Making strides in veterinary pathology

A dedicated career

Mast cell tumours and pancreatic diseases are common in dogs but also present to a lesser degree in other veterinary species, including cats and horses. For these and many other diseases of veterinary species, diagnostic methods and criteria were not well characterised and made determination of prognosis difficult. Changing this, with decades of research into the pathology of veterinary diseases, is Dr Shelley J Newman, owner/operator of Newman Specialty VetPath, USA, an independent anatomic pathology consulting business.

D r Shelley J Newman, owner of Newman Specialty VetPath, USA, is widely known for her expertise in veterinary pathology and education, but in this article, we will spotlight her contributions to the diagnostics of canine mast cell tumours (MCTs) and pancreatic disease in dogs, cats, and horses. Since 2000, a large proportion of her work has been performed in conjunction with the Gastrointestinal Laboratory at Texas A&M University, and this continues today, as she is an adjunct professor there, part of the diagnostic endoscopic biopsy service team, and a committee member for a PhD student.

Her most cited work surrounds the pathologic characterisation of canine MCTs. MCTs are one of the most common tumours affecting the skin (cutaneous) of dogs of various ages, but with a breed predisposition for Boxers, Boston Terriers, and Weimaraners, amongst others. At diagnosis, most dogs present with a single mass. However, in 3–14% of cases there are multiple masses – and around 50% of these tumours are malignant, especially in older predisposed breeds. Many factors determine prognosis, but the histological (study of tissue) grade of the tumour is most important. Histological examination has always been required for tumour grading, as it helps to more accurately predict their behaviour, something cytology has not yet fully achieved.

During much of Newman’s career, the Patnaik grading system was the only one in use. Newman worked with Dr Patnaik for four years at the Animal Medical Center in NY during the early 2000s. The Patnaik grading system is used concurrently with the newer two-tier Kulpel grading system for histological grading and determining the prognosis of canine MCTs. The Patnaik system classifies canine MCTs into three grades based on various factors, including cellular morphology and invasiveness. Grade I is a well-differentiated MCT characterised by good long-term prognosis, which can be treated effectively by surgery. Grade II is intermediatedifferentiated. Grade III MCT is poorly differentiated and more likely to spread; this makes surgical control less successful.

Surgery is the treatment of choice for cutaneous MCTs; recommended standard excisions remove 3cm of surrounding tissue to a 1cm depth (one fascial plane deep), often further than the visible edge of the tumour. This standard is to ensure that all abnormal (neoplastic) cells are removed. However, surgery does not guarantee that the tumour will not return. Newman’s research on 16 dogs of various breeds found that a 2cm lateral margin and a deep margin of 1cm resulted in complete removal in 91% of Grade I and Grade II MCTs, confirmed by histological staining. Her results suggested that a 3cm lateral margin removal may therefore not always be required. She concluded that further investigations into surgical margins needed for high-grade MCTs (Grade IIB, as using smaller margins for surgery excision could minimise complications associated with large tumour removals. Considerable follow-up studies have since been published by many researchers.

MOLECULAR MCT MARKERS

Although histology is the standard practice for analysis of MCTs, in the early 2000s, molecular techniques became more prevalent. Newman explored various biological markers to predict the clinical behaviour of MCTs more accurately as histological assessment does not always predict clinical outcomes. Newman used newer histological stains, including silver staining of the argyrophilic nuclear organiser region (AgNOR) – present in highly proliferative cells – and antibodies directed towards other highly proliferative cells caused by potentially cancer-causing proto-oncogene defects (including p53, p21, p27, and c-Kit).

The original Patnaik grading system for MCTs did not include subcutaneous (under the skin) variants of MCTs. Using proliferating cell nuclear antigen (PCNA) and new molecular techniques, Newman was the first to characterise the pathology of subcutaneous variants of MCTs and identify the clinical outcomes. Subcutaneous variants of MCTs in dogs were observed to be less aggressive, with an intermediate histological grade, and extended mean survival times – resulting in better long-term prognoses entirely based on location within the skin. Proliferation markers, including Ki67/PCNA/AgNOR/CDK-6 scores which had previously been found helpful in aiding histological diagnosis and grading of cutaneous MCTs, were positively correlated with histological grades in subcutaneous variants of MCTs. Further studies have since expanded on the search for tumours and identified enhanced diagnostic criteria.

PANCREATITIS DIAGNOSIS IN CANINES

Newman’s research interests also extend to the diagnosis of pancreatic diseases in various animals, but her primary focus is on dogs. Canine pancreatic disease has been difficult to diagnose due to the lack of highly specific and sensitive tests, although this has been achieved during her career. Pancreatitis is one of the most common diseases of the exocrine pancreas in dogs – and a significant cause of morbidity and mortality.

Pancreatitis is one of the most common diseases of the exocrine pancreas in dogs – and a significant cause of morbidity and mortality. Through her research, the disease process is being better characterised, enabling improvements in the accuracy of pancreatitis diagnosis. Notably, Newman showed that pancreatitis in dogs displays a random distribution of lesions. She therefore recommends that multiple sections of the pancreas be assessed for necrosis or inflammatory changes both post-mortem and ante-mortem. Newman emphasises the need for a functional grading system for characterising pancreatitis to improve diagnosis and prognosis of the disease, as it is clear from her post-mortem studies that a single biopsy is not sufficient. The development of an improved diagnostic system for exocrine surrounding peri-pancreatic fat, resulting in saponification (soap formation), a characteristic histologic change. The latter is also usually associated with abdominal pain.

Few studies reported the histological lesions of dogs with pancreatitis, and no studies until Newman’s sentinel work have evaluated the localisation of inflammation, fibrosis, and necrosis (tissue death) associated with this condition in a large number of dogs. Newman sheds light on these previously unexplored factors in post-mortem studies of dogs in an attempt to create a predictable distribution of lesions.

To test the sensitivity of serum markers for the diagnosis of canine pancreatitis, Newman assessed thousands of pancreatic tissue samples from dogs, something not previously extensively studied. A variety of diagnostic tests have been trialled for testing tryptic-like immunoreactivity (TII) as well as serum amylase and lipase levels, which are typically elevated in humans with acute pancreatitis. Since these ground-breaking studies, a canine pancreatic lipase immunoreactivity (cPLI) test has been used more widely by veterinarians...
due to its increased sensitivity and specificity in the diagnosis of pancreatitis in canines. FNA can also be used as a biomarker of damage in the pancreas and has been incorporated in survey testing for pancreatitis around the globe. Following assessment of numerous canine pancreatic samples, serum reference ranges were able to be calculated, and the test is available online as a useful aid in canine pancreatitis diagnoses utilizing a blood sample.

However, as pathological lesions are randomly distributed in pancreatitis in dogs, diagnosis via single biopsies is difficult. On the other hand, fine needle aspiration (FNA) results were not well documented. Newman found that the non-invasive FNA for pancreatic sampling produced high-quality cytological samples, enabling their analysis for diagnosis. FNA prevented any significant damage to the pancreas and/or the development of any further complications. This was reflected by the stable CPE levels. This technique has improved the diagnosis of pancreatitis in dogs and prevented complications or assisted in the form of more aggressive biopsy procedures.

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