THE HISTOPATHOLOGICAL EVALUATION OF DOGS ADRENAL GLANDS

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Abstract

The aim of the study was to evaluate histopathological changes in adrenal glands in dogs. 32 dogs (0.5–18 years of age) were examined during a routine autopsy. Dogs were divided into 3 age groups: young dogs (0.5–5 years, n=9), middle-age dogs (6–10 years, n=11) and old dogs (11 years and more, n=12). Morphological and histopathological examinations were performed. Percentage of adrenal glands pathology in dogs increased with age: the incidence of pathology in young dogs accounted for 22.3 % and in old dogs and more 91.7 %. Most common histopathological changes were: adrenal cortex hyperplasia (diffuse, nodular), atrophia, degeneration of *z. fasciculata* and *z. reticularis*, hyperemia. Also there were lymphocytic–plasmocytic inflammation, cortex adenomas, pheochromocytomas, cortex hemorrhagia, and cortex atrophy. Single cases of extramedulary haemopoesis, atherosclerosis and metastasis into adrenal gland capsule were identified.

Keywords: dog, adrenal gland, histopathological, examination.

Introduction

The size of dogs' adrenal glands is still not clearly determined, providing wide range of measurements (Douglass et al., 1997). Their size is not always associated with the size of the dog. The main criterion of adrenal glands assessment is the ratio of cortex and medulla; for dogs it is 1:2 (Kierszenbaum, 2002). Grooters and others (1996), found significant enlargement of bilateral diffuse cortex adrenal glands with homogenous echogenicity in dogs with pituitary hyperadrenocorticism (Grooters et al., 1996).

The data about dogs' adrenal glands histopathological evaluation are scanty. In 1960, Dämrich identified some changes in dogs' adrenal glands: deformation, disintegration, pseudoglobuli in *zona glomerulosa*, and invasion of *zona fasciculata* to *zona glomerulosa*, tumors. Later were added: atrophy, degeneration, hypertrophy, hyperplasia, inflammation, tumours, congenital abnormality (van Dijk et al., 2007). Congenital abnormalities such as agenesis, duplicate glands, congenital cortex hyperplasia, and accessory nodule of cortex are rare. Accessory cortical nodules are associated with disturbed embryogenesis of these organs (Zachary et al., 2007). Congenital adrenal glands cortex hyperplasia – *syndromum adrenogenitalis* – is a condition when both hypoadrenocorticism and hyperadrenocorticism occurs. Due to congenital 21-hydrolase deficiency, the supply of cortisol and aldosteron decreases while secretion of ACTH increases (as breed predisposition observed in Pomeranian dogs) (Zachary et al., 2007).

Some degenerative changes can occur in adrenal glands: lipofuscin accumulation, especially in *z. reticularis* (the amount increases with age) (van Dijk et al., 2007); hemosiderin accumulation, fatty changes, hialinosis, calcinosis, melanosis, and amyloidosis (Schulz et al., 1991).

Diffuse and nodular hyperplasia is common in the dogs' adrenal glands and is associated with an elevated ACTH value in blood serum (it is a feature of adaptation) (van Dijk et al., 2007).

Inflammation is an uncommon pathological change in these glands. Autoimmune reactions are its main cause. Also various infection agents, such as viruses, TBC, *Cryptoccocus neoformans, Streptococcus zooepidemicus*, *Hystoplasma capsulatum*, *Toxoplazma goondi*, *Neosporum caninum* can localize in the adrenal glands and produce varying degrees of inflammation (Garnett et al., 1982; Schulz et al., 1991; Barber et al., 1996; Zachary et al., 2007).

Circulatory disturbances that occur in adrenal glands are hyperemia, bleeding, and embolism. Hyperemia of *z. reticularis* and inner part of *z. fasciculata* is observed during septic-toxic shock, cardiogenic shock, and euthanasia (pharmaceuthical). Bleeding in adrenal gland can be bilateral, multifocal or diffuse. Bleeding with necrosis frequently occurs in conjunction with strong stress, trauma, surgical procedures, very difficult parturition, anticoagulant therapy, and intoxication with cumarin type agent. Massive, diffuse, often bilateral cortical haemorrhage with necrosis associated with sepsis and endotoxic shock is known as Waterhouse-Friderichsen syndrome (van Dijk et al., 2007). Infarcts in adrenal glands are often caused by bacteria or tumour cells embols (Kajihara et al., 1983).

Hyperplasia and tumours neuroblastoma, ganglioneuroma, and pheochromocytoma are the most frequent pathology of adrenal medulla (Peterson et al., 1982; van Dijk et al., 2007; Zachary et al., 2007).

Aim of the study: to evaluate pathological changes in adrenal glands of dogs.

Animals and methods of investigation. Adrenal glands of 32 dogs from 0.5 to 18 years were obtained at routine autopsy at the Pathology Centre of Veterinary Academy of Lithuanian University of Health Sciences. Dogs were divided into 3 age groups: young – 0.5–5 years

(n=9), middle aged – 6–10 years (n=11) and old – 11 years and more (n=12). There were 19 males, 13 females, 10 mongrels and 22 purebred dogs.

Each adrenal gland was evaluated macroscopically and sectioned sagitally for estimation of cortec - medulla ratio. Tissue samples were fixed with 10 % formalin solution. The paraffin blocks were made using „Shandon Pathcentre“ and „TES 99 Medite Medizintechnik“ equipment. Five micrometer sections were obtained using “Sakura Accu-Cut SRM“. Sections were stained H&E and Congo Red according to standard histological techniques.

Results

According to our results, a normal cortex–medulla ratio was found in 12 dogs – 37.5%. The percent of affected adrenal glands increased with dogs age statistically reliably ($p<0.005$).

The Congo Red staining procedure did not reveal amyloid in any group.

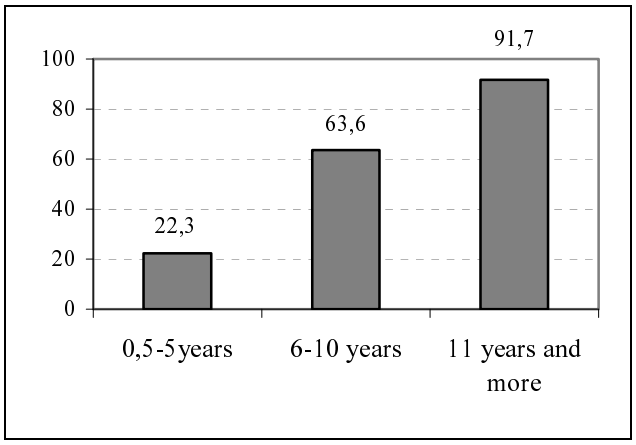

Fig. 1. **The percentage of affected adrenal glands during macroscopic evaluation in age groups**

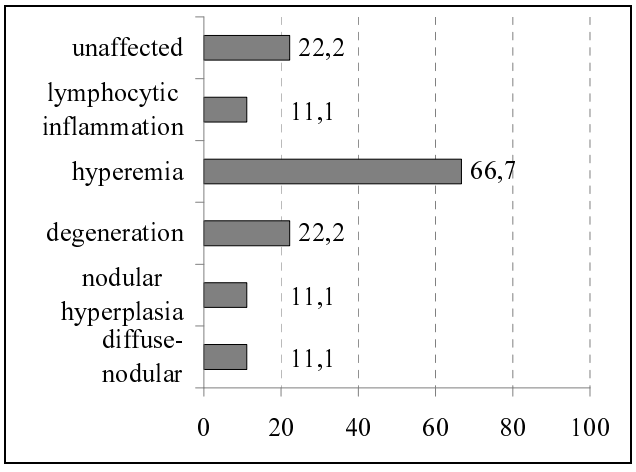

Fig 2. **Histopathological changes in dogs' adrenal glands in first age group**

Few common pathological lesions as hyperemia in cortex and medulla, degeneration of cortex *z. reticularis* and *z. fasciculata* were found in some macroscopically unaffected adrenal glands. More than one pathology (hyperplasia, degeneration and inflammation, or atrophy, adenoma and bleeding) were found in glandular cortex.

Macroscopically unchanged adrenal glands were found in 77.7% of cases. During the histological examination, the identified pathological changes were distributed as shown in Fig. 2.

There were no macroscopic or microscopic changes in 2 adrenal glands (22.2%).

Hyperplasia of adrenal gland cortex was diffuse (n=1) (Fig. 5.) and nodular (n=1) (Fig. 6.). Cortex degeneration was found in *z. reticularis* and *z. fasciculata*. The lymphocytic inflammation was detected in 1 case (*z. fasciculata*) (Fig. 9).

In the second age group, 4 dogs (36.4%) had macroscopically unchanged adrenal glands. During histopathological examination, different pathological processes were identified (Fig. 3). Only 1 gland was without macroscopic and histological changes.

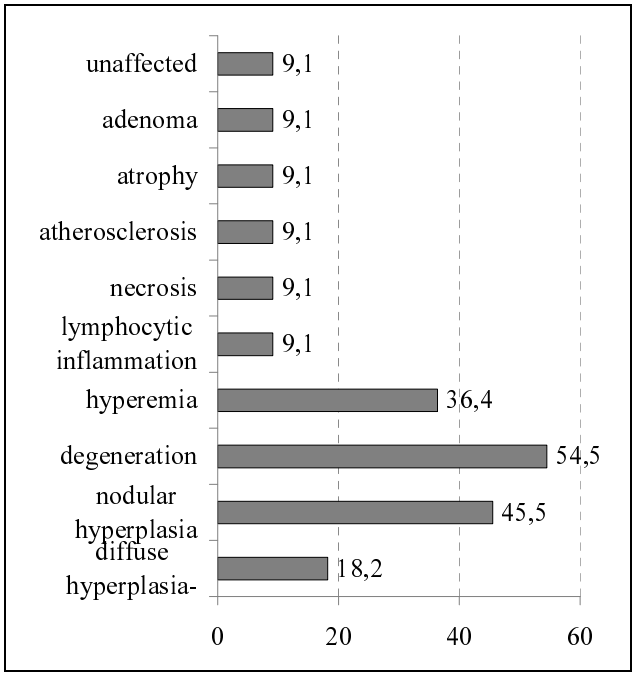

Fig. 3. **Histopathological changes in dogs' adrenal glands in the second age group**

The most common alteration in dogs' adrenal glands was diffuse, nodular or mixed hyperplasia (n=7, or 63.6%). The second most common pathological process was degeneration (54.5%). The degree of degeneration varied within wide ranges – from very low to severe. In the case of degeneration very big, giant cells in *z. reticularis* and *z. fasciculata* with much expressed lipid accumulation, pycnotic nucleus were found (Fig..7.). Cytoplasm of some cells was ruptured. Cortical bilateral necrosis of adrenal glands was found in 1 dog (Fig. 14). We found 1 case of unilateral cortex adenoma (Fig. 11) with following cortex atrophy of other adrenal gland (Fig. 8). Adenoma had necrosis foci, bleedings, cysts and cholesterol crystals accumulations (Fig. 16) Adrenal gland blood vessels atherosclerosis was observed in 1

case (Fig. 13.).

In the third age group were found only 8.3% (n=1) macroscopically unaffected adrenal glands The most common histopathological findings were: nodular hyperplasia 66.7% (n=8) and degeneration 33.3% (n=4) (Fig. 4).

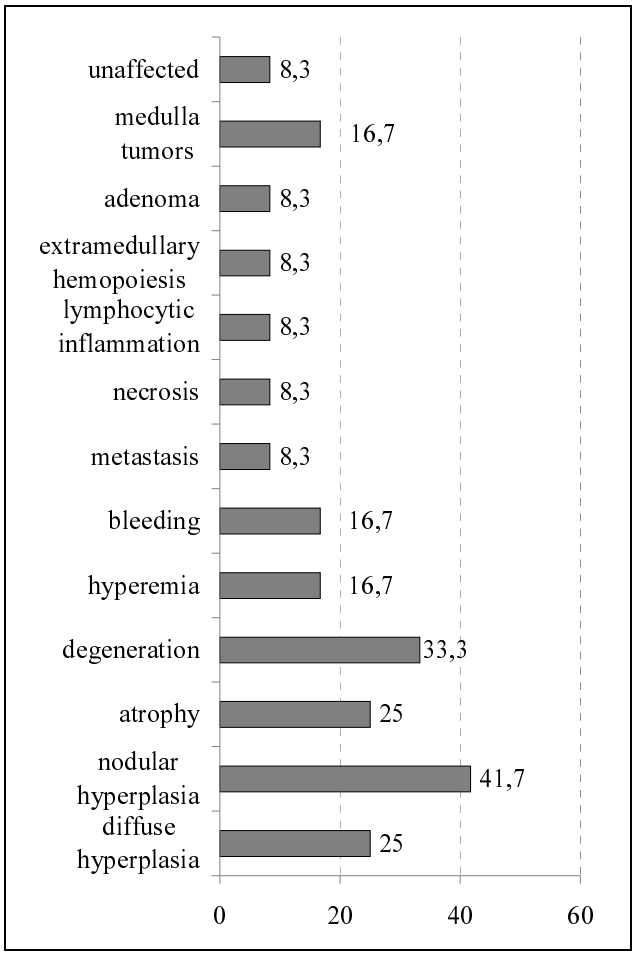

Fig. 4**. Histopathological changes in dog's adrenal glands in the third age group**

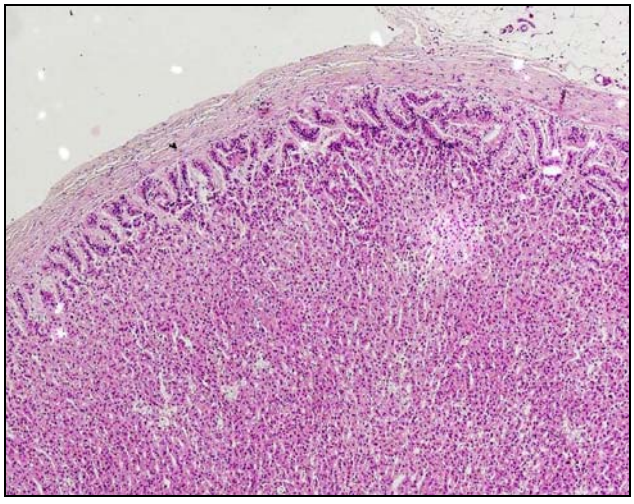

Fig. 5. **Diffuse adrenal gland hyperplasia, HE, low magnification**

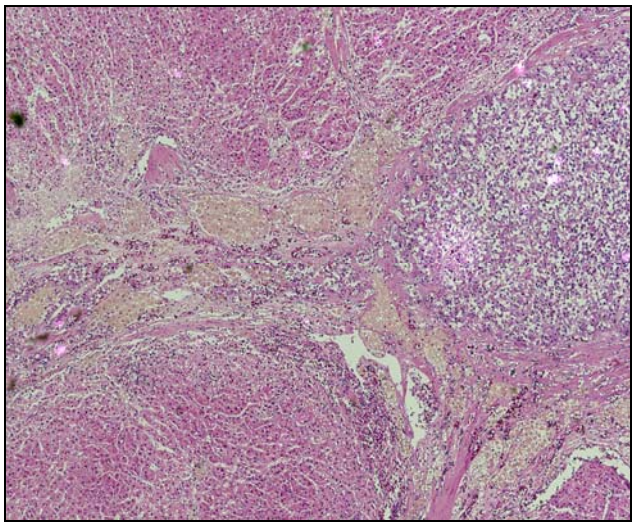

Fig.6. **Nodular adrenal gland hyperplasia, HE, low magnification**

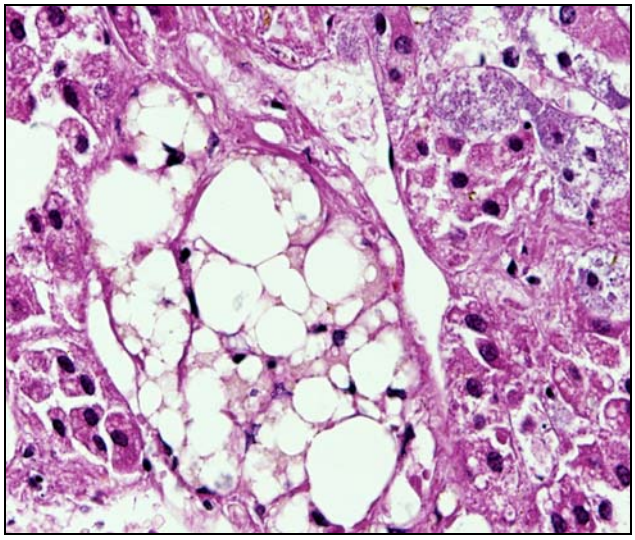

Fig. 7**. Adrenal gland cortex *z. reticulata* degeneration, HE, high magnification**

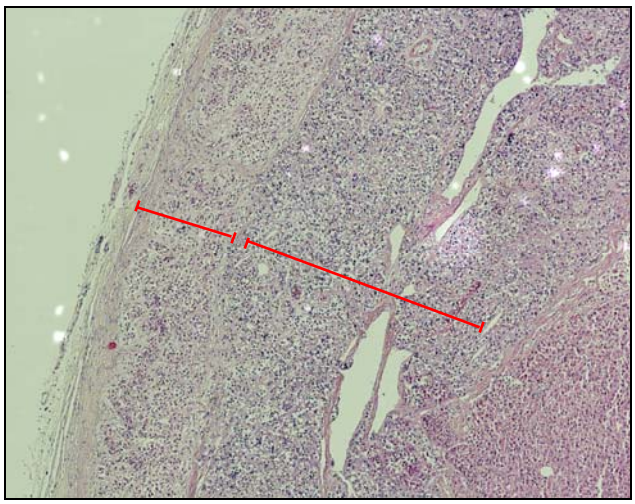

Fig. 8. **Adrenal gland cortex atrophy, HE, low magnification**

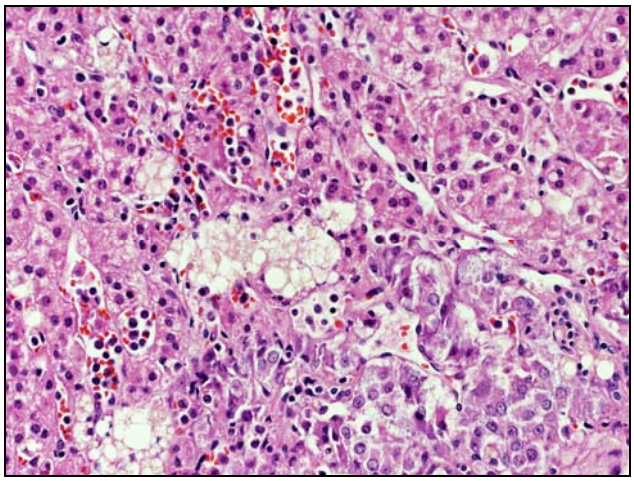

Fig. 9. **Infiltration of lymphocytes and plasmocytes in adrenal gland cortex *z. fasciculata* and *z. reticularis*, HE, medium magnification**

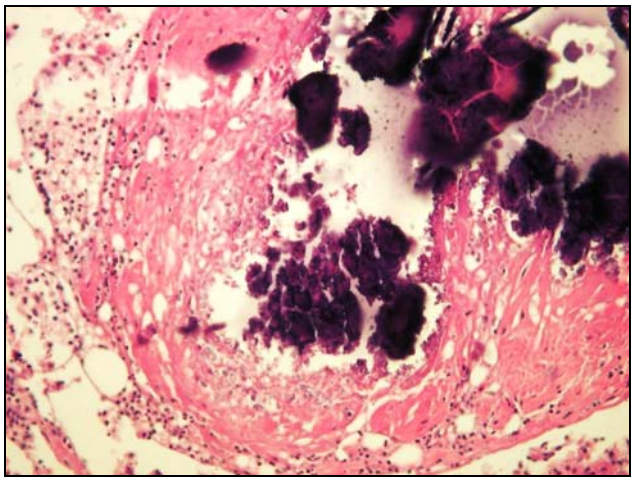

Fig. 10**. Adrenal gland cortex adenoma a with necrosis, and calcification, HE, low magnification**

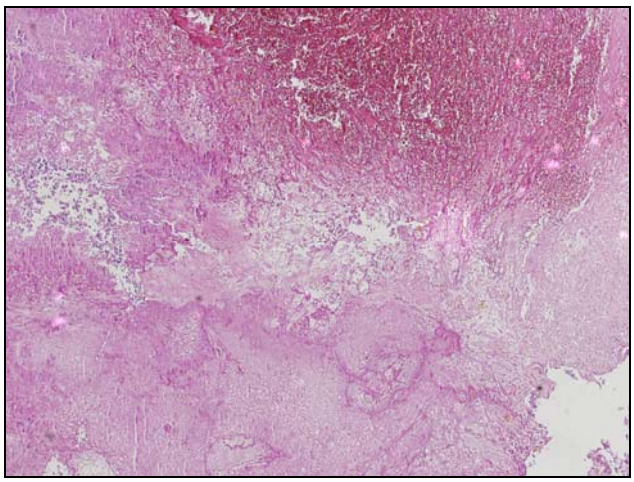

Fig. 11. **Adrenal gland cortex adenoma with bleeding and necrosis, HE, low magnification**

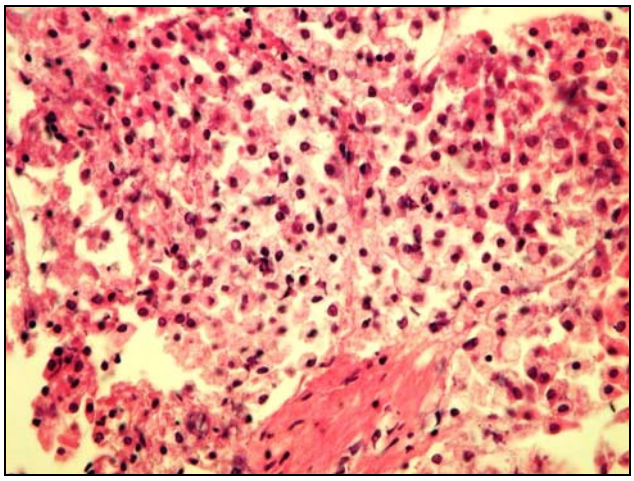

Fig. 12. **Adrenal gland cortex adenoma with necrosis, HE, medium magnification**

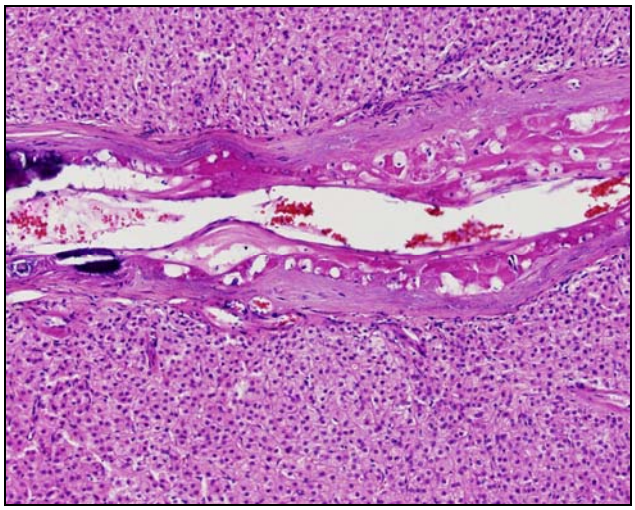

Fig. 13. **Atherosclerosis in adrenal gland blood vesels, HE, medium magnification**

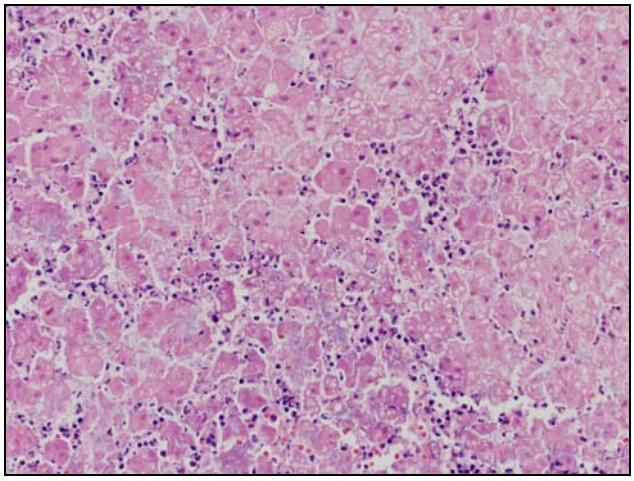

Fig. 14. **Acute diffuse severe bilateral adrenal glands cortex necrosis with bleeding and neutrophils infiltration, HE, medium magnification**

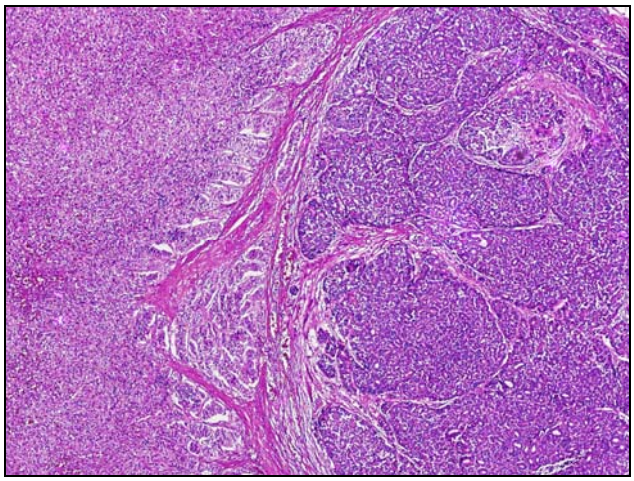

Fig. 15. **Mammary gland adenocarcinoma metastasis in to adrenal capsule, HE, low magnification**

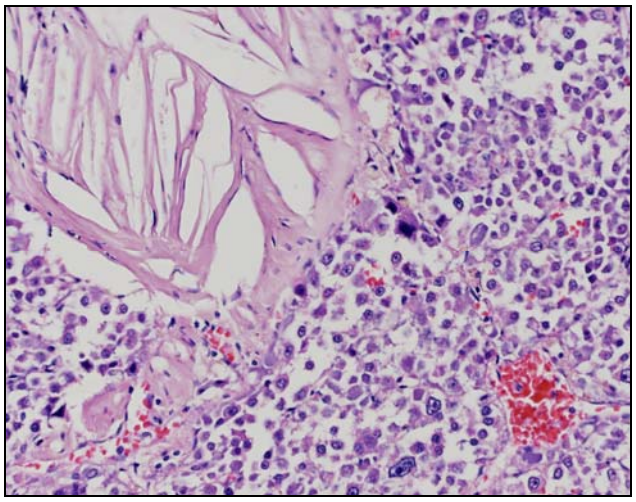

Fig. 16**. Adrenal gland cortex adenoma with cholestherol crystals accumulation, HE, medium magnification**

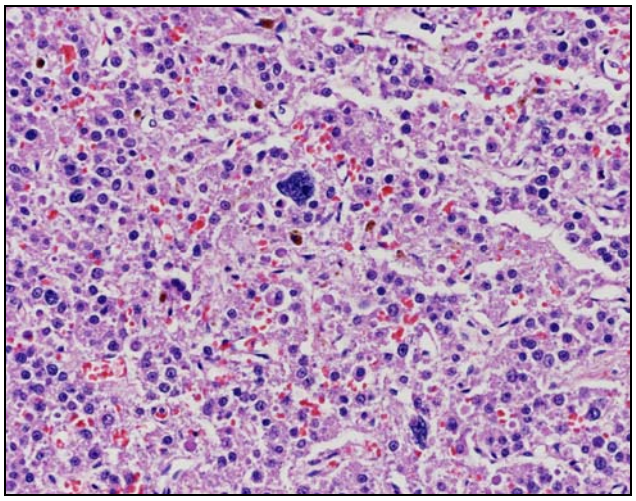

Fig. 17. **Ekstramedullary haemopoiesis in adrenal gland cortex, HE, medium magnification**

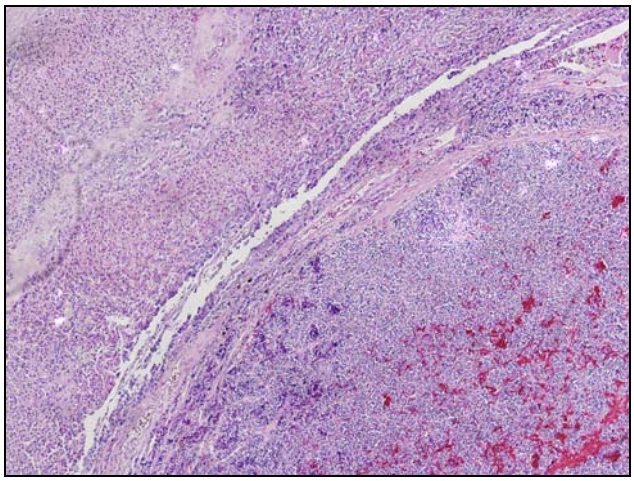

Fig. 18. **Adrenal gland medulla tumor – pheochromocytoma, HE, medium magnification**

We found one case of 10 cm^3 gross adrenal cortex adenoma with massive foci of necrosis and calcinosis (Fig. 10) and with severe bleeding into pelvic cavity. Lymphocytic-plasmocytic inflammation was observed in one case, as extramedullary hemopoiesis (Fig. 17) and mammary glands metastasis into adrenal capsule (Fig. 15). Adrenal medulla tumour, phemochromocytoma, was found in 2 cases (Fig. 18).

Discussion and conclusions

This is a pilot study about dogs' adrenal glands pathologies in Lithuania. According to our results, the percentage of affected adrenal glands increases with dog age. Cortex hyperplasia was most common finding in age groups II and III: 63.6 and 66.7% respectively ($p>0.05$), and in age group I only 22.2% ($p<0,005$). In the case of both diffuse and nodular hyperplasia of cortex, the cortex cells hypertrophia and hyperplasia were detected. Electron microscopy showed that in the case of nodular hyperplasia the ultrastructural changes of cells are degenerative while such changes as an increased amount of endoplasmic reticulum and other organelles in cases of diffuse cortex hyperplasia indicate the intensification of cell functions and hyperactivity (Appleby, Sohrabi-Haghdoost, 1980). In the case of nodular hyperplasia well defined nodules are found in *z. glomerulosa* or *z. fasciculata* (Zachary et al, 2007). The fatty degeneration is often seen in the cells of such nodules. Nodular hyperplasia is more common in older dogs. Sometimes functionally active nodules can be found in *z. reticularis* with overproduction of androgens and virilisation signs (Schulz et al., 1991). Diffuse adrenal gland hyperplasia can be unilateral, bilateral, and is localised more commonly in *z. fasciculata* and *z. reticularis* and is accompanied with severe fatty degeneration of cells – *Z. glomerulosa* is often atrophic. Diffuse hyperplasia is adrenal cortex response to autonomic ACTH hyperstimulation (for example, pituitary adenoma). Clinical expression of adrenal cortex hyperfunction in dogs manifests as Cushing syndrome. There are typical signs for this syndrome (due to gliuconeogenic, lypolytic,

protein catabolic and antiinflammatory, immunosupressive effect of glucocorticoids): reduced body weight/obesity (proteins break down/ lypomatosis), poluria, appetite and food intake often are increased (polyphagia) as a direct result of either the hypercortisolism or damage caused by compression of appetite centre, steroid hepatopathy (hepatomegaly), pendulous abdomen (due to muscle atrophy, low protein catabolism, hepatomegaly), atrophy of epidermis, symmetric alopecia, hyperceratosis, comedones, hyperpigmentation, dystrophic mineralisation of collagen, elastic fibres, basal membranes in lung, stomach, gut, kidney, hair follicle, increased susceptibility to infections, hypercholesterinemia, hyperglicemia (steroidal diabetes), hypercoagulation, eosinopeny, lymphopeny, involution of lymphoid organs, osteopeny (Schulz et al., 1991; Zachary et al., 2007). It was determined that in dogs with Cushing syndrome the amount of cancellous bone is lower by 25% than in healthy dogs than the amount of osteoblasts, osteoid and trabeculaes (Norrdin et al., 1988).

The percentage of fatty degeneration was highest in the first age group – 66.7%, somewhat lower in the second age group – 54.5% and lowest in the third age group – 33.3%. Lipid droplets in adrenal cortex cells are normal findings due to synthesis of steroid hormones. Cholesterol is synthesized from acetates at endoplasmic reticulum, and it is converted to pregnenolon at mitochondrias (Kierszenbaum, 2002). Fatty degeneration is not associated with the functional status of adrenal glands. Widespread, severe fatty degeneration with death of separate cells and formation of lipid cysts is found in aged dogs (Schulz et al., 1991).

The spectrum of pathological processes widens with dogs' age: in the first age group 4 pathological processes such as hyperplasia, degeneration, inflammation and hyperaemia were found, in the second age group, beside the mentioned processes, adenoma, atherosclerosis, atrophia, and necrosis were found, and in the third age group there appeared tumour metastasis, extramedullary hemopoesis, bleedings and medulla tumour respectively.

Unaffected adrenal glands or glands with simple pathological changes such as hyperemia and degeneration were found in 50% of mongrels and 36.4% purebred dogs respectively and in 69.2% of female and 21.1% male dogs respectively.

Atrophy of adrenal gland cortex is mostly associated with decreased value of ACTH in blood serum due to pituitary alteration (for example adenoma) or its suppression with some drugs and causes hypoadrenocorticism. Adrenal cortex atrophy can induce treatment with glucocorticoids, aminoglutetimide, mitotane in human and with trilostane (Reusch et al., 2007), or lisodrene (Feldman et al., 1996) in dogs. Some chemicals act as adrenotoxic such phosphor organic compounds (Schulz et al., 1991). Adrenal glands cortex can be destroyed by inflammation (viral, bacterial or autoimmune) and primary and secondary tumours, Waterhouse-Friderichsen syndrome or due to idiopathic atrophy (Zachary et al., 2007). Idiopathic adrenal glands cortex atrophy in dogs as in humans is caused supposedly by autoimmune inflammation (Feldman et al., 1996). Hypoadrenocorticism can be congenital and causes absence of all cortical hormones as glucocorticoids, mineralcorticoids and sex hormone with corresponding clinical signs. This status can be found in standard poodles, Portuguese water dogs, border collies, and New Scotland duck tolling retrievers (Schulz et al., 1991, Zachary et al., 2007). For dogs with secondary hipoadrenocorticism the mineral corticoid deficiency is uncommon because ACTH has a tropic effect on *z. glomerulosa* (Kintzer et al., 1997).

Unilateral cortex atrophy develops in dogs with functionally active cortex adenoma in other adrenal glands (Schulz et al., 1991; van Dijk et al., 2007; Zachary et al., 2007).

Adrenal cortex hyperplasia is associated with an increased ACTH secretion. The causes of elevated ACTH secretion are stimulation of pituitary, functionally active tumour of pituitary, and ectopic source of ACTH. Presumably the ectopic source of ACTH is absent in dogs and other animals, but there was one case in a dog when the ectopic ACTH source in pancreas occurred (Galac et al., 2005). An elevated ACTH value causes glucocorticoids overproduction and is followed by clinical signs – hyperadrenocorticism. One case is known of ACTH independent hyperadrenocorticism in a dog which was caused by wheat grain and meal rich feeding (Galac et al., 2008).

Lymphocytic plasmocytic adrenalitis is considered at present as autoimmune disease (Zachary et al., 2007). It has been reported that together with T lymphocytic adrenalitis lymphocytic B hypophysitis and primary thyroid follicle atrophy and collapse can manifest and this condition is similar to human II type autoimmune polyendocrine syndrome (MEN) called Schmidt syndrome (Adissu et al., 2010).

Adrenal glands cortex primary tumours are adenoma and carcinoma and they are typical in old dogs. Cortex adenoma has yellow colour, with partial or complete capsule, develops together with nodular hyperplasia and can be confused with hyperplasic nodules. Carcinoma is a rarer tumour without gender or breed predisposition. It often can be bilateral an invade the whole adrenal gland and give metastasis to liver, kidney, mesenteric lymphnode, and lung (Schulz et al., 1991). Adrenal cortex carcinoma tends to direct spreading in *v. cava caudalis* and formation tumour embols inside. Tumour embols inside *v. cava caudalis* can be determined during ultrasonography (Davis et al., 2012).

Secondary adrenal glands tumours are metastasis from of tumours in other organs. 21% of metastases in dogs were caused by 26% of different tumours in lungs, mammary gland, prostate, stomach, pancreas carcinoma and melanoma. Only 42% of metastases are found at macroscopical examination of adrenal glands in dogs, and the rest are detected only during histopathological examination. Secondary adrenal glands tumours account for 26.7% of all adrenal glands tumours in dogs (Labelle, De Cock, 2005).

Pheochromocytoma causes acute or chronic lethargy

and vomiting, but biochemicals and hematological parameters often are unspecific (Van Aalst, 2007). This tumour can cause fatal heart and vascular failure. Only some of these tumours give metastasis (regional lymphnode, liver, lung, kidney, spleen, and bone or spread directly to *v.cava caudalis*, pelvic aorta and other regional blood vessels (Bouayad et al., 1987). Tumours manifest in middle age and old dogs, but sex or breed predisposition was not established (Barther et al., 1997). Pheochromocytoma in dogs can be associated with MENS – multiple endocrine neoplasia syndrome (Proverbio et al., 2012).

Conclusions

1. The percentage of affected adrenal glands increased with dogs' age statistically reliably ($p<0.005$): from 22.3% in young dogs to 91.7% in old dogs.
2. The most frequent pathological findings were hyperplasia (diffuse, nodular), degeneration, and hyperemia. Inflammation (lymphocitic), adenoma, bleeding and atrophia were less frequent findings.
3. Single cases of blood vessels atherosclerosis, extramedulary hemopoesis, and metastasis of mammary gland adenocarcinoma were identified.
4. Percentage of pathologies and their degrees increases with dogs' age.
5. More affected were adrenal glands from purebred dogs.
6. The percentage of affected adrenal glands was markedly lower in female dogs.

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