Cytology of Lumps and Bumps
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Cytology of cutaneous and subcutaneous masses represents an opportunity to screen potential surgical cases and determine an etiologic agent or rule out potential neoplasia. This session will focus on common non-neoplastic and neoplastic tumors that present to practitioners. Helpful hints are given how to best diagnose the conditions.

Cytodiagnostic groups for cutaneous and subcutaneous tissues include:

- Normal/Hyperplasia
- Cystic Mass
- Response to Tissue Injury
- Inflammation
- Neoplasia

Normal/hyperplasia
The normal skin involves the outer portion (epidermis) which is composed of keratinocytes in several layers from external to internal involving the outer keratinized layer, granular layer, spinous layer, and most innermost the basal layer. Below the epidermis is the dermis which contains the adnexal structures (hair follicle, sweat glands, and sebaceous glands) as well as smooth muscle bands, blood and lymphatic vessels, nerves, and connective tissues elements (collagen, elastic fibers). Below the dermis is the subcutis composed of loose adipose tissue and collagen bundles.

An example of a hyperplastic mass is sebaceous hyperplasia, which is a common nonneoplastic hyperplastic condition that presents as a wart-like growth. It is frequently pedunculated, hairless with a cauliflower or papilliferous surface. Cytologically, numerous sebocytes compose the mass which are morphologically normal. These cells have abundant mixed granular and vacuolated cytoplasm. Distinction between sebaceous hyperplasia and sebaceous adenoma cannot be made cytologically as this is a histologic determination.

Cystic mass
These are poorly cellular nonneoplastic swellings that may be soft or fluctuant.

Seroma
A clear or lightly basophilic background contains occasional erythrocytes and macrophages.

Follicular cyst
This nonneoplastic lesion may also be termed epidermal inclusion cyst or epidermoid cyst. These cysts are found in a third to a half of the nonneoplastic noninflammatory tumor-like lesions removed in dogs and cats, respectively. The cyst occurs most frequently in middle to older aged dogs. They may be single or multiple, firm to fluctuant, with a smooth, round, well circumscribed appearance. These are often located on the dorsum and extremities. The cyst lining arises from mature stratified squamous epithelium. Keratin bars, nonnucleated squames, or other keratinocytes predominate on cytology. Degradation of cells within the cyst may lead to the formation of cholesterol crystals which appear as negative stained, irregularly notched, rectangular plates best seen against the amorphous basophilic cellular debris of the background.

The behavior of these masses is benign, but rupture of the cyst wall can induce a localized pyogranulomatous cellulitis with evidence of acute (erythrophagocytosis) and/or chronic (blue-black granules) hemorrhage. When this occurs, neutrophils and macrophages may be frequent. To prevent this inflammatory response, surgery is frequently suggested and the prognosis is excellent.

Cytologic differential diagnosis: intracutaneous cornifying epithelioma, dermoid cyst, follicular tumors

Response to tissue injury
In addition to hemorrhage and cholesterol crystals, protein debris is common within the background.
Mucocele or Sialocele
Duct rupture related to trauma or infection leads to an accumulation of saliva within the subcutaneous tissues. The presence of a fluctuant mass containing clear to bloody fluid with string-like physical features suggests a salivary gland duct rupture. The cytologic specimen often stains uniformly purple from the high protein content. The background may contain scattered pools of pale basophilic, amorphous material, consistent with saliva. The fluid is often bloody with evidence of both acute and chronic hemorrhage. Erythrophagocytosis is common and occasional yellow rhomboid crystals may be seen. These are termed hematoidin crystals and are associated with chronic hemorrhage. The nucleated cell population consists predominately of highly vacuolated macrophages displaying active phagocytosis. Distinction between these cells and secretory glandular tissue may be difficult, especially when cells are individualized and nonphagocytic. Nondegenerate neutrophils are common, becoming degenerate when bacterial infection occurs.

Inflammation
The presence of inflammatory cells may arise in noninfectious as well as infectious conditions.

**Nodular panniculitis/steatitis**
This condition may have an infectious or noninfectious etiology. Causes of noninfectious panniculitis include trauma, foreign bodies, vaccination reactions, immune-mediated conditions, drug reactions, pancreatic conditions, nutritional deficiencies, and idiopathic. The condition appears in the cat and dog as solitary or multiple, firm to fluctuant, raised, well demarcated lesions. These may ooze an oily yellow-brown fluid. Sites of prevalence involve the dorsal trunk, neck, and proximal limbs. Cytologically, nondegenerate neutrophils and macrophages predominate against a vacuolated background composed of adipose tissue. Prognosis is usually best for solitary lesions which respond to surgical excision. Multiple lesions are often associated with systemic disease in young dogs and treatment involves glucocorticoid administration. Dachshunds and poodles may be predisposed to this form of the disease. Culture or histopathologic examination is recommended to rule out infectious causes. Fungal stains should be applied to cytologic specimens.

Vaccination reaction
Small lymphocytes and plasma may be numerous, especially in lesions induced by vaccination reactions. Frequently, macrophages present with abundant foamy cytoplasm or as giant multinucleated forms. When chronic, evidence of fibrosis is indicated by the presence of plump fusiform cells with nuclear immaturity. The fibrosis may be so extensive as to suggest a mesenchymal neoplasm. A purple amorphous material representing vaccine adjuvant may appear in and around inflammatory cells.

Sporotrichosis
This is a multinodular condition on the trunk or head of cats, dogs, and horses. Nodules occur in the dermal and subcutaneous tissues and there may or may not be ulcerations involved. It is transmitted by puncture wounds from thorns or claws. *Sporothrix schenckii* is a saprophytic fungus that appears in a cigar-shaped yeast form having a clear halo around it. Important is the zoonotic potential of transmission from cats to people. This is likely related to the large number of organisms in feline lesions compared with very few in other species.

Bacterial infection
Most cocci and rod bacteria stain basophilic with Romanowsky stains, they should appear within neutrophils or closely in contact with the damaged neutrophil. These damaged or degenerate neutrophils display a pale staining nucleus termed karyolysis that indicates rapid cell death in a toxic environment. The nuclear shape is less distinct and may not possess well-defined lobes. Degenerate neutrophils will predominate in bacterial infections, particularly involving gram negative types. A careful search is required to find intact bacteria which may be confused with dispersed cellular debris. Extracellular bacteria may be discounted if contamination is suspected. The cytoplasm may become basophilic and vacuolated in response to the infection.

Neoplasia
Neoplastic lesions are generally divided into 4 morphologic categories based on the presence of cell aggregates or individualized cells as well as the level of integrity to the cytoplasmic border. The four types are called epithelial (aggregate, intact borders), mesenchymal (individual cells, indistinct borders), round (individual cells, discrete borders), naked nuclei (loose aggregates, indistinct borders).
Sebaceous adenoma

This lesion appears as a single, smooth, raised, hairless cauliflower mass or as an intradermal multilobulated mass. Ulceration is common. Fifty percent of these tumors in older dogs occur on the head. Although uncommon in the cat, these tumors are most often found on the head and back. Cytologically, mature sebocytes arranged in lobules or clusters predominate that are characterized by pale foamy cytoplasm having a small dense centrally placed nucleus. A variable number of germinal epithelial cells having basophilic cytoplasm and a higher nuclear to cytoplasmic ratio may accompany the secretory cells. Treatment consists of surgical excision or cryosurgery. Prognosis is excellent.

KEY POINT: Histologic examination is necessary to distinguish between hyperplastic and adenomatous sebaceous tumors.

Cytologic differential diagnosis: sebaceous hyperplasia

Perianal gland adenoma

This is a common tumor mostly associated with intact male dogs suggesting androgen dependency. The tumor may be single or multiple occurring generally near the anus, but may also be found on the tail, perineum, prepuce, thigh, and along the dorsal or ventral midline. Initially they grossly appear as smooth, raised round lesions which become lobulated and ulcerated as they enlarge. The tumor arises from modified sebaceous gland epithelium. Cytologically, sheets of mature round hepatoid cells predominate characterized by abundant finely granular pinkish-blue cytoplasm. Nuclei resemble those of normal hepatocytes appearing round with an often single or multiple, prominent, nucleolus. A low number of smaller basophilic reserve cells having a high nuclear to cytoplasmic ratio may also be present, but these lack features of cellular pleomorphism. Perianal gland adenomas are benign tumors which respond to surgical excision or cryosurgery, coupled with castration. Prognosis is good to excellent. The malignant counterpart of this tumor is infrequently encountered. Nuclear pleomorphism is generally marked in those cases.

Cytologic differential diagnosis: perianal gland hyperplasia, well-differentiated perianal gland carcinoma

Perivascular wall tumors

These are common tumors generally considered to affect dogs only. The neoplastic cells are derived from the pericytes (hemangiopericytoma) or myopericytes (myopericytoma), both cells which are located in the wall of blood vessels, excluding the endothelium. The tumors are often solitary with a predilection for the joints of the limbs, but are found commonly on the thorax and abdomen. They are firm to soft, multilobulated, and often well circumscribed. Cytologically, preparations are moderately cellular. Plump spindle cells may be individualized or arranged in bundles, sometimes found adherent to the surface of capillaries. Nuclei are ovoid, with one or more prominent central nucleoli. Multinucleated cells are occasionally seen. Associated with cells may be a pink amorphous collagenous stroma. The cytoplasm is basophilic and may contain numerous small discrete vacuoles. Lymphoid cells have been found in approximately 10% of cases. The behavior for the hemangiopericytoma is aggressive with recurrent disease. Myopericytomas distinguished by muscle immunomarkers responds to surgical excision.

Cytologic differential diagnosis: neural sheath tumors, well-differentiated fibrosarcoma, myxomatous tumors, malignant fibrous histiocytoma

Melanoma

This is a common tumor of dogs occurring in about 5% of skin lesions, and an uncommon tumor of cats. Older animals are usually affected as are those with dark skin pigmentation. Gross features differ for benign and malignant forms. Benign tumors are mostly dark brown to black, circumscribed, raised, dome-shaped masses covered by smooth hairless skin. Malignant tumors are variably pigmented, infiltrative, frequently ulcerated and inflamed. Cytologically, cells are pleomorphic ranging from epithelioid to fusiform, or occasionally as discrete round cells. In well-differentiated tumors, nuclei may be masked by numerous fine black-green cytoplasmic granules. Poorly differentiated tumors may contain few or no cytoplasmic granules. Nuclei in benign forms are small and uniform compared with characteristics of anisocytosis, anisokaryosis, coarse chromatin, and prominent nucleoli seen in the malignant melanomas. Treatment usually involves wide surgical excision. Prognosis depends on tumor site of origin and histologic characteristics. Benign skin tumors frequently have a good prognosis.
Malignant forms arise more often from the nail bed, lip and other oral mucocutaneous junctions in dogs. The latter forms carry a guarded or poor prognosis related to frequent recurrence and metastasis.

KEY POINT: Numbers of melanin granules will vary within a tumor as deeper regions composed of fusiform cells have fewer granules than superficial areas composed of epithelioid cells.

Cytologic differential diagnosis: benign - normal skin melanocytes, normal pigmented basal cells, melanophages, hemosiderin-laden macrophages;

**Canine histiocytoma**
This is a very common benign rapidly growing tumor of mostly young dogs, involving about 12% of skin masses. Its origin is the Langerhans cell of the epidermis, a type of dendritic cell. The tumor appears as a small solitary, well circumscribed, dome-shaped, red ulcerated, hairless mass, the so-called “button tumor.” It occurs commonly on the head, especially ear pinna, as well as on the hindlimbs, feet, and trunk. Cytologically, cells have round to indented nuclei with fine chromatin and indistinct nucleoli. Cells exhibit minimal anisocytosis and anisokaryosis. The cytoplasm is abundant and clear to lightly basophilic with indistinct cell borders. A variable number of small well-differentiated lymphocytes are common in regressing lesions. Treatment involves surgical excision if necessary. Prognosis is excellent to good as tumor frequently regresses spontaneously within three months and recurrence is rare.

Cytologic differential diagnosis: lymphoma, plasmacytoma, benign cutaneous histiocytosis, systemic histiocytosis, nodular granulomatous dermatitis

**Plasmacytoma**
This tumor is present in less than 2% of canine skin tumors and rare in cats. They present as mostly solitary, well circumscribed masses often on the digits, ears, and mouth. Cytologically, aspirates are moderately to markedly cellular. Individual cells have variable amounts of basophilic cytoplasm in which borders are discrete. Anisocytosis and anisokaryosis are prominent features. Nuclei are round to oval with fine to moderately coarse chromatin and indistinct nucleoli. The nuclei are often eccentrically placed and frequently binucleated. Multinucleated cells may be present. Amorphous eosinophilic material, representative of amyloid is seen in less than 10% of plasmacytomas. Treatment involves wide surgical excision. Prognosis is generally good, but local recurrences may be common.

Cytologic differential diagnosis: lymphoma, histiocytoma, amelanotic melanoma, neuroendocrine (Merkel cell) tumor