Disorders of Cell Growth & Neoplasia

Lecture 3
Neoplasia: Malignant tumors
Malignant

- designation of malignancy indicates an aggressive, life-threatening tumor.

- malignancy is characterized by:

  1. anaplasia
  2. rapid rate of growth
  3. local invasion of tissue
  4. metastasis
- **Differentiation**: the extent to which neoplastic cells resemble comparable normal cells. (“Benign tumors are faithful imitations of the original tissue, malignant tumors are rather caricatures”)

- lack of differentiation is called anaplasia and often characterizes malignancy.

- most cancers likely arise from transformed stem cells that show varying degrees of differentiation.
i) **Pleomorphism**
- variation in size and shape of both the cells and their nuclei.

Anaplastic sarcoma, heart, mouse. This tumor exhibits marked nuclear pleomorphism and has a fairly high mitotic index. The inset shows a notably abnormal mitotic figure.

**Splenic hemangiosarcoma**

- Most common malignant tumour of the canine spleen

**Histology:**

- Blood-filled vascular spaces lined by anaplastic endothelial cells
ii) **Abnormal nuclei**

- nuclei often large (high N/C ratio)
- chromatin often coarsely clumped and marginalized.
- nucleoli often large and/or multiple.

**Hepatocellular carcinoma**, chimpanzee. The cells show nuclear pleomorphism and marked anisokaryosis. Some cells are multinucleated or show multilobulated nuclei. Their nucleoli are often prominent and magenta.
iii) Mitoses
- increased numbers of mitotic figures.
- ± abnormal (atypical to bizarre) mitotic figures.

Fibrosarcoma, dog. Several mitotic figures evident. The two marked with large arrows have the chromosomes aligned at the equatorial plane (metaphase plate), the three marked small arrows have the chromosomes at the cellular poles (anaphase / telophase). Inset: Atypical mitotic figures.
iii) **Mitoses**

- increased numbers of mitotic figures.
- ± abnormal mitotic figures.

Anaplastic tumor showing cellular and nuclear variation in size and shape. The prominent cell in the center field has an abnormal tripolar spindle.

iv) **Loss of Polarity**

- cells lose their nuclear polarity & grow in an disorganized fashion.

**Uterine adenocarcinoma, bovine.** Two acini, surrounded by smooth muscle, are present. The neoplastic cells show features of anaplasia including anisokaryosis and particularly, loss of polarity; ie in many cases the nuclei are not in the normal basal location and also the cells tend to pile up on each other (pseudostratification) instead of forming a single layer of cuboidal epithelium along the basement membrane of the acinus. The photo in the left shows normal polarity of nuclei with a basal location (prostatic glands).
v) **Other**

- tumor giant cells.

**Anaplastic tumor** of the skeletal muscle (rhabdomyosarcoma). Note the marked cellular and nuclear pleomorphism, hyperchromatic nuclei and tumor giant cells (with large single or multiple nuclei).

v) Other
- ischemic necrosis / hemorrhage

**Metastatic carcinoma**, liver, dog. The cut surface of the tumor shows areas of hemorrhage (red) and numerous white-yellow areas of necrosis (arrows), good indications that the tumor is growing rapidly and is malignant.
• not all features of anaplasia are necessarily seen in a given malignant tumor.

• anaplastic features usually call for a poor or guarded prognosis.

• some malignant neoplasms are composed of well differentiated cells.

• the whole clinical, morphologic (gross & microscopic) and epidemiologic aspects of each tumor must be evaluated in order to provide an accurate prognosis.
Rate of Growth (Tumor Cell Kinetics)

- in general, growth rates of neoplasms correlate with their level of differentiation / anaplasia.

i) doubling time of tumor cells

- after clinical detection, doubling times can range from 1-12 months (average 2-3 months)

Robbin’s fig 7-12. Biology of tumor growth. Minimal estimates of tumor cell doublings that precede the formation of a clinically detectable tumor mass. By the time a solid tumor is detected, it has already completed a major portion of its life cycle as measured by cell doublings.
ii) fraction of tumor cells in the replicative pool ("growth fraction")

- tumors with low growth fraction are more refractory to treatment.

Robbin’s fig 7-13. Schematic representation of tumor growth. As the cell population expands, a progressively higher percentage of tumor cells leaves the replicative pool by reversion to $G_0$, differentiation, and death.

iii) rate of cell loss from the tumor

- for tumor growth, cell production must exceed cell loss (apoptosis, shedding, etc).
Malignant Local Invasion of Tissue

- cancer growth is characterized by progressive infiltration (invasion) and destruction of surrounding tissues.

**Osteosarcoma** of the nasal cavity, dog. The neoplasm has invaded the adjacent nasal sinuses, the hard palate (white arrows), and the calvarium / brain (black arrow).
Osteosarcoma, distal region of the right femur, dog. This tumor has destroyed and distorted the femur (f); it is also invading the surrounding soft tissues. Hemorrhages within the neoplastic mass are also consistent with a malignant process.
Metastasis

- metastasis refers to tumor implants discontinuous with the primary tumor.
- unequivocally indicates malignancy & what kills the majority of cancer patients.

i) Lymphatic spread
Mammary gland carcinoma, dog (c), with lymphatic dissemination and pitting edema of the right hind limb (arrow). Note the presence (permeation) of tumor cells within a lymphatic vessel (top right) and neoplastic tissue partially effacing a local lymph node (bottom right, arrows).
Mammary gland carcinoma, dog. Hematogenous dissemination involving the liver and spleen.
Hemangiosarcoma of the right atrium (left, arrow) with metastases to the lungs (right). These tumors contain irregular vascular channels filled with blood which explains its dark red color. They are very common in the heart, friable and prone to rupture. Hemopericardium and dissemination to the lungs are common complications.
iii) Seeding of Body Cavities and Surfaces ("exfoliation and implantation")

Peritoneal carcinomatosis, renal adenocarcinoma, dog. Note multiple, white-yellow, raised nodules disseminated throughout the serosal surface of the abdominal viscera. These metastatic sites are the result of numerous individual neoplastic cells that have exfoliated from the surface of the primary tumor and after random movement through the peritoneal cavity fluid have implanted on the peritoneal surface and grown into individual tumor masses.

Renal adenocarcinoma (cystadenocarcinoma), dog.
iii) Seeding of Body Cavities and Surfaces (transcoelomic metastasis)

Splenic hemangiosarcoma, dog. The primary tumor is in spleen (large arrow) with numerous tumor implants attached to the omentum (top, right) and diaphragm (bottom, right).
Benign vs Malignant Neoplasms

Robbin's Figure 7-22  Comparison between a benign tumor of the myometrium (leiomyoma) and a malignant tumor of similar origin (leiomyosarcoma).