RESEARCH COMMENT

Concurrent endocrine neoplasia: more common than you thought?

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OVER the past decade, multiple endocrine neoplasias in dogs and cats have been presented in case reports and small case series. Various combinations of endocrine neoplasias have been described, with involvement of the parathyroid, thyroid, anterior pituitary and adrenal glands being the most common.[1–8]

The term multiple endocrine neoplasia (MEN), used to describe the condition in people, cannot simply be applied to dogs and cats, because the concurrent lesions in animals do not resemble the condition that occurs in people;[9] for example, in people, several types of MEN are classified based on organs affected. Patients with MEN1, for instance, have tumours of the parathyroid glands, pancreas and pituitary. MEN2. MEN3 and MEN4 involve other endocrine tumors. Until recently, the term MEN-like syndrome has been used in animals instead, but in a study summarised on p 322 of this week's issue of *Vet Record*, Beatrice and others[10] introduce the term concurrent endocrine neoplasias (CEN), as an alternative to MEN-like syndrome, for animals. While CEN is still considered to be rare, it is more common than previously thought. The information provided in the study about the most frequent co-involvement of endocrine neoplasias in dogs and cats provides novel insights into the clinical management of the condition.

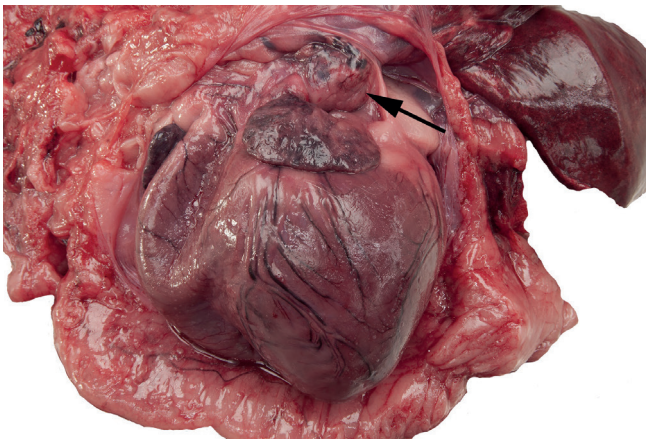
In dogs, concurrent adrenal medullary, adrenal cortical and/or pituitary gland pathology was found most commonly, with the most frequently reported combination of tumours being pheochromocytoma and an adrenocortical tumour, and an adrenocorticotropic hormone (ACTH)-secreting pituitary tumour with adrenal tumour. However, differentiation between spontaneous hypercortisolism and pheochromocytoma may be difficult, because they both present with similar clinical signs, such as polyuria and polydipsia, panting, weakness and tachypnoea.[11]

The availability of endocrine testing for a pheochromocytoma has improved its diagnosis in recent years. Capability to measure plasma and urinary metanephrines (an adrenaline metabolite) is also now available in specialised laboratories. However, clinicians should take into account that the cut-off values for metanephrines in dogs with hypercortisolism are two to four times the upper limit of the reference range, because chronically elevated cortisol concentrations can lead to elevated circulating concentrations of adrenaline metabolites.[12]

Reaching a specific diagnosis in a dog suspected of an adrenocortical and/or medullary tumour is important, because the treatment options differ. Currently, adrenalectomy is the best treatment option for a pheochromocytoma following pre-treatment with phenoxybenzamine to reduce the risk of complications associated with adrenaline release during surgery.[13] Co-existence of an ACTH-secreting pituitary adenoma has been reported to occur in around 10 per cent of dogs with a cortisol-secreting adrenocortical tumour.[14] Nowadays most dogs with hypercortisolism are treated medically with trilostane, an inhibitor of cortisol secretion.[15] Although this approach leads to an improvement of clinical signs of hypercortisolism, it does not affect tumour growth. In other words, an ACTH-secreting pituitary tumour, although benign, will continue to grow. A large pituitary tumour may lead to reduced appetite, headaches, and behavioural and neurological problems.[16] Similarly, an adrenocortical

WHAT YOU NEED TO KNOW

- The most commonly affected endocrine organ with concurrent lesions is the adrenal gland in dogs and the thyroid gland in cats.
- About 50 per cent of dogs with concurrent endocrine neoplasias had an adrenocortical tumour in combination with an ACTH-positive pituitary adenoma or a pheochromocytoma.
- In cats, concurrent thyroid and parathyroid hyperplasia, as well as thyroid adenoma and carcinoma are most common.
- Thorough evaluation of a dog with an adrenal tumour and a cat on long-term medical treatment for hyperthyroidism is of great importance.



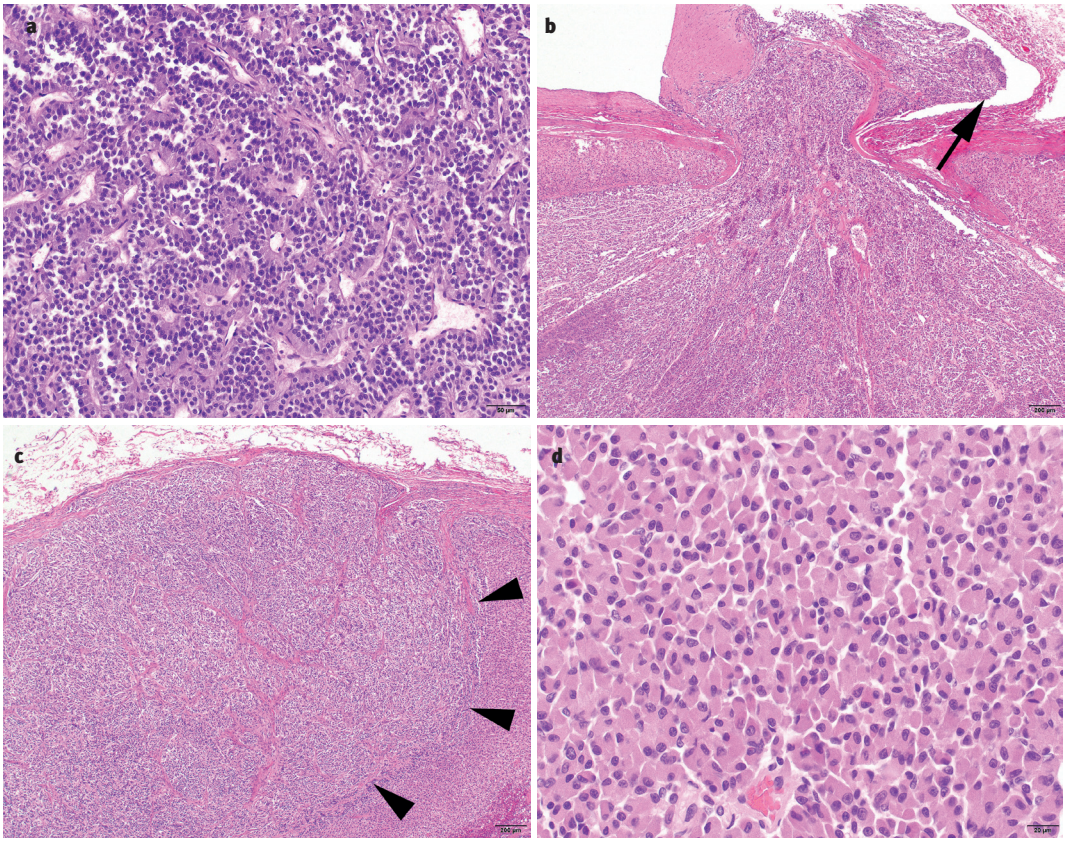
10-year-old Boston terrier dog presented with exercise intolerance, polyuria and polydipsia and weakness, was diagnosed with concurrent endocrine neoplasia: paraganglioma at the heart base (arrow), pheochromocytoma, pituitary adenoma and adrenocortical adenoma.

tumour will expand in size and may metastasise during trilostane therapy.[17,18] The work of Beatrice and co-authors[10] emphasises the importance of diagnostic imaging in dogs with Cushing's syndrome, a disease that causes excess cortisol excretion, to tailor the treatment programme appropriately and provide a realistic prognosis.

In their study,adrenocortical and adrenomedullary markers were used to carry out histological diagnosis[10]; Melan A, inhibin and calretinin can be used as adrenocortical markers.[19] While synaptophysin is a well-recognised marker for adrenal medullary cells,[11] displaying chromaffin granules with a silver stain (SNOBA) has been performed as well.[10] In comparison to other types of tumours associated with CEN, paragangliomas in dogs are hormonally inactive and the value of medullary markers in confirming the diagnosis by immunohistochemistry is so far unknown. In the future, immunohistochemical markers should become a routine part of histopathological evaluation of adrenal gland tumours, independently of the clinical endocrine diagnosis.

Diagnosing malignancy of an endocrine tumour remains challenging. The general principles in histopathology teach us that infiltrative growth of the tumour, spread beyond the organ capsule and/or infiltration into adjacent blood vessels and distant metastasis are characteristics of a carcinoma.[20] However, in adrenal and thyroid tumours use of these characteristics to diagnose malignancy remain controversial. While there is no doubt that the presence of distant metastasis is the most reliable indicator of malignancy, the significance of capsular and vascular invasion by neoplastic cells remains debatable.

Maybe even more challenging is the differentiation between hyperplasia and adenoma. Classically,



a) Histology of the paraganglioma (H&E stain); b) Histology of a pheochromocytoma demonstrating invasion of the phrenicoabdominal vein by neoplastic tissue (arrow) (H&E stain); c) Histology of an adrenocortical adenoma. Arrowheads indicate the junction between adenoma and normal cortex. (H&E stain); d) Histology of a pituitary adenoma (H&E stain)

hyperplasia is defined as diffuse and uniform enlargement of the target gland due to an increased number of cells with identical morphological characteristics in all its cells responsive to the trophic factor.[21] Next to a diffuse hyperplasia of an endocrine organ, nodular hyperplasia can also be encountered, presumably driven by intrinsic processes.[22] This is one of the arguments in favour of including primary nodular hyperplasia in a study of CEN. In MEN syndromes (in people), hyperplasia is regarded as a precursor of tumour formation in the adrenal and thyroid glands.[23–25]

The significance of progression from benign to malignant lesions is well-documented in cats with hyperthyroidism receiving long-term treatment of thyreostatica.[26] In the long run, thyroid pathology cannot be arrested by medical management and the thyroid tumours continue to grow and malignant transformation of thyroid adenoma into carcinoma appears possible. Beatrice and co-authors[10] report that the thyroid gland was the most affected endocrine organ in cats, with thyroid hyperplasia being most frequently encountered pathology. Interestingly, they also present a cat with all three stages of thyroid pathology: hyperplasia, adenoma, and a carcinoma with metastases in a lymph node. Although speculative, it is possible that the feline thyroid gland is one of the endocrine tissues in animals which may undergo transition from hyperplasia to adenoma and even carcinoma.

The most important thought which comes up after reading the article of Beatrice and co-authors[10] is that CEN might be more common than assumed so far. An ageing patient population and more sophisticated levels of medical care, combined with increasing awareness of CEN by clinicians, might lead to documentation of more cases in the future. Diagnosing CEN is of clinical importance as it might lead to an adjusted treatment plan. Even when curative treatment of CEN is not possible, reaching a definitive diagnosis can help improve the expectations of owners, with respect to quality of life and life expectancy of their pet. Furthermore, diagnosing CEN can generate interesting data on breed predisposition, can provide material for genetic research and can influence future breeding strategies.

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