

Comparative Pathology Case 175

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Clinical History: A 9-year-old, castrated male domestic shorthaired cat had soft tissue swelling of the right front-leg for 12 months. Radiographs showed erosion and lysis of periosteum of distal humerus, proximal radius and ulna; and capsules and tendon sheaths around the elbow joint. The lesion was explored and showed ruptured joint capsule but tumor was not found. A diagnosis of sarcoma was based on biopsy on April 15, 2000. The leg was amputated on May 23, 2000.

Diagnosis: Synovial myxomatosis in the right elbow joint of a 9-year-old cat.

Gross Finding: Gross examination of the amputated leg revealed multiple cysts filled with large amount of viscous mucous material, destroyed of the elbow joint adjacent soft tissue, muscles, and periosteum and cortex of the distal humerus, and proximal radius and ulna of the cat.

Histopathologic Findings: Multiple sections of soft tissue, muscle, and bone specimens revealed an irregular nonencapsulated infiltrative mass. The mass was composed of abundant intercellular matrix material separated by large numbers of stellate and arborizing neoplastic cells. There was scant to fibrocollagen stroma. Neoplastic cells were generally present in sheets, but in areas where cells were grouped, they were occasionally present in curving and palisading bundles. The acellular spaces contained wispy fine fibrillar material, which varied from lightly eosinophilic to lightly basophilic. The neoplastic cells were stellate to spindle shape with scant to moderate amounts of eosinophilic cytoplasm, variably distinct cell borders, and hyperchromatic spindle to oval fusiform nuclei. Nuclear pleomorphism was mild and mitotic activity was low. There was no evidence of vascular invasion, but neoplastic cells extend to the cut margin multifocally.

Immunohistochemistry Stains: The synovial cells were positive for vimentin, S100, and cytokeratin stains, but the neoplastic stellate cells were negative for S100 and cytokeratin stains and weakly reacted to vimentin stain.

Ultrastructural Findings: The hypocellular neoplasm consisted of myxoid cells had a permanent fibroblastic features, and abundant rough endoplasmic reticulum network was markedly distended and with a cystic dilatation. All cisternae were filled with electron lucent substance, with a similar appearance of the extracellular myxoid collagenous stroma.

Discussion: Multiple cysts filled with mucinous fluid originating from synovium were associated with an aggressive growth causing the destruction of the adjacent joint cavity, synovial membrane, joint capsule, tendon sheath and periosteal and osseous tissue in the elbow joint of a cat. Gross, microscopic, ultrastructural and immunochemistry studies of the neoplastic cells are shown to be myxocytes. The neoplasm is justified as synovial myxomatosis (1). This tumor has not been previously described in humans, animals and birds. Synovial myxomatosis is differentiated from Synovioma in that it is not a synovial cell tumor. Microscopic features of synovioma can be divided into types; the monophasic synovioma consists of predominantly spindle cells, and the biphasic synovioma consists of a mixture of polygonal epithelial cells and neoplastic spindle cells without any cysts filled mucoid viscous material (2-6). Synovial myxomatosis is a tumor of myxocytes with mucoid secretion arising from the synovium and destroying the synovial membrane. Synovial myxomatosis differs from synovial chondromatosis because the latter is a disorder characterized by multiple focal cartilaginous metaplastic growths within the synovium of tendon sheath in human, dog and cat (4,5,8-9). Microscopic findings of synovial chondromatosis are the formation of cellular islands of cartilage in the connective tissue of the joint capsule, beneath, but not involving, the synovial lining cells. Most of loose bodies consist only of cartilage protruding above synovial membrane or lying free in the joint (4,5,7-9). Microscopic and ultrastructural features of synovial myxomatosis are distinct from those of ganglion cysts diagnosed in soft and intraosseous tissue in the patient. The human ganglion cyst is composed of a cavity without a lining that is filled with a mucoid viscous material (10,11). Ganglion cysts were also described in a juvenile dog (12) and the cyst wall consists of inner myxomatous and outer fibromatous fibroblasts. Ultrastructurally, degenerative cells were often observed in inner myxomatous lesions. The ganglion cysts revealed neither apparent synovial lining cells in the multilocular cyst wall nor communication with the joint cavity (12).

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Comparative Pathology Case 176

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Clinical History: A 30-year-old Chinese male was admitted to our hospital due to sudden onset abdominal pain, nausea, and vomiting and intermittent diarrhea. He was well before without significant personal or familial history. Computed tomography of abdomen revealed one well-defined mass over the mucosal wall of ileum.

Diagnosis: Kaposi's sarcoma of ileum

Gross Finding: Exploratory laparotomy with partial segmentectomy of the ileum was performed and submitted for pathological examination. A dark-red, hemorrhagic, half-dome shape and well-margined tumor mass measuring 3.5 x 3 cm in dimension over the ileal mucosa was noted.

Histopathological Findings: The mass consist of well circumscribed, densely packed aggregates of spindle cells and vascular spaces arranged in fascicles that intersect at various angles. Occasional mitoses and nuclear abnormalities are noted in the spindle cells. Various degrees of extravasated RBCs, hemosiderophages, fibrosis and inflammatory infiltrates could also be identified.

Immunohistochemical Results: Neoplastic cells (spindle cells) showed positive activity for CD34 and negative for several special stains, including actin, cytokeratin, c-kit, and S-100. Factor VIII revealed positive result for vascular endothelial cells.

Discussion: Kaposi's sarcoma (KS) may be an early manifestation of of AIDS; it occurs with relatively mild immunosuppression and usually is the initial complication of AIDS. Homosexual and bilsexual men with AIDS are far more likely to have KS than are other people with AIDS. Anal-oral contact is the main route of transmission of the agent of KS, whether associated with HIV infection or not, are caused by the same transmissible agent and that the clinical expression of the disease is determined by a person's immune status.

Diagnostic Criteria:

1. Spindle cell proliferation with recognizing slits that contain RBCs.
2. Various degrees of extravasated RBCs, hemosiderophages, and inflammatory infiltrates.
3. Clinical information.
4. Immunohistochemical reaction (CD34, CD31 (+); actin, desmin, S-100 (--)).

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Comparative Pathology Case 177

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Clinical History: A 5-year-old male canine had a history of bilateral cryptorchidism. The left side one showed enlargement and the right side was normal in size. Both testes were removed on 10/22/1999. The left one measured 4×3×2 cm in size and showed white-yellow color and was soft.

Diagnosis: Seminoma, diffuse type with metastasis, left testicle, canine.

Histopathological findings: This testis was encapsulated, separated into several lobules by several thick bands of thick fibrous septa. These lobules consisted of sheets of medium to large polygonal discrete tumor cells, arranged in an acinar pattern, some were packed and some were loose. Multifocal necroses with occasional hemorrhage were noted within the tumor cells. These polygonal tumor cells were fairly uniform in size and shape, and most of them had moderate to high nucleus/cytoplasm ratio. Their nuclei are large, variable size, bizarre and had dotted chromatin. Multinucleated giant cells and mitotic figures were common. Tumor emboli were often detected in the venules, arteries and lymphatics. The scattered retained seminiferous tubules showed atrophy and had a lymphoplasmacytic infiltrate and necrosis.

Discussion: Seminoma is fairly common in older dogs, less seen in rams, and rare in other species. Seminoma has been listed as the commonest testicular neoplasm in the aged stallion. The avian seminoma has been documented in a pigeons, 2 cockerels, 22 budgerigars, a Jardine warbler and an Amazon green parrot, and their mean age is five years or older. The prevalence age of seminoma in dogs is seven years old or more; the mean age is ten years. It usually affects one testis and more common in the right side. In general, seminoma is usually unilateral and solitary, less in bilateral or multiple, and cryptorchidism was a predisposing factor, approximately 1/3 of all seminomas occur in cryptorchid testicles. One reported of German Shepherd Dogs and Belgian Malinois military working dogs that died in 1992 indicated seminoma was the most frequent malignant tumor. Systemic seminoma

characterized by subcutaneous nodules over the whole body, and the testes were within the normal size has been reported. Seminoma in dogs has infrequent metastasis compared with humans. Metastases are found in 6-11% of canine seminoma and are usually located in the scrotum, spermatic cords, liver, kidney, eyes, peritoneum, brain and pancreases. Histologically, seminoma is divided into two subgroups; intratubular with or without invasion and diffuse type. The features of the intratubular type are numerous clusters of tumor seminiferous tubules with no or few centric space. Numerous large, uniform, polygonal, with high nucleus/cytoplasm ratio, discrete basophilic tumor cells are often filled within the whole seminiferous tubules. Some of the scatter retained normal seminiferous tubules often show atrophy. The tumor cells penetrating out of the tubular basement membrane and forming a sheet of tumor structure are common. The diffuse type is more common and consists of diffusely infiltrating solid sheets of uniform tumor cells, and the normal seminiferous tubules are absent. The tumor cells are tightly packed; well-delineated, large, and round or polygonal, with bizarre nuclei and one to two prominent nucleoli, and multinucleated giant cells are occasionally seen within these tumor cells. Intratumor fibrous septa may separate the seminoma into several lobules. Other testicular tumors in dogs consist of Sertoli cell, Leydig cell or germinal origin and mixed tumors are also frequent. The cellular components of mixed tumors are usually identified by histological examination but sometimes this is difficultly made a diagnosis. By immunohistochemistry, Leydig cells can be identified using an antibody against the LH receptor and an antibody against the steroidogenic enzyme 3 β -hydroxysteroid dehydrogenase (3 β -HSD), both of which are characteristic of Leydig cells in testes. Sertoli cells are identified using an antibody against the intermediate filament vimentin. Seminoma cells did not stain with any of these antibodies.

Diagnostic criteria:

1. Tumor cells arranged by sheets with few atrophic seminiferous tubules structures.
2. Seminoma consists of uniform, large, ovoid to polygonal, high nucleus/cytoplasm ratio, basophilic tumor cells, with bizarre, varied in size nucleoli.

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Diagnostic criteria:

1. Tumor cells arranged by sheets with few atrophic seminiferous tubules structure.

2. Seminoma consists of uniform large, oval to polygonal, high nuclear/cytoplasmic ratio.

3. Atrophic seminiferous tubules with hyaline wall and no germ cells.

4. Atrophic seminiferous tubules with hyaline wall and no germ cells.

5. Atrophic seminiferous tubules with hyaline wall and no germ cells.

6. Atrophic seminiferous tubules with hyaline wall and no germ cells.

7. Atrophic seminiferous tubules with hyaline wall and no germ cells.

8. Atrophic seminiferous tubules with hyaline wall and no germ cells.

9. Atrophic seminiferous tubules with hyaline wall and no germ cells.

10. Atrophic seminiferous tubules with hyaline wall and no germ cells.

Comparative Pathology Case 178

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History: A 24-year-old male was admitted for swelling over Rt inguinal regional for a long time. Right side cryptorchidism was noticed. Total high excision with orchidectomy was performed.

Diagnosis: Seminoma of the testis

Gross Findings: The testis with enveloping tunica and attached spermatic cord measured 9 x 7 x 5 cm and weighed 80 gm. The testis was globularly distorted and firm. There showed a gray, soft tumor measuring 5 x 5 x 4.5 cm. On section, the tumor mass replaced almost the whole testis. The cut surface bulged, and the tumor was homogenous and focally necrotic. The epididymis measured 3.5 x 1.5 x 1.5 cm in size and the spermatic cord showed not remarkable. Totally, 2 LN were dissected.

Histopathological Findings: Seminoma with fairly uniform tumor cells with clear cytoplasm and well-defined cell borders intermixed with fibrous trabeculae. Foci of necrosis and lymphocytes infiltration are noticed, but no granuloma formation. Pericapsular invasion is not noticed. The LN shows reactive hyperplasia with enlargement and prominence of the germinal follicles.

Discussion: Seminomas make up 30% to 40% of all testicular tumors. They are divided into two major categories. The classic seminomas comprise about 93% of all cases. The characteristic gross appearances include moderate size, solid, homogeneous, and light yellow, and may contain sharply circumscribed zones of necrosis. There usually shows no cystic change or hemorrhage, which presence should suspect the possibility of a nonseminomatous component. The individual tumor cells are uniform, with abundant clear cytoplasm, sharply outlined cell membranes, a large centrally located nucleus, and clumped chromatin pattern. The nucleolus is prominent and shows amphophilic staining pattern, apparent multiplicity, elongated shape, and irregular contours. The tumor cells are arranged in nests outlined by

fibrous bands, which are infiltrated by lymphocytes (majority of T-cell type) and plasma cells, possibly the expression of a host reaction to the tumor. A granulomatous reaction containing Langhans-type multinucleated giant cells and epithelioid cells may also be present. The tumor cells' clear cytoplasm contains abundant cytoplasmic glycogen. Immunohistochemically, they exhibit reactivity for placental alkaline phosphatase (PLAP), vimentin, ferritin, and angiotensin I-converting enzyme but are generally negative for keratin, a face of some importance in the differential diagnosis with embryonal carcinoma. Serum levels of placental alkaline phosphatase are elevated in 40% of cases of seminoma, a feature of potential practical use. Spermatocytic seminomas should be clearly separated from classic seminoma and its variants. They comprise 4% to 7% of all seminomas and occur in an older age group. The testicular seminomas that develop not too infrequently in old dogs appear similar to human spermatocytic seminoma.

Diagnostic Criteria: In typical seminoma, the cells stain fairly uniformly although they are less regular in shape. There is considerable cytoplasm, which is usually clear with a distinct cell membrane. It may be ground glass and eosinophilic, but rich in glycogen. Lymphocytic infiltration is almost invariably present, and granulomatous reaction is not infrequent. Giant cells may be tumor giant cells, or syncytiotrophoblastic, or Langhans' multinucleated type of giant cells. The hallmark of anaplastic seminoma is its anaplasia, increased mitotic activity, and decreased lymphocytic infiltration. Otherwise, typical and anaplastic seminoma is similar. Spermatocytic seminoma must be differentiated from typical and anaplastic seminoma on the one hand, and from malignant lymphoma on the other. On the other hand, in spermatocytic seminoma, the three cell types, the absence of glycogen, lakes of eosinophilic precipitate, and absence of lymphocytic stromal involvement characterize the neoplastic process.

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Comparative Pathology Case 179

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Clinical history: An 81-year-old man presented with a 5-year history of serous drainage of left big toe and loosening of nail plate. He visited our 玉里 Tzu-Chi hospital. On initial evaluation a subungual nonpigmented, ulcerated nodule involved the nailbed of the left great toe. Initial biopsy revealed malignant hemangiopericytoma picture. Then he underwent amputation of the toe on Aug 23, 2001. Amelanotic melanoma was diagnosed. Then prophylactic inguinal lymph nodes dissection was performed on Sep 17, 2001.

Diagnosis: Subungual amelanotic melanoma, big toe.

Gross findings: The tumor was whitish ulcerative nodular measuring 2.5×2.5×1.5 cm in size. On cutting, the lobular mass invaded into deep dermis & subcutaneous tissue.

Histopathological findings: The tumor mainly is composed of spindle cells accompanied some bizarre giant cells with staghorn configuration of dilated sinusoidal vessels simulating malignant hemangiopericytoma or angiomatoid type malignant fibrous histiocytoma. Only one foci of tumor nests in the junctional zone with migration into epidermis is noted. Amelanotic melanoma, hemangiopericytoma variant is diagnosed.

Immunohistochemical and histochemical staining: Vimentin and S-100 were strong positive in the cytoplasm of the tumor cells. Factor VIII was positive in the endothelial cells but not in the tumor cells. Fontana-Masson stain failed to show melanin pigment in the tumor cells. So it is diagnostic of amelanotic melanoma.

Discussion: The clinical hallmark of cutaneous melanoma is the presence of varying amounts of pigment within the tumor, represented by shades of black, blue, brown, tan, pink and white. A subgroup of tumors produces little or no pigment (so-called amelanotic melanoma (AMM)), and therefore may mimic a variety of benign and malignant lesions. The reported incidence of amelanotic presentations of melanoma range from 2% to 8% . In one large, retrospective study covering 25 years, 50 (1.8%) of 2881 melanoma patients had an amelanotic primary or

metastatic melanoma with no favored anatomic site. There are three main clinical presentations: AMM on sun-exposed skin with epidermal change, AMM on sun-exposed skin appearing as a skin-colored dermal plaque or nodule and AMM presenting as an exophytic, often eroded nodule. Multiple reports describe AMM in acral location, presenting as an eroded nodule on the plantar foot, subungual verrucous or eroded indurated nodules of the fingers or mimicking plantar warts. A frequent acral presentation occurs subungually, causing obliteration of the overlying nail plate such as our case. Histological diagnosis of any melanoma is more challenging if the lesion deviates widely from the classical criteria. AMM in particular may simulate a variety of other neoplasms, referred to by some as the "great pretender" among poorly differentiated lesions. AMM may histologically resemble atypical fibroxanthoma, malignant fibrous histiocytoma, and malignant schwannoma or spindle cell squamous cell carcinoma. In an attempt to categorize additional variants of AMM, Nakhleh et al examined 335 cases of melanoma accumulated over 30 years, identifying 27 amelanotic lesions that did not display a "well-known growth pattern" and that they characterized further as adenoid or pseudopapillary, small cell, myxoid, hemangiopericytoma-like and signet-ring. In Nakhleh et al's hemangiopericytoid melanoma, cords and clusters of polygonal cells with moderately abundant cytoplasm are separated by "thin-walled, branching tumoral blood vessels" with a "staghorn" configuration such as our case. All above variants, nests of junctional melanocytes provide the key to the diagnosis of AMM, such as our case. The standard melanoma immunohistochemical antigens include S-100 protein, a fairly sensitive but not overly specific antigen and HMB-45, a marker of premelanosomes that stains melanoma cells and melanocytes in some nevi. Once AMM is accurately diagnosed, treatment follows the same as guidelines used for pigmented melanoma. The main challenge lies in defining the clinical margins adequately to ensure the minimal number of procedures for the patients. Some authors have speculated that amelanotic melanoma confers a worse prognosis than pigmented melanoma, but most studies disprove this concept. Supporting the idea of a less favorable prognosis, Huvos et al found a 5-year survival rate of 15% in patients with AMM and regional lymph node disease, compared with 42% in similar patients with stage II pigmented melanoma and regional lymph node disease. In conclusion, the clinician should be careful and take adequate biopsy specimen for definite diagnosis when a patient presented subungual non-pigmented eroded nodule.

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Comparative Pathology Case 180

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Clinical history: This round black-colored skin mass was collected from a 7-month-old, mixed breed finishing pig in an abattoir. The black skin mass was about 5 cm in diameter and invaded inward to subcutaneous layer.

Diagnosis: Melanocytoma, malignant, epidermis and dermis, skin, swine.

Gross findings: A black elevated skin mass was noticed, 5cm in diameter was noticed. The surface of the mass was rough and irregular. The mass had prominent boundaries with the adjacent normal skin. Over the margins of the mass, it presented several vary sized papillary projections and formed the cauliflower outlook.

Histopathological findings: Histopathologically, there was no predominantly keratin layers presented and massive melanoblastic infiltration of the submitted mass could be noticed over the epidermis and dermis. The tumor cells grew upward and downward to the epidermis and the dermis. The varying sized melanin nests could be easily noticed between the collagen fibers of the connective tissues. The hair follicles and sebaceous glands were compressed by the tumor cells and deformed.

Discussion: The normal melanocytes are dendritic cells, they are scattered in the basal layer of the epidermis (epidermal-dermal junction) in the notmal skin. The melanocytes are accompanied with numerous fine cytoplasmic processes that ramifying between the keratinocytes towards the skin surfaces. The numbers of the melanocytes are subject to variation in different species and aregions. The average ratio of melanocyte and basal cell could be about 1:10. The melanoblast is such as precursor of the melanocyte that contains the melanosomes, the special organelle for the melanin-synthesizing reaction. The melanoblasts are derived from the neuroectoderma, by the fetus growth, which can migrate to take up residence at the dermal-epidermal junction of the skin and some in hair bulbs. The melanocyte could also be found in the other tissue that are verified in some species that

include the ocular structure, meninges, adrenal gland, the intima of the heart, and blood vessels. The melanocytic tumors of domestic animals are considered about that be constructed by groupers of the neoplastic melanin-containing cells. The incidences of the melanocytic tumors in domestic animal are most commonly in the dogs, horses, and some certain breeds of swine. The cattle and goat are lesser frequently and quite rare in cats and sheep of the melanocytic tumors. In the dogs, the melanocytic tumor represents from 4 to 7% of all tumors and from 9 to 20% of skin tumors. The highest incidence of melanocytic tumor in dogs is between 7 and 14 years of age. The predisposed breeds include the Scottish terriers, Boston terriers, Airedales, and cocker spaniels. Generally, the dogs accompany with greater pigmentation and with higher incidence of melanocytic tumor. The male dogs appear with higher incidence than females. The melanocytic tumor in dogs is usually solitary and the skin and oral cavity are the most common sites. The predisposed sites of tumor mass include the face, trunk, and extremities. The most common oral sites are located at the gums, buccal mucosa, palate and lips. At least 90% of oral melanocytic tumors are malignant, and most cutaneous melanocytic tumors are accompanied with benign characteristics. In the horse, the melanocytic tumors represented from 6 to 15% of the skin tumor and it consider absolutely that the incidence of melanocytic tumor in horse is accompanied with relationship within the hair-coat color. The gray horses present with higher incidence than the other coat color of the horse. There is a tendency for increasing development of melanocytic tumors, that the elder gray horses are higher incidence, and approximately 80% of gray horses over 15 years of age present clinically with recognizable melanocytic growths. Dermal melanocytoma is the most common melanocytic tumor of the horse. The melanocytic tumors in horse are rare less than 6 years old. In gray horse, it presents with the tendency of melanocytic tumor that develops increase steadily after they become 6 years of age. The Arabian breed is the predisposed breed of the melanocytic tumors in the horse and the gray coat Arabian breed there present with higher incidence than others in this breed. There is no sex predilection has been observed in any horse breed. Melanocytic tumors in horse are usually presents with multiple and originate from the skin. The most common sites of melanocytic tumor of the horse are the perineum and the underside of the root of the tail. In the swine, the melanocytic lesions are common and it is about 3 to 5% of slaughtering pigs have pigmented skin lesions. In the swine, the junctional melanocytoma is the most common melanocytic tumor. The age predisposed is most usually development congenitally or in very young animals. The Duroc-Jersey breed, Hormel and Sinclair miniature swine are the predisposed breed of the melanocytic tumor in swine. There is no sex predilection in swine. The swine melanocytoma may arise from the skin but also the internal organs. In the Duroc-Jersey breed, the flank is the most common site. In Hormel and Sinclair miniature pigs, there are no predisposed sites. In cattle, the melanocytic

tumor is lesser than 2% of all bovine tumors. The melanocytic tumors are usually occurred in young animals and they also can be congenital, these tumors are most commonly encountered in dark-hair coat cattle, the Aberdeen Angus breed is the predilection breed of this tumor in cattle. The subcutaneous melanocytoma is the most common melanocytic tumor in cattle. It has no sex and site predilection in cattle. In human, the melanocytic tumor is presented with significant racial and genetic difference in the melanin synthetic activity of melanocytes. Exposure to the sunlight can enhance melanin synthesis and transfer into keratinocytes. The incidence of the melanocytic tumors is increasing dramatically in white-skin people that excessive sun exposure such as sunburning, is consider to be the principle cause. Almost of the melanocytic tumors have a complete benign course, but the junctional melanocytoma and cellular derma melanocytoma may occasionally accompany with malignant tendency. The metastasis of the melanocytic tumors is firstly by the lymph ducts to regional lymph nodes, then via blood stream, and then systemic metastasis could be observed. The lung is the most common site of the visceral involvement.

Comparative Pathology Case 181

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Clinical history: The sample was submitted from slaughterhouse so the pig (older than 6 months old) didn't reveal any clinical symptom remarkably. Sample was collected by meat inspector and fixed in formalin for several days.

Gross findings: The mass was fleshy, solid and attached firmly to the kidney and it was origin from the parenchyma and 4.5cm in size.

Diagnosis: Nephroblastoma, pig

Histopathological findings: The mass revealed embryonic kidney structure characteristically. Primitive, loose myxomatous mesenchymal tissue predominates. Interspersed in this tissue were primitive tubules lined by elongated, deep staining cells and many structures that resemble primitive glomeruli.

Discussion: Nephroblastomas are common renal neoplasms of pigs and chickens and were usually recognized at slaughter or necropsy. Nephroblastomas are of embryonal origin, arising from metanephric blastema, and, thus, occur in young animals. It is speculated that neoplasms result from malignant transformation during normal nephrogenesis or from neoplastic transformation of nests of embryonic tissue that persist in the postnatal kidney. At necropsy, nephroblastomas may be solitary or multiple masses that often reach a great size and in which renal tissue may be difficult to recognize. They usually are soft to rubbery, gray with foci of haemorrhage, and lobulated on cut surface. Because nephroblastomas arise from primitive embryonal pluripotential tissue, microscopic features vary but are morphologically similar to the developmental stages of embryonic kidneys. (1) Most nephroblastomas are unilateral. They can be classified into four categories: nephroblastic, epithelial, mesenchymal and miscellaneous. (2) Metastases are rare, although the tumor may be large or multiple within a kidney. The large size indicated infrequent metastasis, (Feldman 1928) if metastasis occurred, the host would be killed before the tumor had time to grow so large. Mitotic activity and

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cellular anaplasia are not correlated with tendency to metastasize in this tumor. Metastatic secondaries are found in the sublumbar, renal, mesenteric, and bronchial lymph nodes. Tumor cells are also found in the lung, liver, peritoneum, or opposite kidney (3).

Diagnostic criteria: microscopic features vary but are morphologically similar to the developmental stages of embryonic kidneys.

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Comparative Pathology Case 182

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Clinical history: A 69-year-old man, suffered from erotic lesions over scrotum, penis & suprapubic areas for more than 10 years. Biopsy over scrotum revealed Paget's disease. During operation for total excision, frozen sections were performed to determine section margins. Then, a total excision specimen, measuring 6.5 x 4.2 x 0.8 cm, was sent for pathologic examination.

Diagnosis: Skin, scrotum, wide excision, showing extramammary Paget's disease. (EMPD).

Gross findings: Whitish, eroded plaques, up to 2.2 x 1.4 cm in the central portion of skin.

Histopathological findings:

1. Large atypical cells distributed throughout the epidermis & arrayed as solitary units & in nests within a thickened epidermis.
2. Neoplastic cells extend from the epidermis into the dermis.
3. An infiltrate of inflammatory cells is present in the papillary dermis.

Immunohistochemistry (IHC) results:

1. CEA: (+)
2. PAS: (+)
3. Keratin (Cam 5.2): (+)

Diagnostic criteria:

1. Atypical cells with abundant, pale-staining cytoplasm.
2. Atypical cells arrayed as solitary units & in nests, distributed throughout the epidermis, predominantly in the lower part of the epidermis. (Not in the epidermodermal junction).
3. Atypical cells may extend far down follicular infundibula & eccrine ducts.
4. Nests of atypical cells demarcated sharply from keratinocytes in the adjacent epidermis.
5. Intercellular bridges not visible between pale cells arrayed in nests. (Visible in Pagetoid

Bowen's dx, PBD).

6. Mucin in cytoplasm of neoplastic cells; signet ring cells common (no mucin, no signet-ring cell in SSM).
7. Mitotic figures common.
8. Necrotic cells common.
9. Tubular structures sometimes formed by neoplastic cell.
10. Acinar structures within the epidermis occasionally (not in PBD).

Discussion:

Special stains:

The diagnosis of EMPB has been previously established for all cases using histochemical & immunohistochemical stains.

1. CK 7: Marked all cases (highly specific & 100% sensitive marker for PD).
2. CK 20: Strongly marked Paget cells associated with rectal cancer.
3. Mucins: Sensitive but focal, a potential problem in small biopsy specimens.
(Alcian blue/dPAS, Mucicarmin)
4. AEI/AE3
5. CEA
6. Keratin (CAM5.2)

1. CK7: IHC stain of choice in the diagnosis of PD. There are a variety of routine & IHC stains (CK7, CK20, CEA, Ber-EP4, CAM5.2), used to diagnose MPD & EMPD. Most of the stains commonly used, however, show a positive reaction in the Paget's cells in all cases. CK7 is the IHC stain of choice in the diagnosis of PD. Because CK7 seems to identify single cell, it might also be valuable in evaluating surgical margins for small foci in a tumor such as EMPD, which might have a multifocal origin.

Heterogeneity:

Extramammary Paget's disease (EMPD) is a rare eczematoid disorder occurring mainly in apocrine gland-bearing region, (axilla, eyelid, external canal, penis and scrotum). Its histogenesis is controversial. An underlying malignancy is identified in only 15-33 %. Several investigators have proposed that EMPD is a heterologous entity, with some cases representing a de novo adenocarcinoma in situ arising in the epidermis and others being epidermotropic metastasis or a direct extension of an associated internal malignancy. Using GCDFP-15, in EMPD patient, positive result may indicate a low probability of associated internal malignancy.

Molecular biology:

EMPD is a particular form of skin cancer of unknown histogenesis. To look for the genetic defects underlying the pathogenesis of EMPD, loss of heterozygosity (LOH), P53 and HPV status and the expression of HER-II/neu, bcl-2 protein was examined. Unexpectedly, no LOH was detected at several loci commonly lost in other human cancers (namely 3p, 9p, 9q, 13q, 16q, 17p and 17q). Altered P53 protein was negative in cases & no mutation noted in direct sequencing of exon 5-8 of the P53 gene. PCR amplification of the L1 gene of HPV did not detect the virus that could inactivate P53 and RB tumor-suppressor gene products. HER-II/neu protein was overexpressed, but bcl-2 was negative in all cases. Therefore, molecular events underlying EMPD differ from those of other common epithelial malignancies & those tumor-suppressor genes located in chromosomes regions not examined may be important.

FCM:

Flow-cytometric (FCM) measurements & P53 & HER-II/neu immunostaining performed on paraffin-embedded samples revealed that P53 & HER-II/neu seemed to play no role in the pathogenesis or prognosis in EMPD.

Differential Diagnosis:

1. Pagetoid squamous cell CIS (Pagetoid Bowen's dx)
2. Superficial spreading malignant in situ (SSM). (Ref 9) HMB45 (-), S100 (-), 21N(-), CAM 5.2(+), NKI-C3: +/-.
3. Secondary PD: An associated dermal or internal malignancy: sebaceous ca, breast ca. (TGH cases).
 - A. Primary EMPD: CK7+/CK20-/GCDFP-15 +/
 - B. Secondary EMPD: CK7+/CK20+/GCDFP-15-/
4. Superficial-spreading melanoma (SSM): CK and HMB45 appear to be the most specific marks in D/D PD & SSM.)

	HMB45	S100	21N	CAM5.2	NKI-C3	Mucin
EMPD	-	-	-	+	+/-	+
SSM	+	+	-	-	+	-

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