A multiple endocrine neoplasia syndrome in one dog

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Summary

Endocrine tumors are sporadically detected in animals. Multiple Endocrine Neoplasia (MEN) can occur in the following organs: pancreas, thyroid, parathyroid, adrenal and pituitary glands. Our paper presents a detailed description of a dog with multiple tumors/hyperplastic lesions in various endocrine glands. An adult 10 years old male dog (Caniche breed) was presented to the Faculty of Veterinary Medicine Cluj-Napoca (Romania). Clinical examination and complete necropsy was performed in the Laboratory of Pathologic Anatomy. Following necropsy, harvested tissues were processed by the paraffin technique and stained by regular methods. Some changes were identified in some endocrine glands, such as: bilateral hypertrophy of thyroid glands (5/2.4 cm in size for the right thyroid and 7.3/3.3 cm for the left one); bilateral hypertrophy of parathyroid glands (1.4 to 2.2 cm in size). Histologically, the dog presented the following endocrine lesions: a thyroidal carcinoma in the right thyroid (with metastases in the liver), a thyroidal adenoma (in the left thyroid), the hyperplasia of the right and left parathyroid glands. The suggested endocrine lesions suggested a mixed MEN (or MEN-2b). In order to have a better understanding of MEN syndromes, a detailed description of such cases are further required.

Introduction

Endocrine tumors are sporadically detected in both humans and animals. Primary endocrine neoplasms may arise as solitary or multiple entities. Multiple endocrine tumors can induce a syndrome named Multiple Endocrine Neoplasia (MEN) syndrome that can occur in the following organs: pancreas, thyroid, parathyroid, adrenal and pituitary glands. MEN was described in a limited number of species and cases: in dog (Brever et al, 1991; Walker et al, 2000), horse (De Cock, 1999), cat and ox (Sponenberg, 1983; Gal et al., 2014). MEN are characterized by the existence of at least two endocrine tumors (hyperplastic lesions as well) in the same subject (Walker et al, 2000; Gal et al., 2014).

The prevalence of MEN in dogs was investigated by Rebhun (2010), which mentioned only 3% from 1.722 investigated dogs. Most of the dogs with MEN were females (Rebhun, 2010). Another study showed that the MEN syndrome occurred in 6 to 10 years old dogs, without predisposition of breed. In the same paper authors suggested that tumoral metastasis was at a low rate (Proverbio et al, 2012). The MEN syndrome was rarely reported in cats. So far only MEN-1 was diagnosed in cats. Roccabianca et al. (2006) presented cases of MEN-1 in cats, in which the following lesions were identified: multiple pancreatic carcinomas (with beta cells), corticotroph pituitary adenomas and...
thyroidal hyperplasia with C (parafollicular) cells. Clinically, the cats showed hyperadrenocorticism and insulin-resistant diabetes mellitus (Roccabianca et al, 2006).

There are various theories explaining the pathogenesis of MEN. Wermer et al (1954) suggested the mosaic pleiotropism (i.e., the ability of a gene to influence simultaneously the occurrence of several hereditary characters), while Vance et al. (1972) recommended the nesidioblastosis or insular pancreatic carcinoma (which provides an abnormality in the islets of Langerhans that may cause hypersecretion of one or more hormones) as an important cause of MEN. Concerning nesidioblastosis, a hypersecretion of insulin could lead to hypoglycemia, which in turn induces the secretion of growth hormone and associated pituitary hyperplasia, and adenoma at this level eventually (Vance et al, 1972). Another theory suggested the involvement of APUD (Amine Precursor Uptake and Decarboxylation) structures in MEN pathogenesis (Weichert et al, 1970; Tischler et al, 1977). Genetic substrate (i.e., autosomal dominant gene) was recommended by some authors (Phay et al, 2000; Thakker, 2000).

Our paper presents a detailed description of a 10 years old male dog with multiple tumors/hyperplastic lesions in various endocrine glands (suggesting a MEN syndrome). A comprehensive report concerning the case history, necropsy and histological findings has been done.

Material and methods

Case history
An adult 10 years old male dog (Caniche breed) was presented to the University of Agricultural Sciences and Veterinary Medicine Cluj-Napoca, Faculty of Veterinary Medicine. Clinical examination showed anemia, jaundice, generalized muscular atrophy and a very poor general body condition. With the owner permission, the dog was humanely euthanized due to a number of untreatable disorders. Complete necropsy was performed in the Laboratory of Pathologic Anatomy from the Faculty of Veterinary Medicine Cluj-Napoca, Romania.

Histopathology
Following necropsy, a number of small tissue pieces (cca. 0.5 cm) were fixed in 10% buffered formalin. Harvested tissues were then embedded in paraffin wax, processed by the paraffin technique, sectioned at 5 μm, and stained with Haematoxylin-eosin (HE) method. Microscopic assessment was performed using an Olympus BX51 microscope connected to a digital camera (Olympus DP-25) for image acquisition and analysis.

Results and discussion

Necropsy findings
The following lesions were detected: right heart dilatation (as a result of a chronic valvular endocarditis); left concentric cardiac hypertrophy and chronic valvular endocarditis at this level; foci of intimal hyperplasia in the aorta and pulmonary arteries; jet plaques in both atria; lung congestion and pulmonary edema with multiple miliary areas of mineralization; asymmetrically hypertrophied prostate that was dense at palpation; generalized bilateral renal fibrosclerosis with numerous chronic infarcts; a non-encapsulated nodular mass with a grayish appearance was identified in the liver parenchyma (about 5.2-7.6 cm in diameter); two fractured ribs with a poor consolidation and an exuberant callus were also detected.

Some changes were identified in some endocrine glands, such as: bilateral hypertrophy of thyroid glands (5/2.4 cm in size for the right thyroid and 7.3/3.3 cm for the left one); bilateral hypertrophy of parathyroid glands (1.4 to 2.2 cm in size) and multiple foci of mineralization were noticed in parathyroid glands.

Histopathology
In the right thyroid a noticeable hypertrophy was observed. Into its structure, large thyroid follicles were detected that displayed a large amount of colloid (without evident resorption vacuoles). Follicular cells were cuboidal to squamous due to compression atrophy induced by the colloid. In some thyroidal
follicles, papillary intrafollicular projections were detected following follicular cell hyperplasia. Intensely basophilic structures were also present in the stroma and parenchyma of the thyroid gland. The former structures had different sizes and displayed a concentrically arrangement. Other tumoral lesions were also detected in the right thyroid. In between the hypertrophied follicles (i.e., in the stroma), a cellular proliferation that displayed a trabecular or a solid arrangement was observed (Fig. 1).

The neoplastic cells were relatively uniform in shape and size, with euchromatic nuclei and barely visible nucleoli. The presented neoplastic cells may originate either from the follicular or from the parafollicular thyroidal cells (additional expensive procedures are required). In the adjacent parathyroid glands, a significant hypertrophy was observed. The proliferated chief cells induced a general hypertrophy in all parathyroid glands (Fig. 2). The chief cells were arranged in cords or trabeculae with an anarchic orientation, often flanked by vascular spaces. There were not identified cellular atypias, but numerous mineralization bodies were present in the mass of parathyroids (Fig. 3). Histopathological diagnosis: thyroidal adenoma; double hyperplasia of parathyroid glands; metastatic mineralization of the thyroid and parathyroid glands.

A tumoral mass was identified in the left thyroid gland. The specific histological arrangement of the thyroid gland was not observed anymore, except for some tiny microscopic foci (which presented some thyroidal follicles without colloid, but with intraluminal papillary protrusions). The tumoral mass was made of numerous polygonal cells set in cords or with a solid growth (Fig. 4). The tumoral stroma was poorly represented except for some areas in the central part of the tumor that displayed foci with desmoplastic reaction. In the central part of the tumor were identified large areas of necrosis and hemorrhage (with numerous siderophages; Fig. 5).

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Fig. 4. Carcinoma of the thyroid gland (left thyroid) – follicular cell proliferation arranged in short cords or cell groups; hematoxylin-eosin stain.

Tumoral cells had an acidophilic finely granular cytoplasm, and the nuclei showed a low to moderate nuclear polymorphism. Finely granular mineralization areas with a basophilic appearance (psammoma bodies) were noticed in the tumoral mass. A thick capsule with multiple foci of mineralization surrounded the tumor all around.

Fig. 5. Carcinoma of the thyroid gland (left thyroid) – areas of hemorrhage and necrosis; hematoxylin-eosin stain.

Additionally, tumoral cells set in nests or cords were detected in the capsule (Fig. 6) and beyond the capsule (i.e., in the thyroid-parathyroid interface), suggesting a malignant lesion (Fig. 7).

Fig. 6. Carcinoma of the thyroid gland (left thyroid) – tumor cell invasion in the capsule; hematoxylin-eosin stain.

Vascular micrometastases were also identified around the tumor. Adjacent parathyroid glands were significantly hypertrophied, showing similar lesions with the right parathyroid glands. **Histopathological diagnosis:** thyroidal follicular carcinoma with a solid aspect; hyperplasia of the parathyroid glands.

Fig. 7. Carcinoma of the thyroid gland (left thyroid) – tumor cell invasion in the intratumoral stroma; hematoxylin-eosin stain.

Histologic findings of the hepatic tumour suggested an invasive unencapsulated malignant tumor. The malignant cells displayed an alveolar arrangement (or follicle like structures) with intra-alveolar papillary projections; the polygonal cells had large nuclei, high nucleus to cytoplasm ratio, and a finely granular acidophilic cytoplasm. The nuclei showed a moderate polymorphism,
with large nucleoli and evident nucleoli (1-2 macronucleoli most often). Some tumor cells showed large bizarre nuclei; binucleated cells were identified as well. Histopathological diagnosis: hepatic metastases of the thyroidal carcinoma.

Other histological findings noticed in the lung, kidneys and prostate: pulmonary congestion and edema, pulmonary anthracosis, multifocal mineralization of the lung parenchyma; chronic fibrous interstitial nephritis; benign hypertrophy of the prostate.

A special situation was presented in a 10 years old dog that had multiple endocrine tumors. As observed above, the dog presented the following endocrine hyperplastic/tumoral lesions: a thyroidal carcinoma in the right thyroid (with metastases in the liver), a thyroidal adenoma (in the left thyroid), the hyperplasia of the right and left parathyroid glands. Phay et al. (2000) described 3 types of MEN in dogs (i.e., MEN-1, MEN-2, MEN-2b). The presented dog could belong to a mixed MEN, or according to some other reports the MEN-2b type (Chong, 1975; Graze, 1978).

The MEN-1 or Wermer syndrome is characterized by neoplasms arising in the parathyroid, pancreas, and pituitary glands. The paraneoplastic syndrome occurs due to adenomas or hyperplasia of the parathyroid gland. In fact, the former aspect is the most common manifestation in patients diagnosed with MEN-1 (Kumar, 2010). Clinically, these individuals may be asymptomatic, or may exhibit classic signs of hyperparathyroidism (e.g., nephrolithiasis, bone diseases, depression, abdominal pain and weakness). In humans, the disease incidence is higher in people between 40 and 50 years (Guru, 1998). Tumors occurring in the pancreas (as MEN-1 manifestation) induce usually mortality as a consequence of their aggressively and very high rate of metastasis. The main pancreatic tumors associated to MEN-1 are: insulinoma and gastrinoma (the latter causing a paraneoplastic syndrome or Zollinger-Elison syndrome). The Zollinger-Elison syndrome induces gastric hyperacidity, gastric ulcer, diarrhea and emesis. Insulinoma is clinically manifested by hypoglycemia and nervous signs (Pont, 1980). Concerning the pituitary tumors associated with MEN-1, the most common are the prolactinoma and the somatostatoma (in patients with acromegaly; Kumar, 2010).

However, MEN-2 syndrome is divided into two subgroups, MEN-2a and MEN-2b respectively. In MEN-2a are regularly identified the following: pheochromocytoma, medullary thyroid carcinoma and hyperplasia of the parathyroid gland (i.e., at least two of the three). Medullary thyroid carcinoma occurs in 100% of patients with MEN-2a, usually with a bilateral and multifocal appearance (Graze, 1978). Being a secretory cancer, it can produce a range of hormones (e.g., calcitonin, cortisol, prostaglandins and histamine) with diverse clinical manifestations. Thyroid carcinoma may be asymptomatic; there have been cases with metastases in the liver, bone and lungs (Chong, 1975). MEN-2a includes the hyperplasia of parathyroid glands, which occurs in 20% of patients with pheochromocytoma (Chong, 1975).

The MEN-2b syndrome can include the pheochromocytoma, medullary thyroid carcinoma, mucoid neuroma and hyperparathyroidism (Carney, 1976; Vance, 1973). The mucoid neuroma is clinically manifested by the hypertrophy of nerve fibers in several locations (e.g., cornea, nasal and oral mucosa, eyelids, conjunctival mucosa, skin and gastrointestinal tract). Clinical manifestations of the pheochromocytoma, and medullary thyroid carcinoma associated with MEN-2b are similar to that of MEN-2a (Pont, 1980).

Conclusion

Multiple Endocrine Neoplasia syndrome is an exceptionally rare disease in animals. In nearly all situations the clinical diagnosis is difficult. MEN and MEN-like syndromes are poorly characterized due to a very limited number of cases described worldwide. In order to have a better understanding of MEN syndromes, a detailed description of such cases are further required.
References


