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NEOPLASTIC DISEASE

Correlation of Nodal Mast Cells with Clinical Outcome in Dogs with Mast Cell Tumour and a Proposed Classification System for the Evaluation of Node Metastasis

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Summary

Lymph node metastasis in dogs with mast cell tumour has been reported as a negative prognostic indicator; however, no standardized histological criteria exist to define metastatic disease. The primary aim of this study was to determine whether different histological patterns of node-associated mast cells correlate with clinical outcome in dogs with mast cell tumour. A secondary goal was to propose a criteria-defined classification system for histological evaluation of lymph node metastasis. The Colorado State University Diagnostic Medicine Center database was searched for cases of canine mast cell tumours with reported lymph node metastasis or evidence of node-associated mast cells. Additional cases were obtained from a clinical trial involving sentinel lymph node mapping and node extirpation in dogs with mast cell neoplasia. Forty-one cases were identified for inclusion in the study. Demographic data, treatment and clinical outcome were collected for each case. Lymph nodes were classified according to a novel classification system (HN0–HN3) based on the number of, distribution of, and architectural disruption by, nodal mast cells. The findings of this study indicate that characterization of nodal mast cells as proposed by this novel classification system correlates with, and is prognostic for, clinical outcome in dogs with mast cell tumours.

Keywords: dog; lymph node; mast cell tumour; metastasis

Introduction

The presence of lymph node (LN) metastasis in dogs with mast cell tumours (MCTs) has been reported as a negative prognostic indicator (Cahalane *et al*., 2004; Murphy *et al*., 2006; Thamm *et al*., 2006; Krick *et al*., 2009; Hume *et al*., 2011) and impacts on expected clinical outcome and therapeutic direction. The diagnosis of nodal metastasis is typically established cytologically via fine needle aspirate (FNA) or histologically via LN biopsy. Cytological criteria have been established to define 'metastasis' via FNA (Krick *et al*., 2009); however, no standardized histopathological criteria exist to define metastatic disease via nodal biopsy samples. This can result in significant inter-pathologist variability in the histopathological interpretation and diagnosis of LN metastasis, especially when individual mast cells or aggregates of mast cells are limited to LN sinuses. Recently, the European consensus document on MCTs in dogs and cats stated that poor prognosis is associated with confirmed LN metastasis, but that 'interpretation of nodal involvement is challenging' (Blackwood *et al*., 2012). As the presence or absence of LN metastasis affects prognosis as well as treatment recommendations for dogs with MCT, it is crucial to standardize the manner in which LN metastasis is defined and reported relative to histopathological features.

The primary aim of this study was to determine whether different histopathological patterns of node-associated mast cells correlate with clinical outcome in dogs with MCTs. More specifically, the

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histopathological pattern took into consideration the number and distribution of nodal mast cells as well as any mast cell-associated disruption or loss of nodal architecture based on routine microscopical evaluation. Components such as primary tumour grade, cytomorphological features, or molecular characteristics of node-associated mast cells relative to clinical outcome were not primary objectives of this study, but may warrant future investigation. The secondary aim was to propose a clinically relevant, criteria-defined, histological classification system to standardize microscopical evaluation of lymph nodes in dogs with MCTs. It was hypothesized that different histopathological patterns of nodal mast cells would correlate with clinical outcome in dogs with MCTs and that such patterns could be characterized in a classification system to better standardize means by which pathologists evaluate and report node metastasis.

Materials and Methods

Case Selection

The Colorado State University Diagnostic Medicine Center (CSU DMC) database was searched for cases of canine MCTs, diagnosed between January 2000 and January 2010, which also had a reported diagnosis of LN metastasis or evidence of node-associated mast cells. Additional cases were acquired from a MCT sentinel lymph node (SLN) mapping clinical trial at CSU, in which dogs with MCT had the SLN resected whether or not metastasis was suspected prior to surgery (Worley, 2012). To be eligible for inclusion in the current study, the primary tumour and a regional LN had to have been surgically excised and LN tissue, with or without primary tumour tissue, had to be available for histopathological review. Cases with complete excision or residual microscopical disease that received treatment after surgery were included in the study. Cases treated in the setting of gross disease (inability to resect all gross disease of the primary mass or to achieve curative intent with radiation) were excluded.

Case Evaluation

Medical records of eligible cases were reviewed. Data collected included animal demographics, prior treatment for MCT (if any), primary tumour information, staging tests performed and any sites of confirmed metastatic disease at the time of diagnosis. Treatment information collected included dates of surgical excision of the primary tumour and LN, margin analysis, radiation therapy and/or chemotherapy protocols and status of disease (microscopical residual disease or adequate local therapy [ALT]) at the time of starting treatment. ALT was defined as having no evidence of MCT at the surgical margins on histopathology, or treatment with 'curative intent' radiation therapy following incomplete surgical resection. Date of disease progression and type of progression (i.e. local recurrence, distant metastasis or de-novo MCT) as well as treatments pursued following disease progression were recorded. Follow-up data were obtained from medical records and telephone calls to referring veterinarians. The date of last contact with the patient, the patient's status at that time (alive or dead) and whether death was due to MCT were recorded.

Lymph Node Classification

Routine haematoxylin and eosin (HE)-stained sections of LNs and primary tumours (when available) were reviewed by a single pathologist (DAK) blinded to treatment and clinical outcome. LN sections were evaluated to identify any node-associated mast cells. Sections were scanned at low magnification (×20 and ×40 total magnification) for any suspect areas containing mast cells. Suspect areas included regions with loss or disruption of normal nodal architecture or sinuses with increased cellularity. If no suspicious areas were identified at low magnification, nodal tissue was further evaluated in its entirety at ×100 total magnification. Each LN was classified based on the histopathological criteria according to the novel classification system developed for the study (Table 1). The classification system consisted of four classes (HN0–HN3), where 'HN' represents 'histological node'. The abbreviation 'HN' was adopted to avoid confusion with 'N' alone, which is used in the World Health Organization (WHO) staging TNM classification (Owen, 1980). Toluidine blue-stained sections, which were available in a subset of cases ($n = 11$), were also reviewed following evaluation of HE-stained sections and LN classification.

Primary Tumour Grade

Neither the association of primary tumour grade to clinical outcome nor primary tumour grade to node classification was a primary objective of this study; however, primary tumour grade data were collected and are included for interest. When available, routine sections of the primary mass were evaluated by the study pathologist (DAK) and graded according to the Patnaik system (Patnaik *et al.*, 1984). In some cases, the primary tumour was removed by the referring veterinarian and thus primary tumour tissue was not available for review. For these cases, the original grade assessed at the time of diagnosis was recorded.