A COMPARATIVE STUDY OF CANINE AND HUMAN DERMATOLOGY

II. CUTANEOUS TUMORS—THE MAST CELL AND CANINE MASTOCYTOMA*

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In a previous report (1) we discussed the importance of comparative studies; reviewed basic comparative (dog to man) anatomy, physiology and reaction patterns; and delineated several interesting dermatologic entities of canines, including mastocytoma (in this paper mastocytoma will be represented by the initials MCT).

The increasing awareness of the mast cell in health and disease and the ready availability of canines with mast cell tumors has prompted the authors to study intensively 13 cases of canine MCT and investigate the comparative aspects. Nickel (2) has recently presented a comprehensive study of urticaria pigmentosa (mastocytosis, human mast cell disease). Because of the extensive bibliography included in the latter report, only salient references will be listed in the present study.

Many case presentations and discussions of various facets of urticaria pigmentosa emphasize the systemic ramifications. Since MCT of dogs has systemic potential from its onset we may well ask:

1. Is mast cell disease in dog and man related (aside from the obvious fact of mast cell involvement in both)?

2. If they are related, then what information can be obtained from their comparative study?

MAST CELL

Michels (3) devotes 119 pages in Downey's *Handbook of Hematology* to discussion of the mast cell. Only those segments which are germane to the present topic will be presented. Mast cells are of histogenous origin. Their supply in a normal adult is maintained by homoplastic and heteroplastic regeneration; the former accomplished by mitotic division of pre-existing mast cells and the latter by elaboration of mast granules in various connective tissue cells (lymphocytes, plasma cells, clasmocytes, adventitial cells, endothelial cells and possibly reticuloendothelial cells).

Michels further states that tissue mast cells occur in all areas of the mammalian body, though there may be quantitative differences between species. Their numbers are proportional to the amount of connective tissue present. Parenchymatous organs such as the kidneys, adrenal and liver have little connective tissue and therefore few mast cells are present. The canine liver is an exception. Nielsen and Cole (4) emphasize their frequency around small blood vessels in canine skin and liver. The amount of connective tissue, and therefore the number of mast cells, is greater in the testis, ovary, salivary glands, heart, pancreas, lymph nodes and spleen. In the tonsils, spleen and lymph nodes many mast cells are present in the capsule, adventitia of the large vessels, trabeculae and medullary strands. Not infrequently mast cells lie free in the lymph sinuses but apparently never in the efferent lymphatics. Mast cells are numerous in the serous membranes, pars nervosa of the hypophysis, various layers of the digestive and respiratory tracts and organs which have a large amount of connective tissue (tongue, lung, omentum, subcutaneous and intermuscular connective tissue, etc.). Mast cells are fairly abundant in the normal bone marrow of mammals. Cartilage and bone (except for the periosteum and perichondrium) are the only tissues devoid of mast cells.

Lever (5) states that in man the relatively few mast cells in the normal skin are spindle-shaped and grouped around blood vessels and hair follicles, and in the papillary layer of the dermis. Johnson (6), however, writes that "the normal human skin has somewhere between 2000 and 7500 mast cells per cubic millimeter depending on the area from which it is taken." In the normal skin of the dog mast cells are abundant, particularly around small blood vessels. Their cell outline is pleomorphic (fusiform, spherical, and stellate), the nucleus round or ovoid (never lobulated) and the cytoplasm abundant and filled with coarse...
granules denoting maturity. The same cell morphology pertains in those conditions in the canine in which there is benign proliferation of mast cells (dermatitis, etc.).

There is evidence in both species that the mast cell cytoplasm contains histamine, heparin and hyaluronic acid in its metachromatic granules. Despite the heparin content macroscopic hemorrhage concomitant with MCT is rare, although Larson (7) reports severe post-excision hemorrhage in a significant number of cases (though only a slight increase in the coagulation time).

West and Parratt (8) state that there is no parallelism between the concentration of mast cells and 5-hydroxytryptamine (serotonin) in the skin of the guinea pig, rabbit, man, cat, mouse, hamster and dog, despite previous reports to the contrary. They further uphold that even in conditions of mast cell proliferation (MCT of dogs, and urticaria pigmentosa of man) there is no appreciable increase in skin 5-hydroxytryptamine.

The tendency for mast cells to occur in densely packed clusters is augmented under pathologic conditions. Lever states that an increased number of mast cells accompanies granulation tissue, most itching dermatoses (atopic eczema, contact dermatitis and lichen planus, etc.), neurofibromas, the stroma of cutaneous carcinoma, urticaria pigmentosa and lupus erythematosus. In the latter, the number of mast cells closely parallels the intensity of metachromatic staining. Michels states that mast cells are decreased during acute inflammation, absent in scar tissue and markedly increased in chronic inflammation and lymph stagnation. The authors have observed an increased number of mast cells in acute and chronic canine dermatitis (Fig. 1).

**CANINE MASTOCYTOMA**

Mast cell tumors are frequent in dogs and rare in other species. Of 1000 canine neoplasms collated by Mulligan (9), 201 were sarcomas, 87 of which were of mast cell origin. The MCT constitutes 10 to 13.2% of all canine tumors. Bloom (10) was the first to give a detailed pathologic description of this condition (Table I). Nielsen and Cole (4) present 100 cases (including 8 autopsies) collected over an 8-year period.

This condition shows a predilection for Boston Terriers (over 40% of all neoplasms in this breed), Boxers (over 30% of neoplasms) and Fox Terriers (9% of all neoplasms). The incidence of MCT increases uniformly with age, the majority of the subjects being six years or older. There is no sex predilection.

The hindquarters (particularly the thigh)
<table>
<thead>
<tr>
<th>Author</th>
<th>Species</th>
<th>Clinical</th>
<th>Mast Cell</th>
<th>Skin</th>
<th>Lymph Node</th>
<th>Spleen</th>
<th>Liver</th>
<th>Bone Marrow</th>
<th>Lung</th>
<th>Other Organs</th>
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<tbody>
<tr>
<td>Bloom¹⁰</td>
<td>Canine—1st</td>
<td>Recurrence post-</td>
<td>Atypical MCT,</td>
<td>See mast cell.</td>
<td>Peripenile—numerous M.C. capsule, trebeculae, sinuses &amp; interfollicular tissue; pattern obscured, sinuses lost identity.</td>
<td>Pattern undisturbed, throughout pulp numerous M.C. in nodules, solitary M.C. diffuse, frequently invade Malpig. Corps.</td>
<td>Generalized moderate parenchymal degeneration periportal collections of M.C.</td>
<td>2.2% of marrow cells are neoplastic M.C., reversed of myeloid-erythroid ratio.</td>
<td>Throughout inter-alveolar tissue numerous M.C. (single or grouped).</td>
<td>Omentum-mesenteric</td>
</tr>
<tr>
<td></td>
<td>Report—MCT.</td>
<td>excision, intense pruritus, generalized skin tumors, peri-penile lymphadenopathy.</td>
<td>many multinucleated giant cells, occasional mitotic figures.</td>
<td></td>
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<tr>
<td>Ellis¹⁰</td>
<td>Human—1 yr.</td>
<td>Numerous nodular lesions skin &amp; oral mucosa, hepatomegaly, wasting, G.I.T. symptoms.</td>
<td>2 types: 1) mature deep metachromatic granules (closely packed), 2) immature fewer more widely spaced granules, take up less dye.</td>
<td>Proven by biopsy.</td>
<td>Mesenteric—lymphoid cells in reticulum replaced by eosinophils &amp; M.C.—M.C. scattered throughout capsule trebeculae. 2nd in no. of M.C.</td>
<td>Large no. eosinophils &amp; many M.C. in red pulp. No M.C. in white pulp capsule or trebeculae. 2nd in no. of M.C.</td>
<td>Extreme widening of portal areas by connective tissue, many M.C. in fibrotic areas. M.C. most numerous of any organ.</td>
<td>Large no. M.C. &amp; eosinophils adjacent to endosteum.</td>
<td>Marked intra-alveolar hemorrhage.</td>
<td>Kidney, pancreas, pituitary capsule.</td>
</tr>
<tr>
<td></td>
<td>child 1st autopsy report—urticaria pigmentosa.</td>
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<tr>
<td>Loewentalh et Al¹⁰</td>
<td>Human—71 yr. male.</td>
<td>Disseminated mac-pap-nod., cutaneous involvement, hepatosplenomegaly, cachexia. Oral involvement.</td>
<td>Polygonal or round with abundant cytoplasm packed with fine granules; nuclei pale, round or oval (sometimes elongated or bilobed).</td>
<td>Dense M.C. under epithelium.</td>
<td>Some M.C. in sinuses &amp; around blood vessels.</td>
<td>Great accumulation of M.C. in red pulp (discrete masses).</td>
<td>Large nos. M.C. in portal tracts, sinusoids distended, disorganized liver cords with destruction parenchymal cells.</td>
<td>During life up to 30% of all W.B. C. were M.C.</td>
<td>Some areas considerable infiltrate M.C. intra-alveolar septum, in connective tissue M.C. are in relation to blood vessels (except veins).</td>
<td>Pituitary capsule, kidney, palate, aorta pancreas, prostate, adrenal.</td>
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</table>

* M.C. stands for Mast Cell.
scrotum and vulva are frequent sites of occurrence. Mulligan states that 40% of the tumors occur on the scrotum, abdomen, axilla and eyelid; 30% on the posterior extremities; 20% on the vulva, perineum, anterior extremities, thorax and neck; and the remainder on the ear, mammary gland, lip, penile sheath and mesenteric and mediastinal connective tissues. The present authors could find no other report of the occurrence of a primary MCT in an extracutaneous location.

Clinically a lesion may be noted for one to two years prior to examination; then grow rapidly in a few months to significant size. The growth originates as a small dermal mass which gradually infiltrates the epidermis and the loose connective tissue of the subcutis, but has little tendency to involve the deeper fascia and muscles (11).

In Bloom's initial report (10), he presents 3 cases of solitary (benign?) and 2 of multiple (apparently malignant?) MCT. He assumes that the neoplastic cells result from a proliferation of tissue mast cells (homoplastic regeneration). In the process the cells become more uniform (oval or spherical) and acquire a large vesicular nucleus. He describes intracytoplasmic bodies which have not been mentioned in subsequent literature or observed in our own material.

Mulligan divides the MCT into mature and anaplastic varieties. In the mature type mast cells are discrete and polyhedral and their cytoplasm pale, acidophilic and sometimes vacuolated. The nuclei are round or slightly oval, centrally placed, and have a fine chromatin network bordered by a heavy perinuclear membrane. Mitotic figures are infrequent. The cells of the anaplastic type have indistinct borders and unevenly enlarged nuclei with irregular mitotic figures. Occasional multinucleated forms are observed.

Nielsen and Cole (4) state that eosinophils are common in MCT. In addition they note binucleated and trinucleated giant cells, somewhat similar to Reed-Sternberg cells in 3% of their cases. At times the latter together with immature cells, many eosinophils, necrosis and fibrosis suggest human Hodgkin's disease. Only the metachromatic stain could definitely separate these conditions. These authors further point out that there are areas of MCT which contain no stainable granules. In general mast cell hyperplasia (in dermatitis etc.) and slow growing MCT have an abundance of mature cells with coarse, deeply-stained granules in their cytoplasm. Rapidly growing tumors contain immature cells with tiny dust-like cytoplasmic granules, a few large granules or no granules.

Paff and co-authors (12) in studying the behavior of neoplastic mast cells in tissue culture, note spontaneous ameboid movements, amitotic cell division and multinucleated cells. Oliver and co-authors (13) show that the heparin content of the MCT varies with the degree of anaplasia; the mature tumor containing 50 times and the immature 1.7 times the concentration of the normal dog liver.

There are multiple opinions as to the causal nature of the MCT. Hangartner (14) considers them to be infectious granulomata while Bloom (10) states that single tumors are benign and multiple tumors generally malignant. Nielsen (11) believes that all tumors (single or multiple) may be sarcomatous.

Involvement in the regional lymph nodes (26% in Nielsen and Cole's (4) series), spleen and liver is common in MCT. The general health of the dog usually is not affected except in the terminal stages where anemia, cachexia and other signs may be manifest.

Nielsen and Cole (4) point that it is difficult to differentiate between hyperplasia and neoplasia since transitional forms are well known. They state that the cardinal criterion for malignancy is a growth which will kill the host by invasion and/or metastasis. This criterion cannot be satisfied frequently in the canine, because dogs are commonly euthanized before reaching a terminal state. They believe that many cases of MCT possess the following features of a sarcoma:

1. rapid infiltrating growth of immature cells;
2. recurrence after surgical removal often associated with rapid invasion of the surrounding tissues;
3. metastases to regional lymph nodes or internal organs.

The therapy of choice for the small MCT is surgical excision. Adrenalcortical hormones produce a marked reduction in the number of normal mast cells. Bloom (15), utilizing this knowledge, treated a case of recurrent multiple MCT with cortisone (900 mg. over a 9-day period). After 3 days of therapy there was a sudden reduction in the size of the lesions. Microscopic examination revealed an ample number of mast cells with cytoplasmic vacuolation and clumping of gran-
ules. By the ninth day the nodules had completely disappeared; histopathologic examination revealed almost complete absence of mast cells, with those present undergoing degeneration. Six weeks later, however, a new nodule appeared at a distant site and inguinal nodes were enlarged. The pathologic changes in the mast cell in Bloom’s study were the same as those observed by Asboe-Hanson (16) in independent study. The benefits of cortisone therapy in MCT were not verified by Larson (7).

Urbach and co-authors (17) used desoxycorticosterone (DOCA) in the treatment of 7 patients with urticaria pigmentosa. In one, a 54-year-old white woman, a decrease in whealing was noted in 2—3 months and a flattening of the lesions in 6 months. Some degree of relapse was noted three months after discontinuing therapy.

METHODS AND MATERIALS

One hundred dogs with cutaneous tumors were studied over a one-year period (May 1957 to May 1958). Seventy-six canines were examined at the University of Minnesota Veterinary Clinic. In an additional 24 cases tumor tissue, together with clinical data, were submitted by veterinarians in the surrounding area. A majority of the cases of the Veterinary Clinic were presented because of cutaneous tumor(s); the remaining cases were discovered during examination for some other condition. Thirteen per cent of these tumors were of mast cell origin. The other tumors will be the subject of a subsequent communication.

Complete physical examination was done on all the clinic animals. A punch or excision biopsy was performed on one or more tumors in each of the dogs. Touch smears and bleeding and clotting time were determined in those cases in which MCT was suspected.

Punch Biopsy—Hair was removed with a scissors and the site anesthesized with Frigaderm®. A punch biopsy was performed in the usual manner and the tissue fixed in 10% buffered Formalin for at least 24 hours. Hematoxylin-eosin and toluidine blue stains were performed in the usual manner on all tumors.

Excision Biopsy—This was performed under general anesthesia (pentobarbital sodium) and the tissue fixed and stained as above.

Touch Smears—A dry, clean slide was pressed gently against the fresh cut surface of the excised tumor. The slide was allowed to dry and stained with Wright's stain. Purple-red granules in cells 8—18 in diameter were considered diagnostic of mast cells.

The authors obtained clinical data and tissue in 7 cases of urticaria pigmentosa from the Division of Dermatology for comparison with the biopsy findings and clinical data of MCT.

RESULTS

A. Clinical Study of MCT (See Table II)

1. Age—14 weeks to 14 years; average 7.9 years.
2. Breed: Boston Terriers—4 (30%); Terriers—3 (23%); Dachshund—2 (15%); Boxer, Black Labrador, Chesapeake, and English Setter, 1 each.
3. Sex—8 female (62%) and 5 male (38%).
4. Duration before seen by veterinarian: 1—19 months; Average: 6.3 months.
5. Location of primary lesion—posterior extremities—4 (30%); scapular region—3 (23%); groin and scrotum—2 (15%); trunk—2 (15%); lower lip—1 (7.7%); forearm—1 (7.7%).
6. Clinical features (Fig. 2, 3)—the last 3 cases in Table II were submitted without complete description and, therefore, will not be included in some of the statistics.
a. Surface—yellow or white; ulcerated—3 (30%); alopecia—4 (40%).
b. Size (diameter)—0.5 to 15 cm.; average 4.7 cm.
c. Form—firm, raised, papular-nodular—4 (40%), cystic—2 (20%); fixed to skin and free below.
7. Clinical diagnosis—correct in 4 (30%); incorrect in 9 (70%); misdiagnosed as reticulum cell sarcoma, lipoma, fibrosarcoma, etc.
8. Number of tumors—3 cases (23%) with multiple tumors.
9. Physical examination—lymphadenopathy (Fig. 4)—3 (23%).
10. Hematologic data (4 cases)—no abnormal bleeding or clotting time found.
11. Bone survey (2 cases—Case # 10 showed a discrete cystic area of rarefaction of the ischium (Fig. 5).
12. Touch smears (4 cases)—positive in all cases performed (Fig. 6).
13. Pathology—typical in 8 (62%); atypical in 5 (38%).

Brachvogel-Hovey, Los Angeles, California.
<table>
<thead>
<tr>
<th>No.</th>
<th>Age</th>
<th>Breed</th>
<th>Sex</th>
<th>Duration</th>
<th>Loc.</th>
<th>Clinical Description</th>
<th>No. of Tumors</th>
<th>Physical Exam</th>
<th>Hemat.</th>
<th>Skel. Sur.</th>
<th>Touch Smear</th>
<th>Path</th>
<th>Treat.</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3½ yrs.</td>
<td>Boston Terrier</td>
<td>M</td>
<td>1 yr.</td>
<td>Left Scapula</td>
<td>White, raised, ½ cm. diameter, firm, fixed to skin, free below, alopecia, surface smooth</td>
<td>1</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>Simple excision</td>
<td>No recurrence</td>
</tr>
<tr>
<td>2</td>
<td>14 yrs.</td>
<td>Boston Terrier</td>
<td>F</td>
<td>1 mo.</td>
<td>5th digit left leg</td>
<td>Yellow, 1½ cm., firm, fixed to skin, free below, alopecia, ulcer anteriorly</td>
<td>1</td>
<td>Neg.</td>
<td>Clotting &amp; bleeding time normal</td>
<td>—</td>
<td>Positive</td>
<td>Typical</td>
<td>Excision of digit</td>
<td>No recurrence</td>
</tr>
<tr>
<td>3</td>
<td>14 wks.</td>
<td>Dachshund</td>
<td>F</td>
<td>6 wks.</td>
<td>Inter. Scapular</td>
<td>White, ½ cm. flat papule, firm, fixed to skin, free below, no alopecia</td>
<td>1</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>Simple excision</td>
<td>No recurrence</td>
</tr>
<tr>
<td>4</td>
<td>8 yrs.</td>
<td>Boston Terrier</td>
<td>F</td>
<td>—</td>
<td>Forearm</td>
<td>White, 5 cm. cystic nodular, fixed to skin, free below, no alopecia</td>
<td>1</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>Simple excision</td>
<td>No recurrence</td>
</tr>
<tr>
<td>5</td>
<td>14 yrs.</td>
<td>Terrier</td>
<td>F</td>
<td>13 mos.</td>
<td>Knee</td>
<td>White, largest lesion 5 cm., satellites 1½ cm., all firm, fixed to skin with ulceration, no alopecia</td>
<td>7</td>
<td>Inguinal lymphadenopathy</td>
<td>C.B.C. normal</td>
<td>Clotting &amp; bleeding</td>
<td>—</td>
<td>Atypical (appearance of reticulum cell lymphoma)</td>
<td>Previous simple excision of primary lesion after 10 mos., 5 mos. later satellites appeared</td>
<td>Recurrence of primary lesion after 10 mos., 5 mos. later satellites appeared</td>
</tr>
<tr>
<td>6</td>
<td>3½ yrs.</td>
<td>Dachshund</td>
<td>F</td>
<td>2 mos.</td>
<td>Lower lip</td>
<td>Erythematous, 1½ cm., firm, fixed to skin, free below, no alopecia, ulcerated</td>
<td>1</td>
<td>Submaxillary lymphadenopathy</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Atypical (appearance of reticulum cell lymphoma)</td>
<td>Simple excision</td>
<td>No recurrence</td>
</tr>
<tr>
<td>7</td>
<td>11 yrs.</td>
<td>Black Labrador (cross breed)</td>
<td>M</td>
<td>2 mos.</td>
<td>Right groin</td>
<td>Erythematous. Main lesion 15 cm., firm, nodular, free below, alopecia, ulcerated, subcutaneous, satellite 4 cm., lesions, abdomen</td>
<td>6</td>
<td>Neg.</td>
<td>Clotting &amp; bleeding time normal</td>
<td>—</td>
<td>Positive</td>
<td>Atypical (both larger lesions diagnosed reticulum cell lymphoma)</td>
<td>Excision subcutaneous mass</td>
<td>Euthanized (resistant wound infection &amp; eczematization, permission autopsy denied)</td>
</tr>
<tr>
<td>8</td>
<td>13 yrs.</td>
<td>Chesapeake</td>
<td>F</td>
<td>1 yr. Sud-</td>
<td>Popliteal region</td>
<td>Yellow-white, 15 cm., pedunculated cystic, fixed to skin, free below, alopecia, smooth</td>
<td>1</td>
<td>Popliteal lymphadenopathy</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>Simple excision (gland &amp; primary)</td>
<td>No recurrence</td>
</tr>
<tr>
<td>9</td>
<td>5 yrs.</td>
<td>Terrier</td>
<td>F</td>
<td>4 mos.</td>
<td>Scapula</td>
<td>Yellow-white, 5 cm. soft, fixed to skin, free below, skin smooth</td>
<td>1</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Atypical (appearance of reticulum cell lymphoma)</td>
<td>Simple excision</td>
<td>No recurrence</td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Breed</td>
<td>Gender</td>
<td>Duration</td>
<td>Location</td>
<td>Size</td>
<td>Clotting</td>
<td>Discrete</td>
<td>Positive</td>
<td>Atypical</td>
<td>Treatment</td>
<td>Recurrence</td>
<td></td>
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<tr>
<td>10</td>
<td>7 yrs.</td>
<td>Boston Terrier</td>
<td>M</td>
<td>2-8 mo.</td>
<td>Thorax (largest) right &amp; left thigh</td>
<td>3 cm. firm; 1½ cm. firm</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>No recurrence</td>
<td></td>
<td></td>
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<tr>
<td>11</td>
<td>8 yrs.</td>
<td>Terrier</td>
<td>M</td>
<td>1 mo.</td>
<td>Scrotum</td>
<td>2½ cm., spherical, firm</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>No recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>10 yrs.</td>
<td>English Setter</td>
<td>M</td>
<td>9 mo.</td>
<td>Knee</td>
<td>2½ cm., firm</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>No recurrence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>6 yrs.</td>
<td>Boxer</td>
<td>F</td>
<td>—</td>
<td>Flank</td>
<td>White-yellow, 4 cm., firm</td>
<td>Neg.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Typical</td>
<td>No recurrence</td>
<td></td>
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</table>
15. Course (complications)—recurrence in 1 (7.7%); new lesions—2 (15%); 1 case euthanized (autopsy permission denied).

B. Histopathologic Findings

1. Typical (Fig. 7, 8)
   a. Cytology—8-18 μ diameter; outline distinct cells look like fragments of a mosaic; in some area cells separated by clear spaces. Cytoplasm—eosinophilic (at times red-purple), some areas vacuolated; granules not seen without special stain. Nucleus—5 to 10 μ diameter, large, vesicular, basophilic, centrally located; outline variable (usually round or oval, C-shaped, reniform); occasionally binucleate; nucleoli—(none, 1 or 2); occasional mitotic figures.
   b. Architecture—Epidermis—One-third of cases ulcerated with subjacent necrosis, polymorphonuclear and fibrotic response; if intact regular acanthosis. Corium—Tumor usually fills corium; no grenz zone; tumor cells push aside connective tissue (some remaining strands surround linear arrangement of tumor cells); some areas simulate hepatic parenchyma; tumor sharply outlines appendages and blood vessels (Fig. 9) but in no instance invades these structures; numerous eosinophils (fig. 10) were scattered among the tumor cells; occasional hemorrhage observed.
   c. Toluidine blue stain—red-purple granules vary in size and intensity of staining; usually fill cytoplasm, if diffuse obscure cell detail.

2. Atypical—(frequently diagnosed as retic-
Fig. 4. Popliteal lymph node (case 8). Numerous mast cells disrupt architecture. Toluidine blue; × 75.

Fig. 5. Cystic area of rarefaction of ischium (case 10).

ulcer cell lymphoma until special stains done).

a. Cytology—anisocytosis (fig. 11). Cytoplasm—lesser amount, foamy appearance. Nucleus—more frequent mitotic figures, multinucleated giant cells. (One case suggests Hodgkin's disease.)

b. Architecture—no marked difference from the typical variety; eosinophils present.

c. Toluidine blue stain—less positive, smaller granules; some areas have no granules (fig. 12).

3. Comparative Study—7 cases of urticaria pigmentosa in humans.
   1. Age—5 months to 24 years; average 4.5 years.
   2. Sex—female 5 (71%); male—2 (29%).
   3. Clinical—macule dominant lesion in 4 (57%), nodule dominant in 3 (43%) cases. There was no evidence of systemic involvement (skeletal survey done in 2 patients). All lesions urticated on stroking (Darier's sign). None of the dogs with MCT had a positive Darier's sign.

4. Histopathology
   a. The findings in the macular type corresponded to Lever's description (majority of cells spindle-shaped resembling fibroblasts); these cells were indistinguishable from normal canine mast cells as described by Bloom (10)
Fig. 6. Touch smear of MCT nodule. Wright's stain; × 720

Fig. 7. Typical MCT. Hematoxylin-eosin; × 720
Fig. 8. Typical MCT. Toluidine blue; \( \times 720 \)

Fig. 9. Typical MCT; tumor cells outline appendages but do not invade them. Toluidine blue; \( \times 330 \)
Fig. 10. Typical MCT; numerous eosinophils scattered among tumor cells. Hematoxylin-eosin; X 330

Fig. 11. Atypical MCT. Malignant appearance together with polymorphism suggests a lymphoma (Hodgkin's disease, etc.). Hematoxylin-eosin; X 720.
Fig. 12. Atypical MCT. Some areas have paucity of granules. Toluidine blue; × 720.

Fig. 13. Human nodular urticaria pigmentosa. Note similarity of cells to those of typical MCT. Hematoxylin-eosin; × 720.
and seen by the authors; also indistinguishable from normal mast cells associated with benign proliferation (dermatitis etc.).
b. The findings in the nodular type (fig. 13) corresponded to Lever's description (tumor-like aggregates extending throughout entire dermis and subcutis, cuboidal with angular cytoplasm); cells were strikingly similar to those of typical MCT.
c. Eosinophils were present in quantity in one case (nodular type).
d. Most of the mast cells of the nodular and macular types stained heavily with metachromatic stains.

**COMMENT**

The statistics in our series of cases of MCT agree with those of the literature with the following exceptions: lesions were examined earlier and were smaller, there was slight female preponderance and relatively frequent scapular involvement. The series is too small for these differences to be significant.

The cases with atypical pathology (38% of the series) comprise 2 out of the 3 dogs with lymphadenopathy and all of the cases (3) with surface ulceration and multiple lesions. They also include the only case with an abnormal skeletal finding and 2 of the 3 dogs in which recurrent or new lesions developed after excision. Thus the atypical variety appears to be more malignant.

The atypical case is more difficult to diagnose on histologic examination. In most instances a reticulum cell lymphoma was simulated and in one, Hodgkin's disease. The diagnosis could be established only by using metachromatic stains. Nielsen and Cole (4) report that the histologic appearances in some cases of MCT is similar to that of Hodgkin's disease. Reports of the pathology of Hodgkin's disease, however, are rare in the dog (18). In the autopsy of a case of urticaria pigmentosa (Table I) Ellis (19) considered Hodgkin's disease as a possible underlying process where there were numerous eosinophils and fibrosis (but no Reed-Sternberg cells). However, he found few mast cells in 10 cases of verified Hodgkin's disease.

It would not be amiss in canine or human medicine to examine metachromatic stains in cases of suspected sarcomas, unusual mesodermal tumors and in those suspected of having a lymphoma, particularly Hodgkin's disease, and the reticulum cell type. Nickel suggests that a routine stain for mast cells in the most difficult case may give more information than routine connective tissue stains especially in so-called non-specific lymphoblastoma.

The authors were unable to distinguish between the mast cell of the macular type of urticaria pigmentosa and the normal (or benign hyperplastic) canine mast cell and had difficulty distinguishing between the cell of the nodular form of urticaria pigmentosa and the typical canine MCT. This is of interest but does not necessarily imply prognostic import; since the macule may appear in the systemic variety of urticaria pigmentosa (20) and the nodule in the "benign" form. Of similar interest is the striking similarity between the 3 autopsy findings (10, 19, 21) presented in Table I. In the autopsy of the one-year old child the two types of mast cells described could correspond to the typical and atypical histopathologic forms of MCT. Ellis points out the close parallelism between the autopsies of the one-year old girl and Bloom's dog, emphasizing the similar cutaneous, lung, bone marrow, liver and periadrenal involvement.

The cystic rarefaction of the ischium (case 10) is of great interest. Sagher and associates (22) describe two types of bone lesions associated with urticaria pigmentosa: (1) general widespread osteoporosis and osteosclerosis; and (2) similar changes confined to local sites (skull, femur, etc.). The bone changes in our case of MCT might be local. There was no other reason for bone involvement.

The production of a wheal after physical stimulation of a MCT (Darier's sign) has not been recorded. It is well accepted that release of histamine produces the wheal in cases of urticaria pigmentosa. Histamine is thought to be present in MCT. Vereauter (23) points out that horse eosinophils contain a natural antihistamine which can be extracted from preparations of eosinophilic granules. He believes that eosinophils may detoxify histamine. The presence of eosinophils at the site of certain allergic reactions in both species is of interest in this regard. Riley (24) describes an influx of eosinophils in a MCT excised from a dog previously treated with compound 48/80, a histamine liberator. Drennan (25) describes a rapid influx of eosinophils, into a
lesion of urticaria pigmentosa stimulated by trauma, cytoplasmic vacuolization and disruption with loss of metachromasia. All cases of human urticaria pigmentosa included in this study urticated, despite the fact that one nodular lesion had a large number of eosinophils. Further study is necessary to test the thesis that eosinophils inhibit Darier's sign.

It is not clear whether human "malignant" urticaria pigmentosa or the canine MCT represent a sarcoma, systemic hyperplasia, reticuloendotheliosis, or systemic inflammatory process. The finding of the mast cell in lymph nodes, spleen, liver, bone marrow, etc. does not necessarily imply metatases in either species; since, as Michel has pointed out, mast cells are normally present in these areas; therefore, autochthonous development cannot be ruled out.

SUMMARY

A review of some facets of the mast cell and the canine MCT is based on 13 cases studied. Atypical histopathology in a MCT (canine mastocytoma) implies a more malignant potential than the variety with typical histopathology. Touch smears are useful in making a rapid diagnosis of canine MCT. This procedure would likely be a valuable adjunct in the diagnosis of human urticaria pigmentosa (particularly the nodular or tumor types).

The cystic rarefaction of the ischium observed in one of our canine cases coincides closely to some reported cases of bone involvement in urticaria pigmentosa. The inability of canine MCT to wheal on physical trauma may be a function of the large number of eosinophils present (antihistaminic content).

It is suggested that metachromatic stains be performed in canine and human sarcomas, unusual mesodermal tumors and lesions suspected of being a lymphoma (particularly Hodgkin's disease and the reticulum cell type). The cause of canine MCT and systemic urticaria pigmentosa is not known. The presence of mast cells in the viscera may not be evidence of metastasis but may reflect an overgrowth of mass cells present normally.

Since there is a striking similarity between the canine mastocytoma and some cases of urticaria pigmentosa, the canine MCT is suitable for experimentation in relation to human urticaria pigmentosa.

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ADDENDUM

Since the submission of this manuscript, Head (Cutaneous Mast-Cell Tumours in the Dog, Cat and Ox. Brit. J. Derm., 70: 389, 1958) has published a review of mastocytoma in the dog, cat and ox based on the study of 166 animals. He reported 8 cases of canine mastocytoma in which only internal organs were affected, and offered a tentative classification of animal mastocytoma. Gorlin, Clark, and Chaudhry (The Oral Pathology of Domesticated Animals. Oral Surg., Oral Med. and Oral Path., 11: 500, 1958) have reported one case of canine mastocytoma originating on the hard palate and cited Riser (Treatment of Tumors in the Dog: Comparison of Surgery and Physiology, Proc. 91st Annual Meeting, A.V.M.A., p. 279, 1954) as having observed 3 cases in the nose and mouth.

REFERENCES


