INTERACTIVE CASE MANAGEMENT

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How do you proceed with diagnosis?
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Give your differential diagnosis!
DIFFERENTIAL DIAGNOSIS

Abscess
• Inflammation / Cyst
• Granuloma/ Hyperplasia
• Neoplasia
  Round cell tumor: Mast cell tumor/ Cutaneous Histiocytoma/ Cutaneous Lymphoma/ ETVT/ Plasmacytoma
  Epithelial tumor: SCC/ Adenocarcinoma
  Mesenchymal tumor: Fibrosarcoma/ Lipoma/ Osteosarcoma
• Etc........................
Which tests do you want to perform for diagnosis?
• Cytology
• Biopsy
• X-ray
• CT-scan/ ultrasound
• Blood profile
• Bacterial culture & sensitivity
• Etc........
PARANEOPLASTIC SYNDROME ASSOCIATED WITH MCT

Darier’s sign: release of histamine, heparin and other vasoactive amines
Histamine: Erythema & wheal formation of S/C
Vomiting, anorexia, melena, abdominal pain
Gastrointestinal ulceration anemia, peritonitis

Protease: Delayed wound healing

Acute anaphylaxis reaction: sudden onset massive release of histamine
Visceral form (disseminated MCTs)
- Lymphadenopathy, Splenomegaly, Hepatomegaly
- Bone marrow and peripheral blood involvement
PATHOGENESIS OF MCT

C-kit is a type III transmembrane tyrosine kinase-receptor with an extracellular domain bind to stem cell growth factor (KIT)

Normally expressed in hematopoietic cells and mast cells
Internal tandem duplication in exon 11 of c-kit (30% of MCT)
Mutation in juxtamembrane domain of c-kit (duplication, deletion, substitution)
Clinical Stages of Canine Mastocytoma

Stage 1: Focal, confined to dermis without regional LN involvement

Stage 2: Focal, confined to dermis with regional LN involvement

Stage 3: Multiple dermal tumor with or without regional LN involvement

Stage 4: Any tumor with distance metastasis or recurrence with metastasis

a: without systemic signs  b: with systemic sign

Owen L.N., WHO TNM classification of Tumours in Domestic Animal, 1980
To evaluate the consistency of microscopic grading among veterinary pathologists and
the prognostic significance of the Patnaik grading system,
95 cutaneous MCTs from 95 dogs were graded in a blinded study a 2-tier histologic
grading system was devised.
Criteria: High grade: at least 7 mitotic figures in 10 HPF
at least 3 multinucleated (3 or more nuclei) cells in 10 hpf
at least 3 bizarre nuclei in 10 hpf
karyomegaly (ie, nuclear diameters of at least 10% of neoplastic cells vary by at least
two-fold).

High-grade MCTs were significantly associated with shorter time to metastasis or new
tumor development, and with shorter survival time.
The median survival time was less than 4 months for high-grade MCTs but more than 2
years for low-grade MCTs.
Treatment for paraneoplastic conditions

Remove tumor!

Block H1 receptors
Diphenhydramine 2 mg/kg PO q 8h
(or SQ if GI signs)

Block H2 receptors
Cimetidine 5-10 mg/kg PO  q 8 h
Ranitidine 1-4 mg/kg PO  q 12 h
Famotidine 0.5-1 mg/kg  q  24 h
Chemotherapy

Prednisolone: 1 mg/kg/day for 28 days (McCow et al., 1994)
Vincristine: 0.75 mg/m² weekly for 4 weeks (McCow et al., 1997)
Lomustine: 60 mg/m² weekly for 6 weeks (Rassnick et al., 1999)

* Lomustine: 80 mg/m² weekly for 3 weeks
  + Prednisolone 30 mg/m² SID for 7 days or 20 mg/m² SID for 7 days and 20 mg/m² every other day (Baldi et al., 2006)

Vinblastine: 2 mg/m² weekly for 4 weeks and biweekly for 2 months +
  Prednisolone: 2 mg/kg for 1 month and 1 mg/kg for 2 months
  (Thamm et al., 1999; Thamm et al., 2006)
# CLINICAL RESPONSE

<table>
<thead>
<tr>
<th></th>
<th>Gr1</th>
<th>Gr2</th>
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<tbody>
<tr>
<td>Partial response (PR)</td>
<td>53.33 % (8/15)</td>
<td>50% (5/10)</td>
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<tr>
<td>Stable disease (SD)</td>
<td>33.33 % (5/15)</td>
<td>30% (3/10)</td>
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<tr>
<td>Progressive disease (PD)</td>
<td>13.33 % (2/15)</td>
<td>20% (2/10)</td>
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<tr>
<td>Median survival time</td>
<td>108 days</td>
<td>175 days</td>
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<tr>
<td>Median remission duration time</td>
<td>54 days</td>
<td>73.5 days</td>
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<tr>
<td>Median time to progression</td>
<td>42 days</td>
<td>177 days</td>
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Median survival time was 101 days, lower than previous reported due to some cases discontinued treatment or requested euthanasia. 78.2% of case was partial response whilst 21.8% was stable disease.

**Clinical evaluation of canine mast cell tumor treatment between combined vinblastine and prednisolone and single prednisolone**  
A Randomized Trial Investigating the Efficacy and Safety of Water Soluble Micellar Paclitaxel (Paccal Vet) for Treatment of Nonresectable Grade 2 or 3 Mast Cell Tumors in Dogs

Objectives: Demonstrate greater activity for paclitaxel (micellar) compared with lomustine.

Animals: 252 dogs with advanced stage nonresectable grade 2 or 3 MCT.

Methods: Paclitaxel (micellar) (150 mg/m² IV) or lomustineb (70 mg/m² PO) 4 consecutive 21-day cycles

Results: Paclitaxel (micellar)-treated dogs were 6.5 times more likely to have a confirmed response and 3.1 times more likely to experience a biologic observed response. The majority of AE with paclitaxel were transient, clinically manageable.

Clinical Importance:
Paclitaxel’s activity and safety profile are superior to lomustine.
NOVEL APPROACHES TO MANAGEMENT OF MCT
Molecular Target Therapy

Small molecules kinase inhibitors:
Protein kinase dysregulation, aberrant KIT signaling

- Imatinib mesylate (Gleevec, Novartis)
  High dose 400 mg/day/dose  Low dose 100 mg/day/dose
- Gefitinib (Iressa, Astra–Zeneca)
- Molecule (SU11654): Palladia, Pfizer
Action: Palladia kills tumor cells.
   Palladia cuts off the blood supply to the mast cell tumor.
Size: 10, 15 and 50 mg toceranib (as toceranib phosphate per tablet)
Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision.


determine the objective response rate (ORR) following treatment of MCT with toceranib phosphate (Palladia, SU11654), a kinase inhibitor with both antitumor and antiangiogenic activity through inhibition of KIT, vascular endothelial growth factor receptor 2, and PDGFR beta.

Dogs were randomized to receive oral Palladia 3.25 mg/kg or placebo every other day for 6 weeks in the blinded phase. Thereafter, eligible dogs received open-label Palladia.
Multicenter Prospective Trial of Hypofractionated Radiation Treatment, Toceranib, and Prednisone for Measurable Canine Mast Cell Tumors


Hypothesis: The combination of toceranib, prednisone, and hypofractionated radiation treatment (RT) will be well tolerated and efficacious.

Animals: 17 dogs with measurable MCT amenable to RT.
Methods: All dogs received prednisone, omeprazole, diphenhydramine, and toceranib. Toceranib was administered for 1 week before initiating RT, RT consisting of 24 Gy delivered in 3 or 4 fractions.

Results: The overall response rate was 76.4%, 58.8% CR, 17.6% PR
The median time to best response was 32 days,
The median progression-free interval was 316 days.
The overall median survival time was not reached with a median follow-up of 374 days.
Mast Cell tumor in cats: Clinical update and possible new treatment avenues
The average age at the time of diagnosis varies with MCT type and location.

The median age at diagnosis for all tumor types combined is 8.6-11 yrs, although the atypical form of cutaneous MCT often affects younger cats (<4 yrs).

Siamese cats are reportedly predisposed to the development of MCTs of all classifications.

A male sex predilection has been reported previously but has not been supported by subsequent studies.
**Surgery**
Splenectomy is recommended for treatment of splenic MCT in cats and can be accomplished via laparotomy or laparoscopy. Treatment of choice for intestinal MCT, the overall post-surgical prognosis for this disease is poor.

**Plesiotherapy**
In cats with single or multiple cutaneous tumors and no evidence of visceral metastasis, strontium 90 irradiation has been reported as an alternative to surgery. In a single case series, only 1/35 (3%) cats developed recurrence.

**Chemotherapy**
Lomustine, 50–60 mg/m² PO, 4 wks interval
MCTs 38 cases; cutaneous (26), mesenteric LN (7), liver (2), GI (2) or multiple visceral sites (1). Complete or partial responses were 19 (50%); 10/26 cats with primary cutaneous MCTs and 9/12 cats with non-cutaneous MCTs. Toxicity of lomustine in cats is neutropenia, pulmonary toxicity doses of lomustine (200–400 mg/m² cumulative dose).
Other chemotherapy agents: vinblastine, cyclophosphamide, chlorambucil