaplasia are characteristics seen only in the parenchymal cells that constitute the transformed elements of neoplasms.

- The differentiation of parenchymal tumor cells refers to the extent to which they resemble their normal forebears morphologically and functionally.

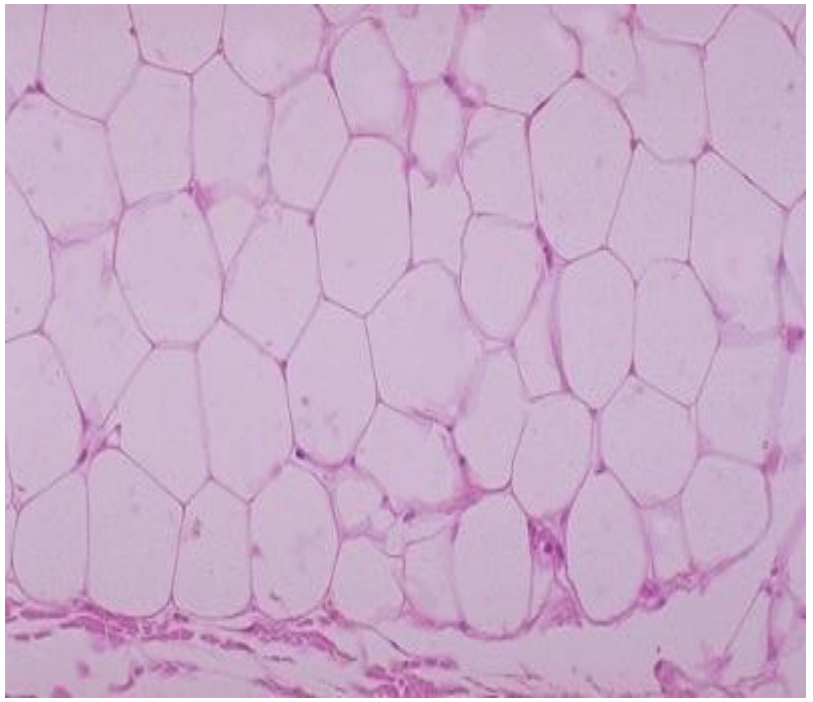
Differentiation and Anaplasia

- Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.
- A lipoma is made up of mature fat cells laden with cytoplasmic lipid vacuoles
- a chondroma is made up of mature cartilage cells that synthesize their usual cartilaginous matrix
- In well-differentiated benign tumors, mitoses are usually rare and are of normal configuration.

Leiomyoma



Lipoma



Differentiation and Anaplasia

- Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation, from well differentiated to completely undifferentiated.

- Between the two extremes lie tumors loosely referred to as *moderately well differentiated*.

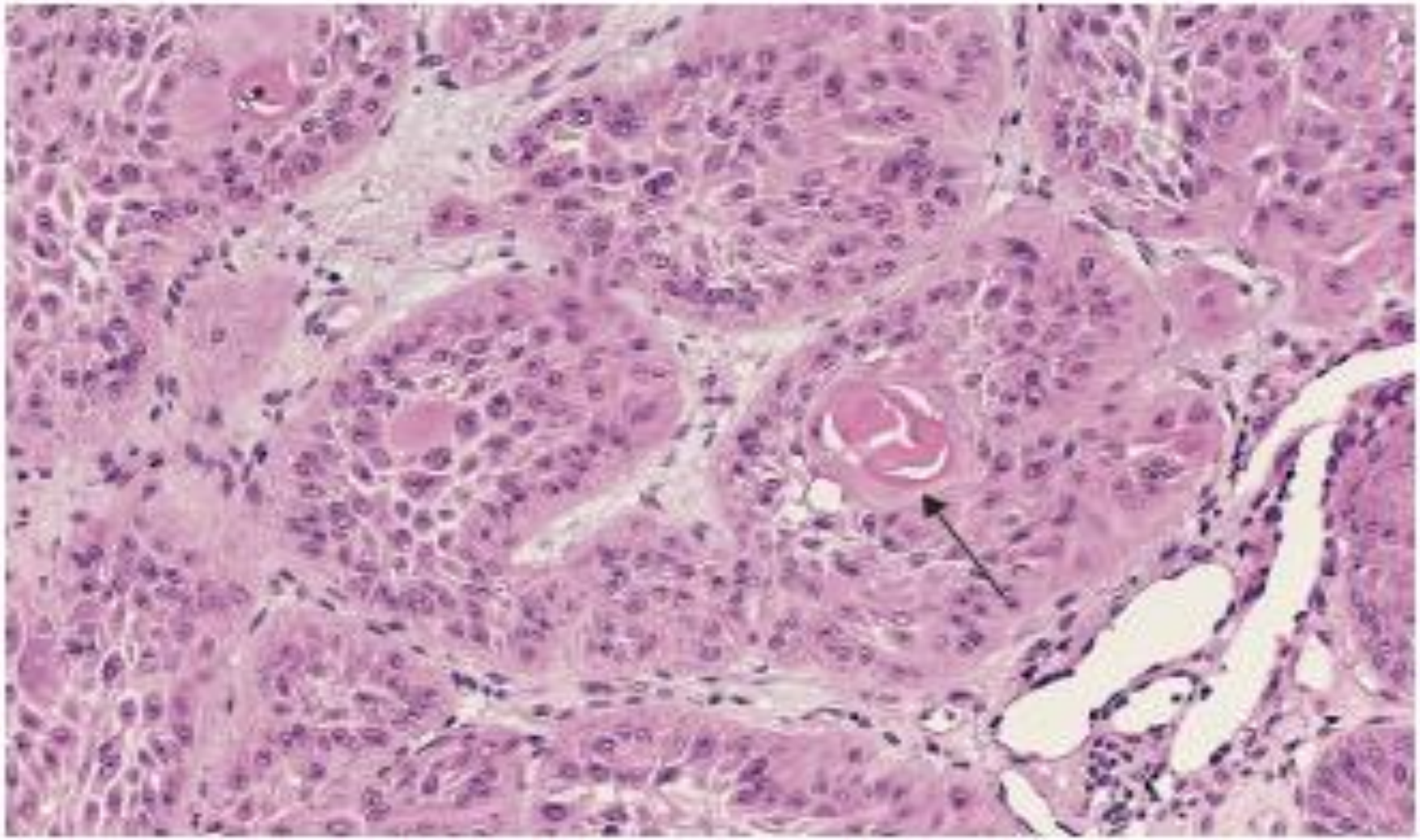
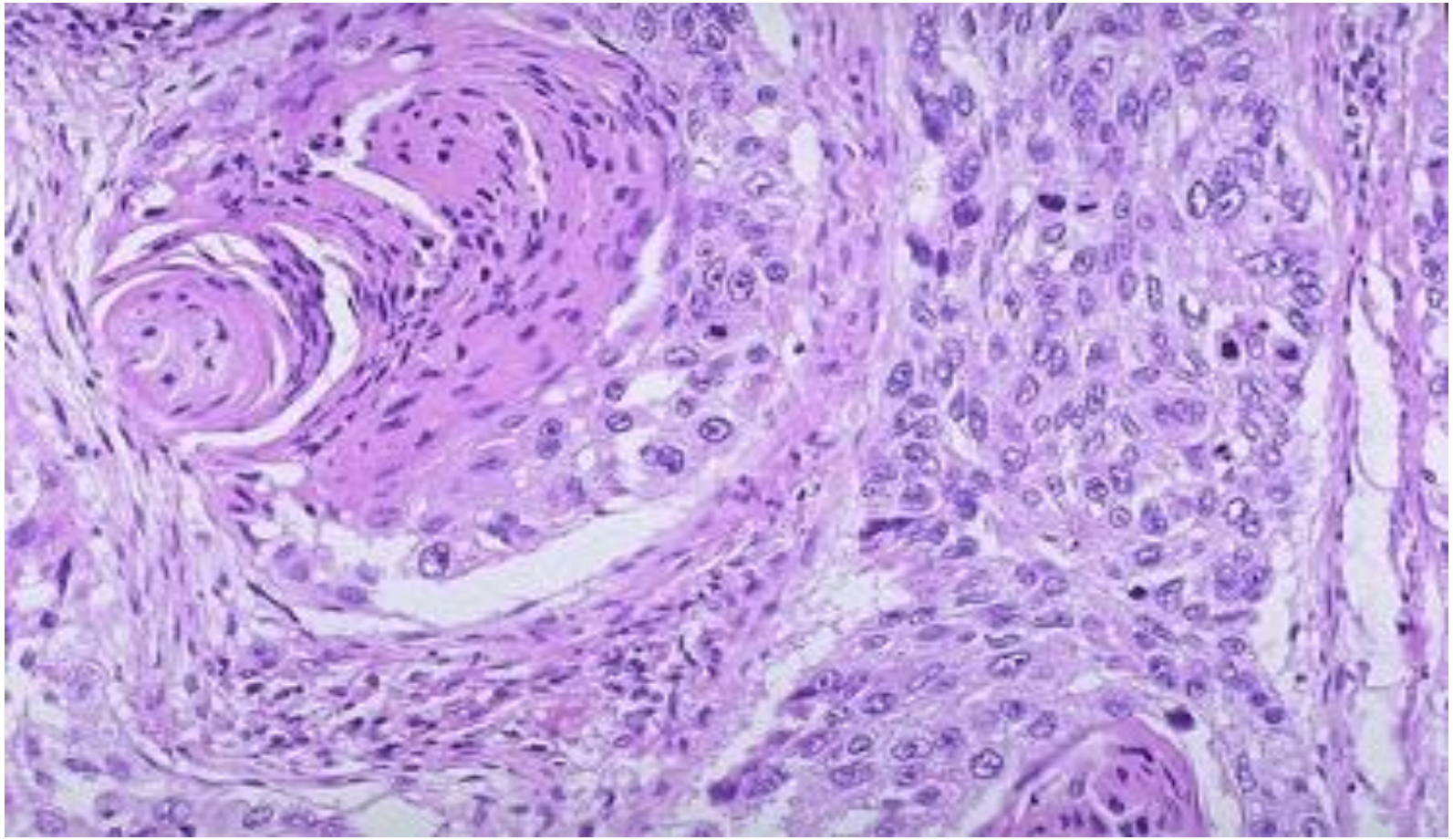


Figure 5–3 Well-differentiated squamous cell carcinoma of the skin. The tumor cells are strikingly similar to normal squamous epithelial cells, with intercellular bridges and nests of keratin *(arrow)*.

(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

Squamous Cell Carcinoma



Differentiation and Anaplasia

- The stroma carrying the blood supply is crucial to the growth of tumors but does not aid in the separation of benign from malignant ones.
- The amount of stromal connective tissue does determine the consistency of a neoplasm. Certain cancers induce a dense, abundant fibrous stroma (***desmoplasia***), making them hard, so-called ***scirrhous*** tumors.

Differentiation and Anaplasia

- Malignant neoplasms that are composed of undifferentiated cells are said to be *anaplastic*.

- ***Anaplasia***: Lack of differentiation, is considered a hallmark of malignancy.

Anaplastic cells

- **Marked *pleomorphism*** variation in size and shape.
- The *nuclei are extremely* ***hyperchromatic*** (dark-staining) and large resulting in an increased **nuclear-to-cytoplasmic ratio** that may approach 1:1 instead of the normal 1 : 4 or 1 : 6.
- ***Giant cells*** that are considerably larger than their neighbors may be formed and possess either one enormous nucleus or several nuclei.
- *Anaplastic* ***nuclei are variable and bizarre*** *in size and shape*. The **chromatin is coarse and clumped**, and **nucleoli may be of astounding size**.
- ***Mitoses*** *often are* **numerous** *and distinctly* **atypical**; ***tripolar or quadripolar*** mitotic figures.
- They **lose normal polarity**: fail to develop recognizable patterns of orientation to one another.

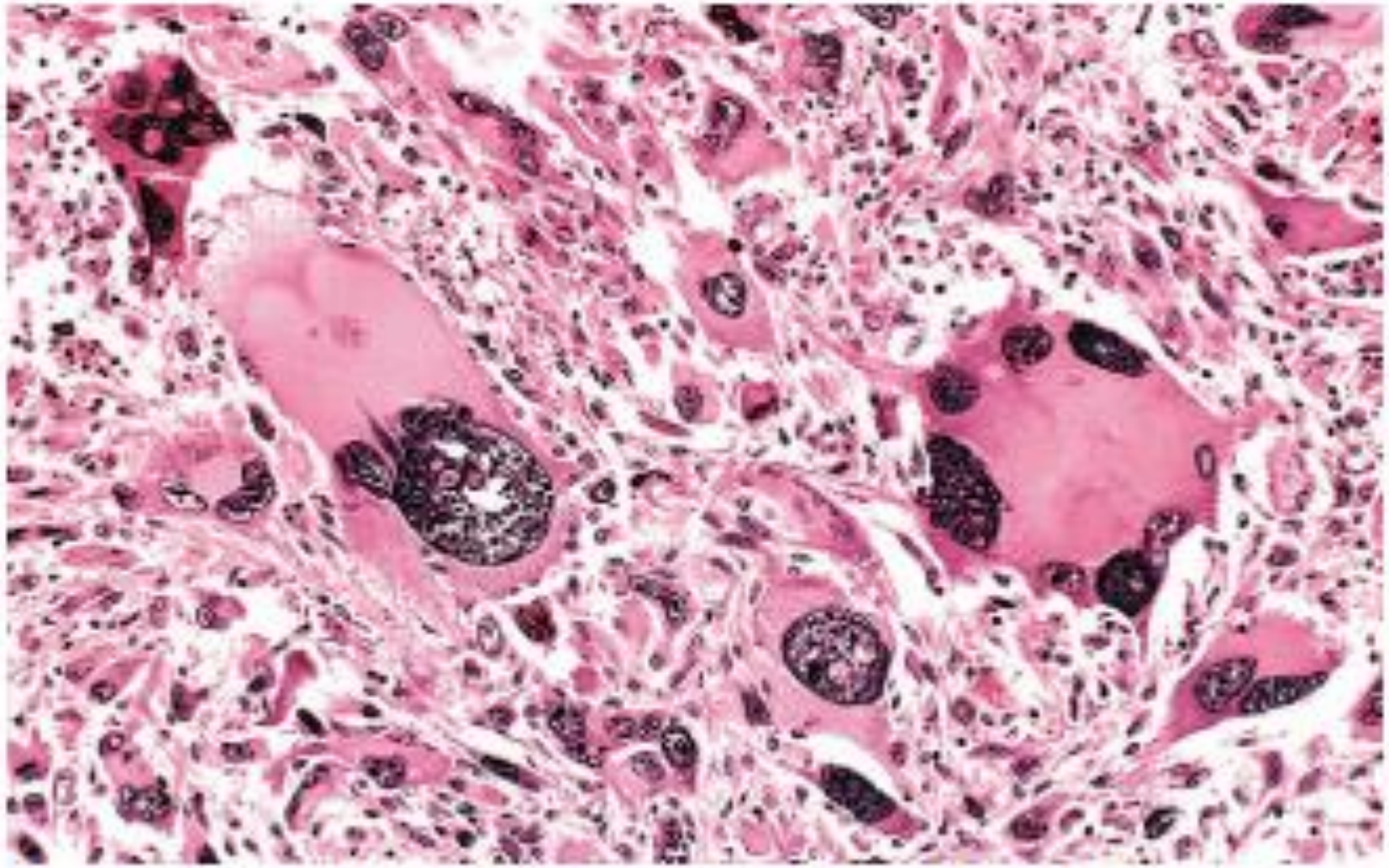


Figure 5–4 Anaplastic tumor of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei, and tumor giant cells.

(Courtesy of Dr. Trace Worrell, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)

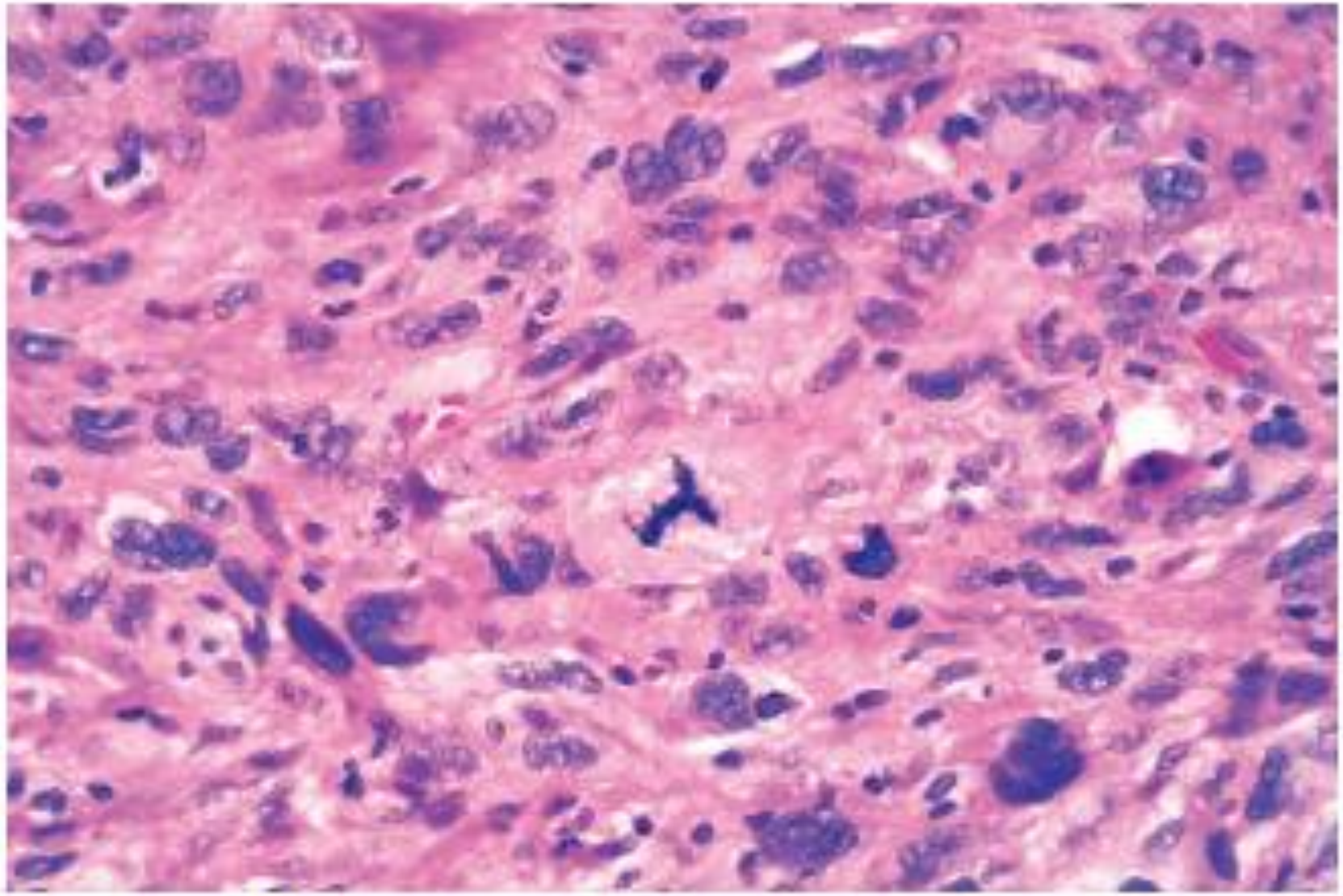
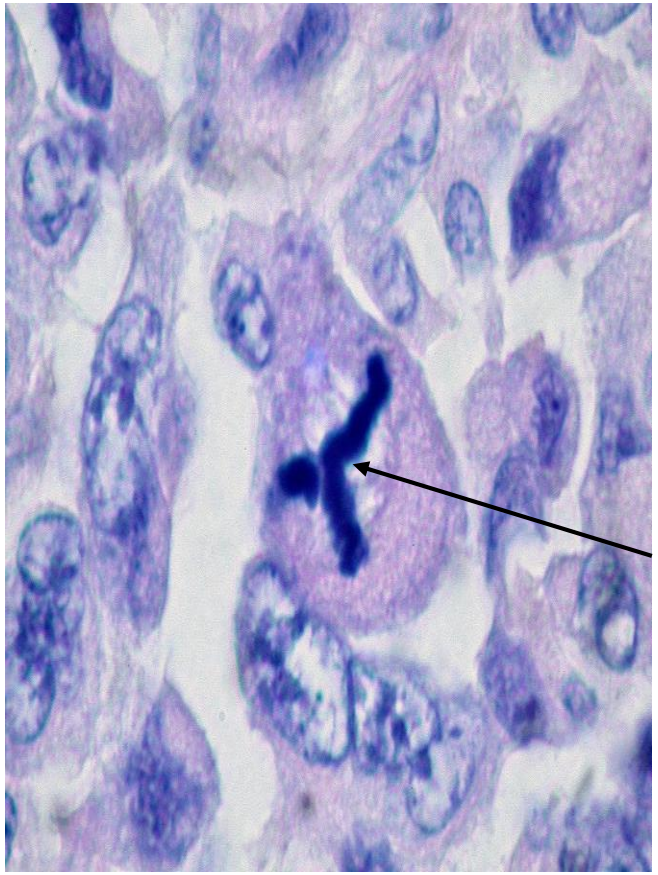
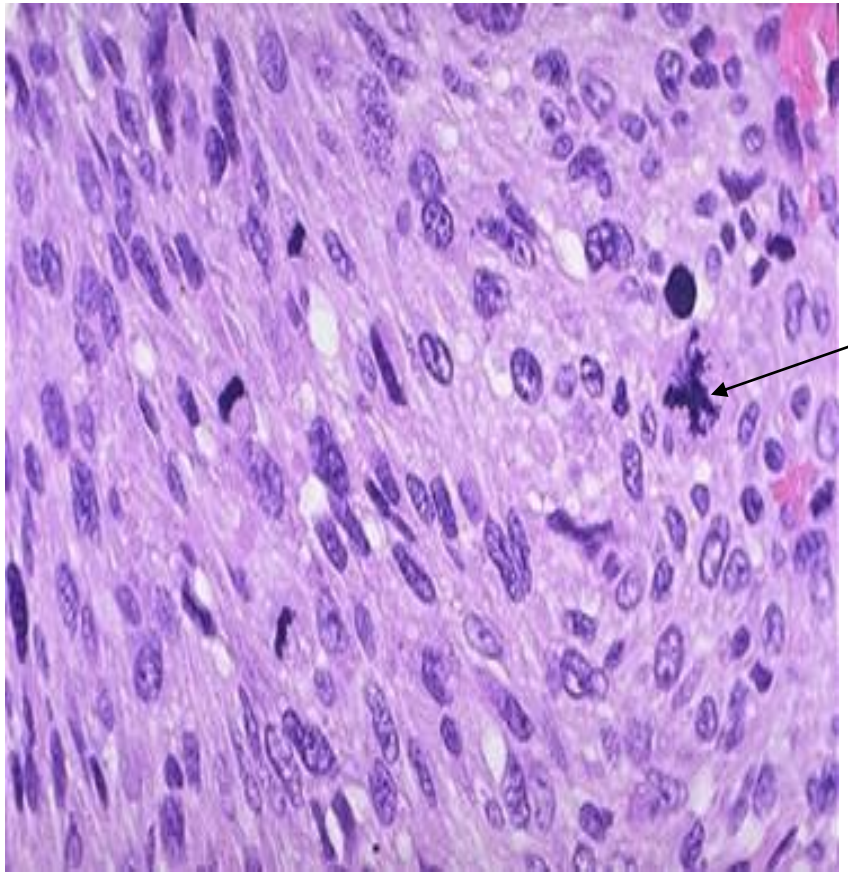
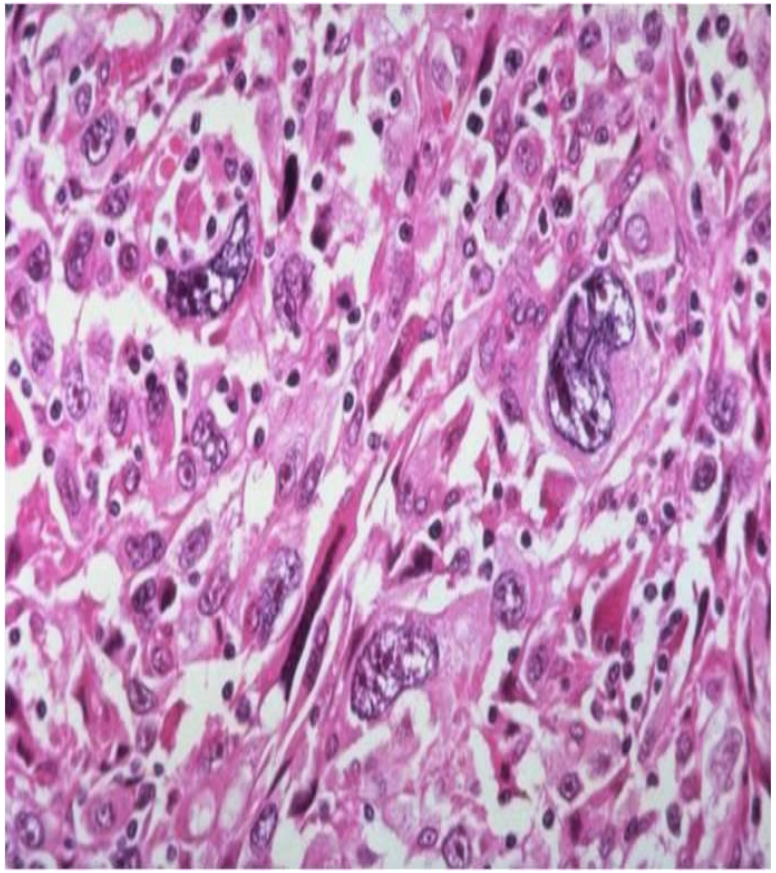


Figure 5–5 High-power detail view of anaplastic tumor cells shows cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.

Anaplasia







Differentiation and Anaplasia

- The more differentiated the tumor cell, the more completely it retains the functional capabilities of its normal counterparts.
- Some cancers may elaborate fetal proteins not produced by comparable cells in the adult. Cancers of nonendocrine origin may produce so-called ectopic hormones.
- *the more rapidly growing and the more anaplastic a tumor, the less likely it is to have specialized functional activity*.

Differentiation and Anaplasia

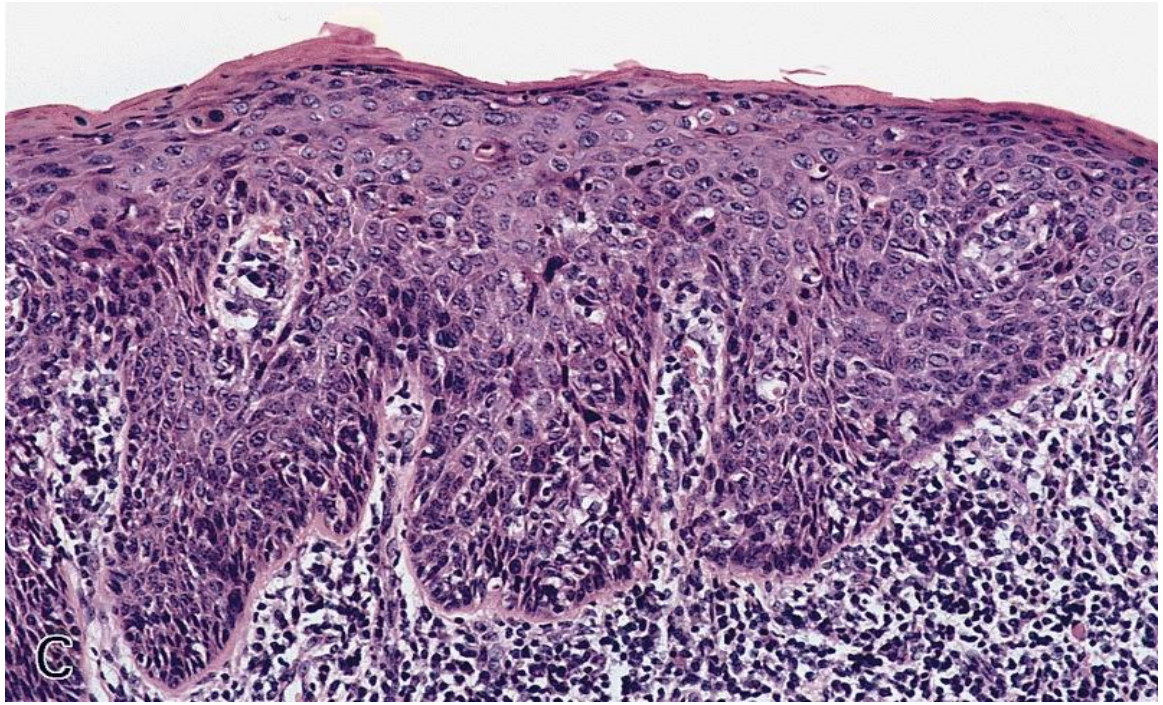
- ***Metaplasia.***
- ***Dysplasia*** is encountered principally in epithelial lesions. It is a *loss in the uniformity of individual cells and in their architectural orientation*.
- Dysplastic cells exhibit considerable pleomorphism and often possess hyperchromatic nuclei that are abnormally large for the size of the cell. Mitotic figures are more abundant than usual and frequently appear in abnormal locations within the epithelium.

Differentiation and Anaplasia

- The term dysplasia is not synonymous with cancer; mild to moderate dysplasias that do not involve the entire thickness of the epithelium sometimes regress completely, particularly if inciting causes are removed.

Carcinoma in situ

- When dysplastic changes are marked and involve the entire thickness of the epithelium, a pre invasive stage of cancer.



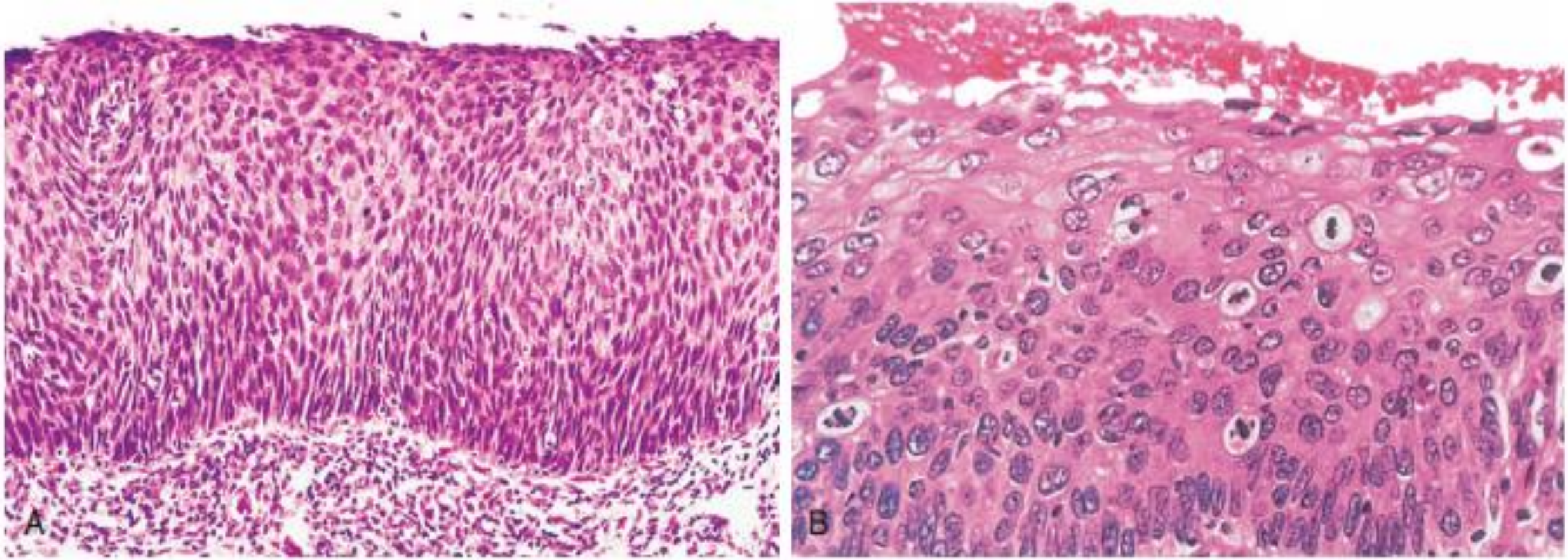


Figure 5–6 Carcinoma in situ. **A,** Low-power view shows that the entire thickness of the epithelium is replaced by atypical dysplastic cells. There is no orderly differentiation of squamous cells. The basement membrane is intact, and there is no tumor in the subepithelial stroma. **B,** High-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface. The intact basement membrane (*below*) is not seen in this section.

Rate of Growth

- Most benign tumors grow slowly, and most cancers grow much faster, eventually spreading locally and to distant sites (metastasizing) and causing death. T
- here are many exceptions to this generalization, however, and some benign tumors grow more rapidly than some cancers.

Rate of Growth

- *The rate of growth of malignant tumors usually correlates inversely with their level of differentiation*.
- Poorly differentiated tumors tend to grow more rapidly than do well-differentiated tumors.
- However, there is wide variation in the rate of growth. Some grow slowly for years and then enter a phase of rapid growth, signifying the emergence of an aggressive subclone of transformed cells. Others grow relatively slowly and steadily.
- Rapidly growing malignant tumors often contain central areas of ischemic necrosis, because the tumor blood supply, derived from the host, fails to keep pace with the oxygen needs of the expanding mass of cells.

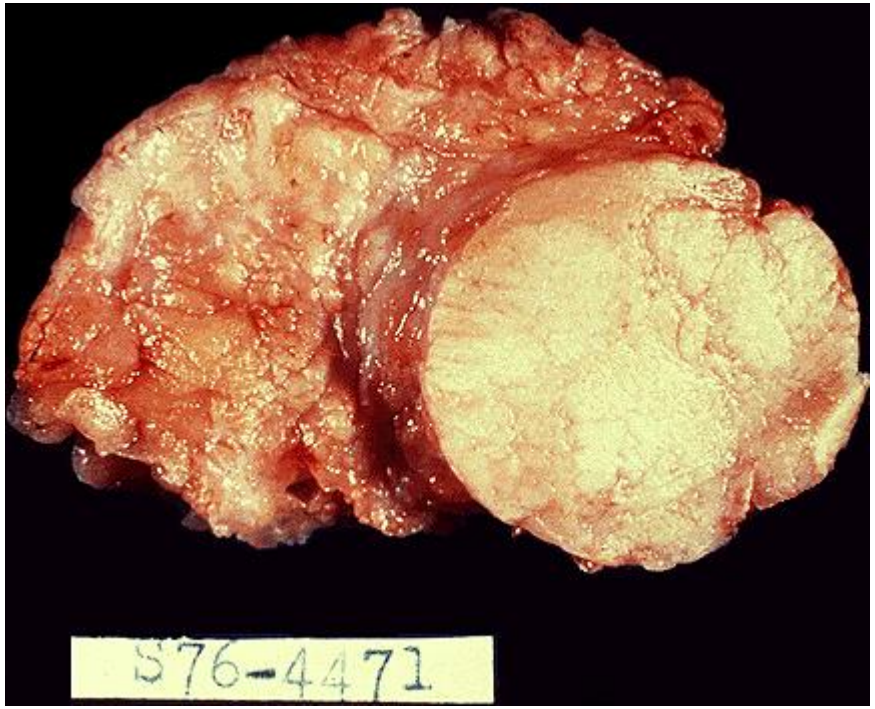
Rate of Growth

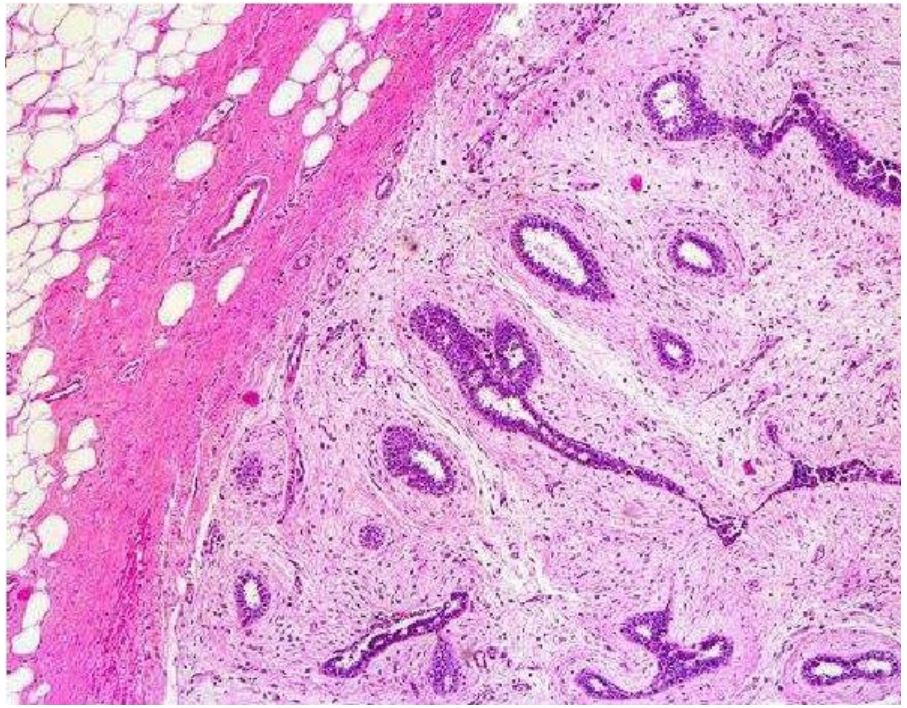
- ***Cancer Stem Cells and Lineages***
- The continued growth and maintenance of many tissues that contain short-lived cells, such as the formed elements of the blood and the epithelial cells of the gastrointestinal tract and skin, require a resident population of tissue stem cells that are long-lived and capable of self-renewal.
- Cancers are immortal and have limitless proliferative capacity, indicating that like normal tissues, they also must contain cells with “stemlike” properties.
- The cancer stem cell hypothesis posits that, in analogy with normal tissues, only a special subset of cells within tumors has the capacity for self-renewal. The concept of cancer stem cells has several important implications. Most notably, if cancer stem cells are essential for tumor persistence, it follows that these cells must be eliminated to cure the affected patient.
- Thus, the limited success of current therapies could be explained by their failure to kill the malignant stem cells that lie at the root of cancer

Local Invasion

- A benign neoplasm remains localized at its site of origin. It does not have the capacity to infiltrate, invade, or metastasize to distant sites, as do malignant neoplasms. For example, as adenomas slowly expand, most develop an enclosing fibrous capsule that separates them from the host tissue.
- *Not all benign neoplasms are encapsulated*.
- Although encapsulation is the rule in benign tumors, the lack of a capsule does not mean that a tumor is malignant.

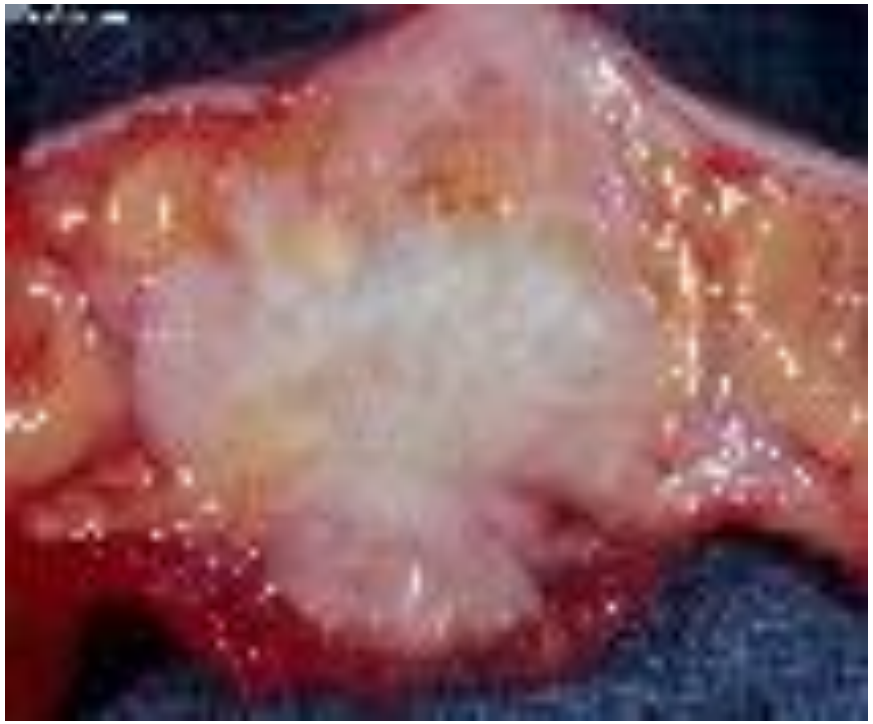
Local Invasion

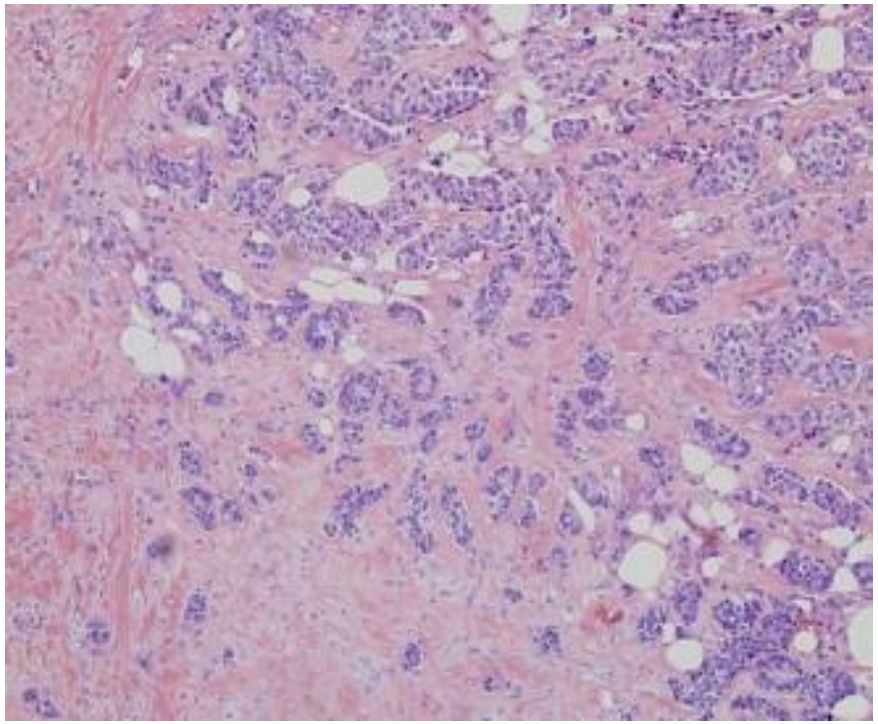




Local Invasion

- *Cancers grow by progressive infiltration, invasion, destruction, and penetration of the surrounding tissue*.
- They do not develop well-defined capsules.
- The infiltrative mode of growth makes it necessary to remove a wide margin of surrounding normal tissue when surgical excision of a malignant tumor is attempted.
- Surgical pathologists carefully examine the margins of resected tumors to ensure that they are devoid of cancer cells (*clean margins*).
- *Next to the development of metastases, local invasiveness is the most reliable feature that distinguishes malignant from benign tumors*.





Metastasis

- *Metastases* are secondary implants of a tumor that are discontinuous with the primary tumor and located in remote tissues
- *More than any other attribute, the property of metastasis identifies a neoplasm as malignant*.
- Not all cancers have equivalent ability to metastasize.
- Approximately 30% of patients with newly diagnosed solid tumors (excluding skin cancers other than melanomas) present with clinically evident metastases.

Metastasis

- In general, the more anaplastic and the larger the primary neoplasm, the more likely is metastatic spread, but as with most rules, there are exceptions. Extremely small cancers have been known to metastasize; conversely, some large and ominous-looking lesions may not.

- **Malignant neoplasms disseminate by one of three pathways:**

(1) seeding within body cavities, (2) lymphatic spread, or (3) hematogenous spread.

Metastasis

- ***Spread by seeding*** occurs when neoplasms invade a natural body cavity. This mode of dissemination is particularly characteristic of cancers of the ovary, which often cover the peritoneal surfaces widely
- ***Lymphatic spread*** is more typical of carcinomas
- ***Hematogenous spread*** is favored by sarcomas.

- There are numerous interconnections, however, between the lymphatic and vascular systems, so all forms of cancer may disseminate through either or both systems.

Metastasis

- **A "sentinel lymph node"** is the first regional lymph node that receives lymph flow from a primary tumor. It can be identified by injection of blue dyes or radiolabeled tracers near the primary tumor.
- Biopsy of sentinel lymph nodes allows determination of the extent of spread of tumor and can be used to plan treatment.
- Although enlargement of nodes near a primary neoplasm should arouse concern for metastatic spread, it does not always imply cancerous involvement. Thus, histopathologic verification of tumor within an enlarged lymph node is required.

Metastasis

- ***Hematogenous spread*** is the favored pathway for sarcomas, but carcinomas use it as well.

- With venous invasion, the blood-borne cells follow the venous flow draining the site of the neoplasm, with tumor cells often stopping in the first capillary bed they encounter.

- Since all portal area drainage flows to the liver, and all caval blood flows to the lungs, *the liver and lungs are the most frequently involved secondary sites in hematogenous dissemination*.

Summery

- **Characteristics of Benign and Malignant Tumors:**
  - Benign and malignant tumors can be distinguished from one another based on the degree of differentiation, rate of growth, local invasiveness, and distant spread.
  - Benign tumors resemble the tissue of origin and are well differentiated; malignant tumors are poorly or completely undifferentiated (anaplastic).
  - Benign tumors are slow-growing, whereas malignant tumors generally grow faster.
  - Benign tumors are well circumscribed and have a capsule; malignant tumors are poorly circumscribed and invade the surrounding normal tissues.
  - Benign tumors remain localized to the site of origin, whereas malignant tumors are locally invasive and metastasize to distant sites.

SUMMARY

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