Extrarenal manifestations of uremia in a keeshond with juvenile nephropathy

by

Jan FREUND
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Extrarenal manifestations of uremia in a keeshond with juvenile nephropathy

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Jan FREUND

Promotors: Dr. Leslie Bosseler
Prof. dr. Koen Chiers

Case Report
as part of the Master's Dissertation

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FOREWORD

I want to thank Hanna Bellmann and our daughter Veerle for their help and patience during the process of writing this thesis. I would also like to thank Felicia Benefield and Petra Bellmann for their interest in this thesis, their suggestions and their corrections. Furthermore, I want to thank Dr. Leslie Bosseler, Prof. dr. Koen Chiers and the department of pathology for their support and for providing this case.
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SUMMARY
This case report is about a male, 9 months old keeshond with the postmortem diagnosis of juvenile nephropathy. In addition to renal lesions, the pathological examination revealed extrarenal lesions that are associated with uremia. In the first part of the thesis, uremia and associated lesions are discussed. The second part describes the specific pathological findings in this case and is followed by a brief discussion.
The term uremia covers the biochemical abnormalities as well as the symptoms and extrarenal manifestations of prolonged azotemia. Symptoms of uremia are rather unspecific, ranging from anorexia to hyperventilation. Extrarenal manifestations occur across all organ systems. In dogs lesions of the digestive, respiratory and cardiovascular tract seem to be most common. The pathogenesis of these lesions is directly related to the kidney's failure to maintain: fluid volume regulation, waste excretion, electrolyte and acid base balance, and hormonal functions. Characteristic lesions are secondary hyperparathyroidism, fibrous osteodystrophy, uremic gastritis and uremic pneumonitis. The latter two lesions were also found in the case. Uremic gastritis in this case was characterized by mucosal ulcerations, hemorrhage, necrosis and laminar mineralization of the smooth muscle. The lungs were resilient and edematous and there was mineralization of the alveolar septa. These lesions were consistent with those previously described in the literature.

Key words: Dog - Extrarenal - Keeshond - Pathology- Uremia

SAMENVATTING
Deze casusbespreking gaat over een 9 maanden oude keeshond die post-mortem gediagnosticeerd werd met juveniele nefropathie. Bovendien werden verschillende extrarenale letsels vastgesteld welke geassocieerd zijn met uremie. In het eerste gedeelte van deze casusbespreking wordt nagegaan wat uremie is en welke verschillende letsels er mee kunnen gepaard gaan. Het tweede deel gaat over de specifieke bevindingen bij deze keeshond en wordt gevolgd bij een discussie. De term uremie beschrijft de biochemische veranderingen als ook symptomen en secundaire letsels die gepaard gaan met aanhoudende azotemie. De symptomen van uremie zijn eerder aspecifiek, zoals bijvoorbeeld anorexie en hyperventilatie. Secundaire letsels van uremie kunnen voorkomen in alle orgaansystemen maar bij de hond zijn vooral het spijsverterings-, ademhalings- en cardiovasculaire stelsel betrokken. De pathogenese van deze letsels hangt samen met het onvermogen van de nieren om het vloeistofvolume, de eliminatie van afvalstoffen, het electrolyten en zuur-base evenwicht en hormonale functies te onderhouden. Secundaire hyperparathyroidie, fibreuze osteodystrofie, uremische gastritis en uremische pneumonitis zijn karakteristieke letsels bij uremie. Uremische gastritis en uremische pneumonitis werden ook in deze casus teruggevonden. De uremische gastritis werd gekenmerkt door ulceraties van de mucosa, hemorrhagie, necrose en laminair mineralisatie van de gladde spieren. De stevig aanvoelende longen waren oedemateus en er was mineralisatie van de alveolaire septa, typisch voor uremische pneumonitis. Deze letsels stokten met wat er in de literatuur is beschreven.

Trefwoorden: Extrarenal - Hond - Keeshond - Pathologie - Uremie
INTRODUCTION

Renal diseases that may result in uremia are common in dogs, cats and humans. There are many pathologies that are associated with uremia and compromised renal function. These pathologies may occur in all organ systems (Cianciolo & Mohr 2015). In dogs lesions of the digestive system, respiratory system and cardiovascular system are most common (Dantas & Kommers 1997).

In humans the advent of hemodialysis has led to a decrease of some lesions, for example uremic pneumonitis, that have been associated with uremia (Khalid et al. 2013). Therefore in human medicine uremic toxins that cannot be dialyzed are now in the spotlight (Vanholder et al. 2008). These toxins are especially associated with cardiovascular, renal and neurological pathologies (Anonymous 2016).

The first part of this case report consists of a literature review. The definition and general pathophysiological mechanisms behind uremia will be discussed without going into detail on the various pathologies that may lead to uremia. The focus will lie on the different extrarenal lesions that are associated with, or caused by uremia. Where possible the lesions seen in dogs, cats and humans will be compared.

In the second part the pathological examination and findings of the case at hand will be described. Afterwards these findings will be discussed and compared with the expected lesions described in the literature.
LITERATURE REVIEW

1. UREMIA AND AZOTEMIA

1.1. DEFINITION
The term azotemia describes an abnormal elevation of non-protein nitrogen compounds in the blood. These are routinely measured as increased serum urea (blood urea nitrogen or BUN) and serum creatinine (Stockham & Scott 2008). Azotemia is typically associated with a decrease in glomerular filtration rate (GFR) but clinical signs are usually absent at this stage (Cianciolo & Mohr 2015). Depending on where the cause is situated, azotemia can be classified as pre-renal, renal and post-renal azotemia (see below).

Uremia on the other hand refers to the clinical and pathological manifestation of renal failure and severe azotemia (Stockham & Scott 2008; Almeras & Argilés 2009). In addition to the biochemical abnormalities (azotemia), it includes the clinical signs and symptoms that result from the loss of the kidney’s regulatory, excretory and endocrine functions (Kumar et al. 2005; DiBartola & Westropp 2014). The biochemical disturbances in uremic patients often result in secondary extrarenal lesions that are also implied in the term uremia (Cianciolo & Mohr 2015; Kumar et al. 2005; DiBartola & Westropp 2014).

1.2. CAUSES AND MECHANISMS LEADING TO AZOTEMIA AND UREMIA
Based on the origin of azotemia, prerenal, renal and postrenal azotemia can be differentiated (see Table 1). In prerenal azotemia there is a reduction of the glomerular filtration rate (GFR) due to a decrease in renal blood flow (hypoperfusion). Possible causes are hypovolemia or reduced cardiac output. In case of hypovolemia, the situation is worsened by the activation of the renin-angiotensin system and the release of ADH, causing vasoconstriction of the glomerular arterioles and enhanced absorption of water and urea in the collecting tube (Stockham & Scott 2008).

Renal azotemia is caused by abnormalities at the level of the renal parenchyma, more specifically, a loss of nephron function. Losing up to 50% of nephron function will result in diminished renal reserve making the patient more susceptible for additional renal insults. A GFR between 25-50% (renal insufficiency) may result in azotemia. If the GFR is further reduced (<25%) renal failure and uremia ensues and homeostasis cannot be maintained. At a GFR of less than 5%, end-stage renal disease ensues (Cianciolo & Mohr 2015). Postrenal azotemia is the result of urinary tract obstruction or leakage of urine into the surrounding tissues or into the peritoneal cavity. Obstruction leads to an increase in intracapsular pressure as well as the release of vasoactive substances, both ultimately leading to a reduced GFR. Leaked urine makes its way in to the bloodstream via diffusion and passive absorption. Additionally, azotemia can be the result of increased production of urinary waste products, for example following proteolysis and degradation of hemoglobin in case of severe intestinal hemorrhage (and insufficient intestinal compensation). This can be considered a form of prerenal azotemia (Stockham & Scott 2008).
1.3. Clinical signs and symptoms

Symptoms of chronic kidney disease in dogs are often rather nonspecific and include symptoms such as anorexia, weight loss, lethargy, poor body condition and a dull coat. Polyuria and polydipsia are often noticed in dogs and cats with chronic kidney disease. Vomiting occurs more often in dogs than in cats. At a late stage, diarrhea might develop in uremic dogs. When polyuria coincides with insufficient water intake, this often leads to dehydration. Ulcers of the oral cavity can be observed in dogs. Bone demineralization can manifest as a “rubber jaw” and occurs mostly in young growing dogs (DiBartola & Westropp 2014). Further hyperventilation may be observed and can be a sign of metabolic acidosis. Additionally, other symptoms associated with the renal pathology itself, such as renal pain or pyuria, may be present (Cianciolo & Mohr 2015). In cats with chronic kidney disease, inappetence and vomiting were observed in 84 and 45 percent of the cases respectively (McLeland et al. 2014).

<table>
<thead>
<tr>
<th>Signs and symptoms of uremia</th>
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</thead>
<tbody>
<tr>
<td>Anorexia</td>
<td>Dull coat</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Polyuria and polydipsia</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Poor body condition</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Clinical signs and symptoms of uremia in small animals. Based on DiBartola & Westropp (2014; Cianciolo & Mohr 2015; McLeland et al. 2014).
2. EXTRARENAL LESIONS CAUSED BY UREMIA

2.1. PATHOPHYSIOLOGY

The described symptoms, as well as the different pathological lesion discussed in this chapter, reflect the failure of the kidneys to maintain and regulate: 1) the excretion of metabolic wastes, 2) the electrolyte and acid-base balance, 3) the fluid volume and 4) its hormone metabolism (Cheville 1979).

2.1.1. Disturbed fluid volume regulation

The disturbance in fluid regulation may lead to either dehydration or generalized edema (anasarca). A reduced ability to concentrate urine due to lesions of the medulla and juxtaglomerular nephrons leads to polyuria, which especially when combined with insufficient water intake, leads to dehydration. Fluid loss can be further aggravated by vomiting and diarrhea. It seems counterintuitive but in some cases anasarca develops. This can be explained by the hypoproteinemia that is a consequence of protein loss at the level of the damaged glomeruli. The decrease in oncotic pressure may lead to extravasation of water (Cianciolo & Mohr 2015).

2.1.2. Retention of wastes and uremic toxins

In addition to urea and creatinine, there are other solutes that are normally excreted via the kidneys that accumulate in chronic renal disease. When these retained substances have a negative impact on normal biological functions, they are called uremic toxins (Duranton et al. 2012). The success of hemodialysis has provided evidence for the toxicity of dialyzable compounds (Depner 2001). According to the Uremic Toxin - Data Base of the European Uremic Toxin Work Group, 130 uremic toxins have been identified. Of these toxins 41,33% are associated with cardiovascular, 17,33% with renal and 9,33% with neurological pathologies (Anonymus 2016).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristics</th>
<th>Prototypes</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small water-soluble molecules</td>
<td>MW &lt; 500 Da, easily removed by any dialysis strategy</td>
<td>Urea, creatinine</td>
<td>Not necessarily toxic</td>
</tr>
<tr>
<td>Middle molecules</td>
<td>MW &gt; 500 Da, removed only through large-pored membranes</td>
<td>β₂-M, leptin</td>
<td>Large array of biological impacts</td>
</tr>
<tr>
<td>Protein-bound molecules</td>
<td>Any MW, difficult to remove with any dialysis strategy</td>
<td>Phenols, indoles</td>
<td>Large array of biological impacts</td>
</tr>
</tbody>
</table>

MW Molecular weight, β₂-M β₂-microglobulin

Table 3: Classification of uremic toxins. Toxicity is primarily associated with other toxins than urea and creatinine. From Vanholder et al. (2008), published in Pediatric nephrology, © Springer

In veterinary medicine, uremic toxins have, among other things, been suggested to be possible emetogens in cats where gastric lesions alone cannot explain gastrointestinal complaints like vomiting (McLeland et al. 2014).

2.1.3. Electrolyte and acid base imbalances

In chronic renal failure, the kidneys fail to regulate the electrolyte balance. In healthy animals, there is a net excretion of K⁺, H⁺, NH₄⁺, and PO₄ and conservation of Na⁺, Cl⁻, HCO₃⁻, Ca²⁺ and Mg²⁺ (Stockham & Scott 2008). One expects the ion concentrations to be diametrically opposite to their normal net excretion or retention, but they are often paradoxical (Cianciolo & Mohr 2015). Table 4 shows some possible effect of electrolyte imbalances. Hypocalcemia is often the result of phosphate retention that arises in chronic renal failure.
Electrolyte Excess Deficit
Na Anasarca, hypertension, pulmonary edema Dehydration, neurological symptoms
K Cardiotoxicity Muscular weakness
Ca Hypercalcemic nephropathy Osteodystrophia
P Hypocalcemia

Table 4: Effects of excesses and deficits of different electrolytes. Based on Cianciolo & Mohr (2015).

Acidosis in uremic patients can result from either increased retention of hydrogen ions at the collecting tube or from impaired resorption of bicarbonate ions at the proximal tube (Stockham & Scott 2008).

2.1.4. Disturbed hormone metabolism
In the kidney, hormones such as erythropoietin, renin, and prostaglandins are produced. Another hormone, vitamin D, is metabolized in the kidney where its activation to 1,25 dihydroxycholecalciferol takes place. Hormonal changes are either the result of renal damage (e.g. impairment of erythropoietin forming cells or are a consequence of electrolyte imbalances as is the case of the development of renal secondary hyperparathyroidism (Depner 2001).

Secondary hyperparathyroidism can either result from dietary imbalances of calcium and phosphorus or from chronic renal failure. Renal secondary hyperparathyroidism is common in dogs but can also occur in cats. The decreased GFR in animals with chronic renal failure leads to a reduced renal clearance of phosphate, resulting in hyperphosphatemia. This in turn causes hypocalcemia which stimulates the synthesis and secretion of parathyroid hormone (PTH) (Slatopolsky et al. 1971; Craig et al. 2015). Normal serum levels of ionized calcium prevent parathyroid hormone secretion and cause degradation of preformed PTH via Ca\(^{2+}\)-sensing receptor. But hypocalcemia is a major stimulus for PTH release and gene expression, as is hyperphosphatemia itself. Furthermore, long term hypocalcemia stimulates parathyroid cell proliferation. Calcitriol on the other hand inhibits PTH gene expression and may also regulate parathyroid cell proliferation. In addition, there is a decrease in the expression of both, Ca\(^{2+}\)-sensing receptor and calcitriol receptor, in secondary hyperparathyroidism (Silver et al. 2002).

Additionally, the hyperphosphatemia induces the production of fibroblast growth factor 23 (FGF23) by osteocytes. FGF23 has multiple effects. On the one hand, it increases renal phosphate excretion, but on the other hand, it reduces the amount of the active vitamin D3 metabolite 1,25-dihydroxycholecalciferol (1,25(OH)\(_2\)D\(_3\)). It does so by inhibiting renal 1α-hydroxylase and inducing 24-hydroxylase, causing decreased production of and increased breakdown of 1,25(OH)\(_2\)D\(_3\) respectively (Craig et al. 2015).

Parathyroid hormone itself influences the bone metabolism in different ways. It has a direct effect on osteoclasts, stimulating bone resorption and increasing bone turnover. Additionally, PTH inhibits sclerostin, increasing bone formation, but due to the low 1,25(OH)\(_2\)D\(_3\) levels in chronic renal failure,
this can result in osteomalacia and fibrous osteodystrophy (renal osteodystrophy) (Craig et al. 2015). The lesions caused by these changes in bone metabolism will be discussed below.

Another hormone produced by the kidney is erythropoietin. It is produced by capillary endothelial cells in the renal cortex in response to hypoxia and stimulates erythropoiesis. The kidneys failure to produce sufficient erythropoietin seems to be an important etiologic factor in the pathogenesis of non-regenerative anemia that is commonly observed in human and canine patients with chronic renal failure (King et al. 1992).

Other hormonal derangements in renal disease are excessive production of renal renin, hypergastrinemia, lower gonadotropin production and high serum levels of melanocyte-stimulating hormone (Depner 2001).

2.1.5. Mineralization

Mineralization is common and affected organs are the stomach, lung, pleura, and pericardium (Cianciolo & Mohr 2015). In addition to abnormal plasma calcium and phosphorus, local acidosis and ischemia may contribute to (gastric) mucosal mineralization (Cheville 1979). Hypergastrinemia in animals with renal disease might contribute to gastric hyperacidity, as gastrin stimulates the release of HCL from parietal cells (McLeland et al. 2014). In cardiovascular and cutaneous lesions, there is dystrophic calcification. At the level of the stomach band-like distribution patterns of mineralization indicate metastatic calcification (Peters et al. 2005).

The type of deposits formed relies on the serum concentrations of calcium, magnesium, phosphate and carbonate. When calcium is higher than magnesium an apatitic compound is formed. The opposite proportion leads to precipitation of whitlockite or amorphous calcium phosphate (LeGeros et al. 1973). In addition to the altered mineral concentrations, the distribution of mineralization is dependent on local factors, such as tissue glycosaminoglycans, cellular factors, local pH and ischemia (Cianciolo & Mohr 2015; Cheville 1979).

2.2. General findings during necropsy

Animals with uremia that are admitted for necropsy are often in a bad condition and show signs of dehydration and cachexia. This is due to prolonged anorexia, vomiting, diarrhea and tissue catabolism (Cianciolo & Mohr 2015). In severe cases, the typical ammonia odor (uremic fetor) can be recognized. There are also diagnostic sticks available that can be used to measure the urea concentration in the intraocular fluid post mortem. The urea concentration within the intraocular fluid approximates the plasma concentration (Hafner-Marx 2007).

Primary kidney pathologies such as hydronephros, polycystic kidney disease, renal hypoplasia or agenesis may be observed hint in the direction of an underlying renal disease. Furthermore, secondary extrarenal lesions may be present and are indicative for uremia. These lesions will be discussed below.
2.3. Extrarenal lesions

Extra-renal manifestations of uremia are common in dogs, cats, and humans. In veterinary medicine, extrarenal lesions do not occur in a constant and predictable fashion. And when they are observed, it is mostly in dogs and more often in patients with chronic renal failure rather than acute renal failure (Cianciolo & Mohr 2015). In a retrospective study of 72 necropsies of dogs with uremia, Dantas and Kommers (1997) found extrarenal lesions in the digestive, respiratory, cardiovascular, endocrine and skeletal systems. The most common lesions in these dogs were uremic gastropathy (79.16%) and uremic pneumonia (40.27%) (see Table 5). In human patients, extrarenal lesions, such as uremic pneumonitis, have become less common since the widespread availability of hemodialysis (Khalid et al. 2013).

Table 5. Type and frequency of extrarenal lesions in 72 uremic dogs

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Number of Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uremic gastropathy</td>
<td>57</td>
<td>79.16</td>
</tr>
<tr>
<td>Uremic pneumonia</td>
<td>29</td>
<td>40.27</td>
</tr>
<tr>
<td>Mural endocarditis / degenerative arteriopathy</td>
<td>25</td>
<td>37.72</td>
</tr>
<tr>
<td>Uremic enteropathy</td>
<td>16</td>
<td>22.22</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>13</td>
<td>18.05</td>
</tr>
<tr>
<td>Parathyroid hyperplasia</td>
<td>11</td>
<td>15.27</td>
</tr>
<tr>
<td>Subpleural mineralization</td>
<td>10</td>
<td>13.88</td>
</tr>
<tr>
<td>Ulcerative stomatitis</td>
<td>8</td>
<td>11.11</td>
</tr>
<tr>
<td>Ulcerative glossitis</td>
<td>6</td>
<td>8.33</td>
</tr>
<tr>
<td>Fibrous osteodystrophy / osteomalacia</td>
<td>4</td>
<td>5.55</td>
</tr>
<tr>
<td>Ulcerative laryngitis</td>
<td>2</td>
<td>2.77</td>
</tr>
</tbody>
</table>

Table 5: Type and frequency of extrarenal lesion in 72 with uremia. Translated from Dantas and Kommers (1997), published in Ciência Rural, © Universidade Federal de Santa Maria

2.3.1. Digestive system

Gastrointestinal lesions may contribute to the clinical signs of vomiting, diarrhea and melena in uremic dogs (Cianciolo & Mohr 2015). As ulcerative lesions are less common in cats, McLeland et al. (2014) suggested that certain uremic toxins may have an emetogenic effect.

Uremic gastritis (or: uremic gastropathy)

In humans and dogs suffering from chronic uremia, uremic gastritis is common (Moustafa et al. 1997; Peters et al. 2005). In cats, ulcerations and hemorrhage are uncommon (McLeland et al. 2014).

The lesions are typically described as hyperemic, edematous, hemorrhagic and ulcerative and confined to the gastric body and fundus (Cheville 1979). Congestion and hemorrhage is linked to hematemesis and melena (Uzal et al. 2015). The mucosa is thickened, edematous and dark red-black with ulcerations and necrosis. The severity varies and at early stages there may only be edema and
thickening of the rugae (Uzal et al. 2015). Cheville (1979) further described stomach contraction and lymphadenopathy of the hepatic lymph nodes that drain the gastric region. He describes the edema as being "blood-tinged pale gelatinous" and notes that the necrotic epithelium is separated from the underlying muscle layer by edematous fluid.

Based on the microscopic lesions, Cheville (1979) described four different manifestations of uremic gastropathy in dogs, namely atrophic, amyloid, ulcerative and necrotic gastropathy. Histopathological changes that were common to all four types were: edema of the lamina propria, mastocytosis, mineralization, gastric gland atrophy and vasculopathy. Capillaries were swollen with extracellular calcium deposition. Arteries showed smooth muscle hypertrophy, endothelial degeneration, necrosis and sometimes thrombus formation. With mastocytosis, deposition of acidic mucous material, fibroplasias and mineralization (Cheville 1979). These findings were for the most part confirmed in a study of 28 dogs with renal failure by Peters et al. (2005). They found edema (61%), vasculopathy (51%), glandular atrophy (50%) and mineralization (46%) to be the most common microscopic abnormalities. The triad of edema, mineralization and vasculopathy was concurrently present in 28% of the dogs. The most notable distinction was that no gastric ulcerations were found (Peters et al. 2005).

In cats with chronic kidney disease, McLeland et al. (2014) found no gastric ulcerations, edema and vascular changes. The most common lesions in this species were fibrosis and mineralization of the stomach. As in dogs, mineralization was correlated with the severity of azotemia and the calcium-phosphorus product (McLeland et al. 2014).

Mineralization of the gastric mucosa is common and directly linked to the calcium-phosphorus ratio (Peters et al. 2005). Additionally, local acidosis and ischemia may contribute to the precipitation of calcium salts (Cheville 1979). The mineralization occurs predominantly in the middle and deep mucosa, but if the mineralization is more extensive it can involve the muscle layers and the submucosal and serosal arterioles as well (Uzal et al. 2015). The lesions are distributed in a band-like pattern, indicating metastatic calcification (Peters et al. 2005). Gastric mineralization is also seen in cases of vitamin D intoxication (Uzal et al. 2015).

The pathogenesis of uremic gastropathy is complex and there are many potential contributing factors (see Figure 1). Some possible underlying causes of uremic gastropathy are uremic toxins, anoxia due to vasculopathy, and ammonia produced from urease-positive bacteria (Cheville 1979). The mucosal ulcerations are initially non-inflammatory, but may become infected by opportunistic bacteria (Cianciolo & Mohr 2015). In human patients undergoing hemodialysis there is an association between gastritis and *Helicobacter pylori* infection (Moustafa et al. 1997). It has been suggested that *H. pylori* utilizes the increased gastric urea concentration in uremic patients. By converting urea to ammonia and buffering the gastric pH these bacteria can protect themselves against the otherwise acidic gastric environment (Peters et al. 2005). The relationship between helicobacter infection and gastritis in dogs is unknown (Neiger & Simpson 2000).
As a consequence of renal disease and reduced plasma extraction hypergastrinemia may develop, resulting in increased HCL secretion and local hyperacidity. Despite hypergastrinemia (stimulates HCL secretion) no ulceration in cats (McLeland et al. 2014) Histamine released from mast cells might also play a role in the pathogenesis of uremic gastritis. It stimulates parietal cells and dogs suffering from mastocytoma have a larger incidence of gastric ulceration (Cheville 1979).

**Figure 1: Overview of possible mechanisms involved in uremic gastropathy.**

**Uremic stomatitis, ulcerative necrotic stomatitis**

In dogs, and less so in cats with chronic uremia, congestion, cyanosis and ulcerations of the oral mucosa are common findings. These lesions are more common in dogs with chronic uremia than in acute cases. The ulcers have swollen hyperemic margins and occur on the tongue, the gingiva and the inner surface of the cheeks and lips (Uzal et al. 2015). The tong and buccal mucosa may also be coated with a brown fetid film (Cianciolo & Mohr 2015). Additionally, there might be a strong smell of ammonia, also known as uremic fetor (Hafner-Marx 2007). The pathogenesis of the oral lesions is not completely understood. The suggested mechanisms are similar to those resulting in uremic gastritis. There might be a caustic effect of ammonia produced by urea-splitting bacteria that utilize salivary urea, but there is a poor correlation between blood urea levels and oral lesions. Therefore, other mechanisms such as uremic vasculitis and an altered microvascular perfusion were suggested as possible causes of uremic stomatitis (Uzal et al. 2015).

Intestinal lesions are less frequent, severe and without mineralization. Otherwise they compare with the gastric lesions (Cianciolo & Mohr 2015).
2.3.2. Cardiovascular system

Lesions in the cardiovascular system due to uremia are uncommon in other animals than dogs (Cianciolo & Mohr 2015). As seen above, arterial lesions and thrombosis are underlying factors in the development of pathologies in various organs of uremic patients, so are capillary lesions at the basis of edema and hemorrhage in uremic gastropathy (Cianciolo & Mohr 2015; Cheville 1979). In uremic dogs arterial degeneration occurs commonly. Together with capillary injuries, the arterial lesions result in ischemia and thus contribute to various renal and extrarenal lesions observed in uremia. Some typical changes of the arterial lesions are the subendothelial deposition of fibrin, necrosis of smooth muscle cells and mineralization (Robinson & Robinson 2015).

Cardiac lesions

Arterial lesions in the myocardium may lead to ischemia and necrosis (Cianciolo & Mohr 2015). Left ventricular hypertrophy and dilation is seen in dogs with chronic uremia. This is possibly initiated or worsened by the hypertension that is also associated with uremia (Cianciolo & Mohr 2015). In human patients with chronic renal disease, increased FGF23 has been associated with cardiovascular changes such as left ventricular hypertrophy and cardiovascular mineralization (Faul et al. 2011).

Another common cardiac lesion in dogs with renal failure is mural endocarditis (see Figure 1). The lesions are usually localized in the left atrium but can also occur in the pulmonary trunk and aorta proximal to the valves. Endocardial lesions and lesions of the major arteries are more common in acute renal failure in comparison to chronic renal failure. The atrial and arterial lesions are identical and their genesis begins with interstitial swelling of the subendocardium or intima. There is deposition of glycosaminoglycans. At this stage the endocardium is still intact and shiny but appears to be slightly raised, wrinkled and opaque. Subsequently, the lesion can either heal and leave uneven areas of fibrosis or, more commonly, progress to subendocardial necrosis. The necrosis results in ulcerations that may even perforate the atrial wall. The ulcerations are infiltrated by leukocytes and become foci for the formation of thrombi. On the degenerate tissue calcium salts precipitate. If uremia is transient the endocardial lesions may heal and leave irregular patches of fibrosis and mineralization covered by endothelium (Robinson & Robinson 2015).

Other cardiac lesions that can occur in uremic dogs are hydropericardium together with dull granulation of the pericardium, also known as uremic fibrinous pericarditis (Cianciolo & Mohr 2015; Kumar et al. 2005).

Abnormalities of the blood

Figure 2: Mural endocarditis in an uremic dog. From Robinson & Robinson (2015), Published in Jubb, Kennedy & Palmer's Pathology of Domestic Animals: Volume 3, © Elsevier
Anemia is a frequent finding in human patients and dogs suffering from chronic renal failure. The anemia is typically nonregenerative, normochromic and normocytic (King et al. 1992). King et al. (1992) found that the hematocrit correlated with the degree of renal failure and that anemic dogs did not show elevated erythropoietin levels as would be expected but normal to low levels. This indicates a failure of the kidney to produce sufficient erythropoietin and suggest that erythropoietin deficiency is an important etiologic factor in nonregenerative anemia of uremic patients. Other factors that may play a role in the development of anemia in uremic patients are increased parathyroid hormone, phosphorus, 2,3-diphosphoglycerate (DPG) as well as increased erythrocyte fragility and gastrointestinal bleeding. King et al. (1992) further found PTH and phosphorous not to be correlated with anemia, where others (source) suggest that PTH may inhibit hematopoesis and even cause hemolysis. They found no abnormal erythrocyte fragility in uremic dogs. A rise in serum phosphate may cause an increased DPG concentration. DGP facilitates oxygen delivery and compensates for a loss of red blood cells. Therefore there might not be enough stimuli to increase erythropoietin production, worsening the anemia (King et al. 1992).

Uremia is a risk factor for the development of acquired platelet dysfunction. How uremia causes this platelet dysfunction is not known (Robinson & Robinson 2015). Furthermore, dogs suffering from nephrotic syndrome tend to hypercoagulability due to the urinary loss of antithrombin and can develop disseminated intravascular coagulation. During necropsy ecchymosis and petechia of the skin, mucosal and serosal surfaces as well as hemorrhages and thrombosis can be found (Robinson & Robinson 2015).

2.3.3. Respiratory system
Clinical signs of respiratory disease are seen on a regular basis in human patients with kidney failure and occasionally in dogs (Le Boedec et al. 2012). Terminal pulmonary edema is often seen in animals dying in uremia and most likely caused by increased capillary permeability. In some animals acute pneumonia occurs, but may be caused by aspiration of vomit and a general state of immunosuppression (Cianciolo & Mohr 2015). Pulmonary mineralization occurs in dogs with acute kidney insufficiency and in chronically uremic dogs (Le Boedec et al. 2012; Cianciolo & Mohr 2015). The mineralization is predominantly found within the alveolar septa and in the walls of the alveolar ducts but sometimes in the bronchioles and the basement membrane of pulmonary vessels as well (Le Boedec et al. 2012). These lesions are sometimes referred to as Uremic pneumonitis or uremic lung. In severe cases the lungs are edematous and resilient and collapse less than usual when the thoracic cavity is opened (Hopps & Wissler 1955). There is interstitial edema, extensive mineralization of the widened...
alveolar septa and the alveolar spaces contain a fibrinous fluid (see Figure 3) (Hopps & Wissler 1955; Cianciolo & Mohr 2015).

Furthermore, there are dull granulations of the visceral pleura of the cranial lung lobes. One of the most common lesions is intercostal mineralization under the parietal pleura, starting cranially and progressing caudally in case of extensive deposition. The lesions have a thickened gray-yellow appearance and are preceded by subpleural necrosis of connective tissue, intercostals muscle and pleura. (Cianciolo & Mohr 2015)

2.3.4. Endocrine system
Renal secondary hyperparathyroidism is regularly found in dogs, cats and humans suffering from chronic renal insufficiency (Brachthäuser et al. 2013; Rosol & Gröne 2015; Silver et al. 2002). As described in chapter 2.1.4., renal phosphor retention in patients with renal insufficiency leads to hyperphosphatemia and subsequent hypocalcemia. Hypocalcemia and hyperphosphatemia are major stimuli for PTH release and gene expression and prolonged hypercalcemia stimulates parathyroid cell proliferation. Normal serum levels of calcium and calcitriol inhibit PTH secretion and calcitriol may also regulate parathyroid cell proliferation, but both are decreased in secondary hyperparathyroidism (Silver et al. 2002). At first this increased stimulation results in hypertrophy, and later in hyperplasia of chief cells, leading to a uniform bilateral swelling of the parathyroid glands (see Figure 4) (Rosol & Gröne 2015).

By indirectly increasing ionized calcium levels, low phosphorous diets can play an important role in preventing the progress and the consequences of hyperparathyroidism even in distinct cases of renal insufficiency (Slatopolsky et al. 1971).

2.3.5. Musculoskeletal system
Renal secondary hyperparathyroidism can lead to fibrous osteodystrophy. Due to the increased PTH levels there is increased osteoclastic activity and bone turnover. PTH also inhibits sclerostin, leading to increased new bone formation (Craig et al. 2015). Early in the disease it may only be notable radiographically as resorption of the mandibular alveolar sockets. Later, the accelerated resorption of the trabecular bone causes the mandibles and maxilla to become soft and pliable, resulting in the so called rubber jaw (Craig et al. 2015). The jaw deformation may further cause teeth malpositioning.
Especially young dogs with familial renal diseases exhibit enlargement of the head and facial features. The bones are softer than normal and can be cut with a knife. On the cut surface focal red-brown zones caused by earlier hemorrhage may be present. In young dogs the costochondral junctions might be enlarged due to concurrent rickets caused by decreased 1,25(OH)$_2$D$_3$ (Craig et al. 2015).

<table>
<thead>
<tr>
<th>Lesions in renal osteodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroscopic</strong></td>
</tr>
<tr>
<td>&quot;rubber jaw&quot;</td>
</tr>
<tr>
<td>soft bone tissue (cuttable)</td>
</tr>
<tr>
<td>facial enlargement and enlargement of maxilla and mandibles</td>
</tr>
<tr>
<td>enlarged costochondral junctions (in case of concurrent rickets)</td>
</tr>
<tr>
<td><strong>Microscopic</strong></td>
</tr>
<tr>
<td>increased osteoclastic bone resorption</td>
</tr>
<tr>
<td>- Howship’s lacunae</td>
</tr>
<tr>
<td>increased osteoblastic</td>
</tr>
<tr>
<td>- Osteoid secretion that becomes poorly mineralized</td>
</tr>
<tr>
<td>- Formation of woven bone</td>
</tr>
<tr>
<td>Pronounced fibroplasias</td>
</tr>
</tbody>
</table>

Table 6: Macroscopic and microscopic abnormalities in renal osteodystrophy. Based on Craig et al. (2015)

In order to not only include renal osteodystrophy but all pathological changes related to divergent mineral and bone metabolism in renal disease the term chronic kidney disease - mineral and bone disorder (CKD-MBD) is used in human medicine (Moe et al. 2006). This comprises:

1) abnormal calcium, phosphate, PTH and vitamin D metabolism
2) abnormal bone turnover, mineralization, volume, growth, strength
3) Vascular or other soft tissue mineralization

2.3.6. Nervous system

Up to 65% of human patients with renal failure show clinical signs of peripheral neuropathy before dialysis. The neuropathy is usually distal, symmetric and can be asymptomatic. Symptoms include muscle cramps, distal disesthesias and reduced deep tendon reflexes. After dialysis recovery is common. In patients with uremic neuropathy there is primary axonal degeneration with fiber degeneration and fiber loss. Secondary demyelination sometimes occurs (Kumar et al. 2005). In an experimental study, Goldstein et al. (1978) showed that excess PTH may contribute to peripheral neuropathy in dogs by increasing the calcium content of peripheral nerves.
In animals uremic encephalopathy is uncommon but has been described in dogs, ruminants and horses. It presents a spongiform degeneration of the white matter with occasional reactive astrogliosis (Cianciolo & Mohr 2015).

2.3.7. Integumentary system
In some human patients with severe azotemia, white crystalline urea, called uremic frost, remains on the skin after sweat evaporation (Jullien et al. 2015). In other cases the disturbances in calcium-phosphate metabolism may lead to dystrophic calcifications and calciphylaxis (Almeras & Argilés 2009). In small animals a dull coat is regularly described in uremic patients (DiBartola & Westropp 2014).
CLINICAL CASE

1. SIGNALMENT
A 9 months old, intact male Pomeranian was submitted for pathological examination to the department of pathology, Faculty of Veterinary Medicine, Ghent University.

2. CASE HISTORY
The dog was admitted to the veterinarian with complaints of vomiting, hemorrhagic diarrhea and lethargy. Initially it was treated with Noroclav® (amoxicillin/clavulanic acid, 12.5mg/kg, BID, PO), Emeprid® (metoclopramide, 1 mg/kg up to 3 times per day, PO) and Promodulate® (pre- and pro-biotic). Two days later, the dog was presented again. The diarrhea had improved, but now the dog suffered from hematemesis, anorexia and hypothermia. During examination, a painful abdomen and abdominal breathing were noticed. The dog was hospitalized and treated with sodium chloride injection (0.9%), Flagyl® (metronidazole, 500mg/100ml), glucose, Cerenia® (maropitant 1mg/kg/d, SC injection) and Noroclav® (amoxicillin/clavulanic acid, 12.5mg/kg, SC injection).

A full blood exam was done (Table 7). The most pronounced abnormalities were an increase in urea and creatinine, respectively 636 mg/dl (16-48 mg/dl) and 17.8 mg/dl (0.5-1.3 mg/dl). There was a mild normochromic, normocytic non-regenerative anemia with a hematocrit of 35% (37-59%). The ionogram showed a hyperkalemia (12.3 meq/l), hypocalcemia (4.6 mg/dl) and hyperphosphatemia (29.0mg/dl). Pancreatic lipase and amylase were increased, 494 U/I (24-221 U/I) and 2486 U/I (402-1375 U/I) respectively. Additionally there was a decrease in total protein (5.1 g/dl) (normal 6.0-8.0 g/l) and an increase in C-reactive protein (2.0 mg/dl) (normal <0.1 mg/dl).

<table>
<thead>
<tr>
<th>Result</th>
<th>Reference</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>5.3</td>
<td>5.4-8.6</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>35</td>
<td>37-59</td>
</tr>
<tr>
<td>MCV</td>
<td>65</td>
<td>63-75</td>
</tr>
<tr>
<td>MCHC</td>
<td>37</td>
<td>30-36</td>
</tr>
<tr>
<td>Lymphocytes, total</td>
<td>0.9</td>
<td>1.1-3.6</td>
</tr>
<tr>
<td>Sodium</td>
<td>insufficient sample</td>
<td></td>
</tr>
<tr>
<td>Potassium</td>
<td>12.3</td>
<td>4.8-5.9</td>
</tr>
<tr>
<td>Chloride</td>
<td>101</td>
<td>101-113</td>
</tr>
<tr>
<td>Calcium</td>
<td>4.6</td>
<td>8.8-11.9</td>
</tr>
<tr>
<td>Phosphate</td>
<td>29.0</td>
<td>2.7-4.5</td>
</tr>
<tr>
<td>Urea</td>
<td>636</td>
<td>16-48</td>
</tr>
<tr>
<td>Creatinine</td>
<td>17.8</td>
<td>0.5-1.3</td>
</tr>
<tr>
<td>Ureum/creatinine ratio</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>2486</td>
<td>402-1375</td>
</tr>
<tr>
<td>Lipase</td>
<td>494</td>
<td>24-221</td>
</tr>
<tr>
<td>Glucose</td>
<td>117</td>
<td>66-99</td>
</tr>
<tr>
<td>Albumine</td>
<td>insufficient sample</td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>2.0</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

Table 7: Results of the pre-mortem blood examination.
The following day, the vomiting stopped and the diarrhea was mucoid without blood. Furthermore, hypersalivation and a very painful abdomen were observed. The dog died the following night.

3. NECROPSY

At necropsy the dog weighed 4 kg and mild post mortem autolysis was noted. The post-mortem interval was 3 days. The body condition score was 2/5. There was a large amount of serosanguineous fluid in the pericardium and the right heart was dilated. The lungs felt diffusely firm and were voluminous and generally edematous. The lungs showed an alveolar pattern. In the pleural cavity, a slightly increased amount of serosanguineous fluid was found.

![Image of lungs](image)

**Figure 6**: The lungs have a glossy appearance and feel resilient. Frothy fluid is present in the trachea.

The liver (140 g) was diffusely congested and had an enhanced zonal pattern. Both kidneys were small and irregular. The left kidney measured 2.8 cm x 1.2 cm x 1.3 cm (length x width x height) and had a focal nodule of 5mm diameter. The cortex was bilaterally thinned. The right kidney was larger and measured 3.2 cm x 2 cm x 2 cm (length x width x height) and the renal pelvis was situated eccentrically. The stomach had an extensive subserosal bleeding that communicated with multiple mucosal ulcers (preperforative lesion). The ulcers varied in size. The mucosa was diffusely thickened and edematous. There was a large quantity of bloody fluid in the stomach and the gastric pH was 7. The duodenum was filled with mucoid hemorrhagic content. The small intestines contained a brown-red, pasty content. In the large intestines the content was darker brown-red. The intestines in general were relative sparsely filled. The omentum was focally attached to the abdominal wall. In total, 5 ml serosanguineous fluid was collected in the abdomen.
4. Histopathology
Tissue from kidneys, lung, stomach, thymus, spleen, pancreas and liver were fixed in buffered formalin, embedded in paraffin, sectioned and stained with haematoxylin and eosin stain. Additionally, kidney and lung sections were stained with von Kossa stain to detect mineralization. Kidney sections were also stained with Congo red to detect amyloidosis.

4.1. Kidneys
In the interstitium of both cortex and medulla, there is a large amount of collagenous connective tissue. This is most pronounced in the transitional zone between the cortex and medulla. The cortex is thin, but the glomeruli have a mature appearance. Most glomeruli are dilated, and there is atrophy of the glomerular tuft. On HE stain (Figure 7a), the glomeruli contain basophilic granular material, suggestive of mineralization. The mineralization was confirmed with von Kossa staining (7b). The parietal sheet of the glomerular capsule is frequently thickened. The remaining tubules are mildly to moderately dilated, and some of the medullar tubules contain dark eosinophilic granular material that is interpreted as hemoglobin (7c). The epithelial cells of the tubules are mildly to moderately vacuolated (7d). There are multifocal to coalescing foci of lymphocytes and plasma cells in the interstitium. The other kidney had a similar histological appearance but the thickening and mineralization of the basal membrane of the tubules was more pronounced.

Figure 7: a) HE-stain of the renal cortex. The glomeruli are dilated and there is basophilic granular material inside the glomeruli. A large amount of collagen is present in the interstitium. b) Von Kossa-stain showing mineralization and thickening of the glomerular capsule. c) HE-stain of the renal medulla with longitudinal sections of the renal tubules. Dilated tubules and tubules filled with eosinophilic material. Proliferation of collagenous connective tissue. d) Mild to moderate vacuolization of the tubular epithelium.
4.2. LUNGS
On the HE-stain (Figure 8), there is a multifocal to coalescing accumulation of basophile, granular material within the alveolar septa. The alveolar lumina are filled with a light eosinophilic, homogenous material. There is multifocal loss of the alveolar septa. The von Kossa stain reveals mineralization of the alveolar septa (Figure 9).

![Figure 8: HE-stain. The alveolar walls are thickened and the alveolar lumen is filled with homogenous eosinophilic material.](image)

![Figure 9: Von Kossa-stain showing mineralization of the alveolar wall.](image)

4.3. STOMACH
The basal membrane and the parietal cells are diffusely hyperbasophilic, which indicates mineralization (Figure 10 b). Also the smooth muscle layer shows laminar mineralization (10c). Additionally, there is multifocal necrosis of the mucosa.

![Figure 10: HE-stains of the stomach mucosa. a) Overview showing hyperbasophilia in the mucosa and smooth muscle layer. b) Hyperbasophilic parietal cells and basal membrane. c) Laminar mineralization within the smooth muscle layer.](image)
4.4. **Thymus**
There is mild, diffuse, physiological atrophy of the lymphoid tissue.

4.5. **Spleen**
The red pulp is infiltrated by hemosiderin-laden macrophages (Figure 11).

![Figure 11: HE-stain of the spleen. Hemosiderin-laden macrophages in the red pulp.](image)

4.6. **Pancreas**
No histological abnormalities were found.

4.7. **Liver**
Hepatocytes appeared vacuolated and swollen indicating degeneration.

![Figure 12: HE-stain of the liver. The hepatocytes are swollen and vacuolated.](image)
5. PATHOLOGIC DIAGNOSIS
The pathologic diagnosis was juvenile nephropathy with secondary signs of renal failure in the form of uremic gastritis and uremic pneumonitis. The case history, as well as the gross and microscopic findings, fit the picture of chronic nephropathy. The hematologic examination confirmed uremia and a failure to maintain the ion homeostasis. The gastric and pulmonary lesions with extensive mineralization are most likely resulting from renal failure and disturbed calcium metabolism. In this case, the early onset of disease is indicative for juvenile nephropathy. Whether this is a familial or hereditary juvenile nephropathy cannot be determined without examination of the littermates and the pedigree.
DISCUSSION

The extrarenal lesions described in this case, uremic gastropathy and uremic pneumonitis, are the two most common lesions in uremic dogs according to Dantas & Kommers (1997). The pathohistological changes are also consistent with what has been described in the literature. Gastric lesions resemble those described by Cheville (1979) and also confirm the presence of gastric ulceration. Occurrence of gastric ulceration had been contested (Peters et al. 2005).

In this case the onset of the disease was early in life, the dog was only 9 months old. Juvenile nephropathy in the keeshond has already been described in the literature. Cianciolo & Mohr (2015) list the keeshond among other breeds that are suspected of familial or breed-related nephropathies. Unfortunately, the way of inheritance or the responsible genes have not yet been identified. Furthermore, the described lesions are cystic collecting ducts and glomerulocystic atrophy (Cianciolo & Mohr 2015). In the case at hand collecting ducts were dilated but not cystic. In order to confirm the hereditary nature of the disease it would have been necessary to examine the littermates and pedigree.

When comparing the lesions found in small animals and humans many similarities can be found. This highlights the commonalities in pathogenesis. It is notable that the cat does not tend to develop gastric ulcerations and also develops oral lesions less frequently. Even though the role of bacteria, especially Helicobacter spp, in the pathogenesis has not yet been established in small animals it is regularly suspected (Neiger & Simpson 2000). Other lesions, like the widespread mineralization, were also found across species and seem to be universal feature of uremia and derailed calcium-phosphorus metabolism.
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Intensive Care Medicine, 41(7), pp.1357–1358.


A case of feline asthma

by

Jan FREUND
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A case of feline asthma

by

Jan FREUND
FOREWORD

I want to thank Hanna Bellmann and our daughter Veerle for their help and patience during the process of writing this thesis. I would also like to thank Felicia Benefield and Petra Bellmann for their interest in this thesis, their suggestions and their corrections. Furthermore, I want to thank Dr. Leslie Bosseler, Prof. dr. Koen Chiers and the department of pathology for their support and for providing this case.
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SUMMARY

This case report is about a cat that was unexpectedly found dead. Initially an intoxication was suspected. Pathological examination resulted in a diagnosis of feline asthma with concurrent hypertrophic cardiomyopathy and atherosclerosis. The first part of this thesis discusses the features of feline asthma based on the current literature. In the second part the pathological findings are being described and discussed. Feline asthma is a chronic inflammatory disease of the airways. Typical symptoms of feline asthma are recurrent bouts of coughing, wheezing and dyspnea due to bronchoconstriction. Attacks can be life threatening but often resolve spontaneously and respond well to bronchodilators. Diagnosis is mainly based on symptoms and the positive response to bronchodilators. The disease is the result of a type I hypersensitivity reaction, caused by exposure to aeroallergens. As in humans, a state of chronic inflammation, airway narrowing and hyperresponsiveness ensues and various irritants can cause bronchoconstriction. The most notable associated histological changes are bronchial smooth muscle hypertrophy, bronchial gland hyperplasia, edema, and infiltration with inflammatory cells, especially eosinophils. These observations are often made in studies of cats with naturally occurring asthma. The pathological findings in this case of naturally occurring asthma were consistent with those described above.

Keywords: Allergy - Asthma - Cat - Lungs - Pathology

SAMENVATTING

Deze casusbespreking gaat over een kat die onverwacht overleed. Eerst werd een intoxicatie verwacht maar pathologisch onderzoek leidde tot een diagnose van felien astma, hypertrofische cardiomyopathie en atherosclerose. In het eerste deel van deze casusbespreking worden de kenmerken van felien astma beschreven. In het tweede deel worden de specifieke pathologische bevindingen van deze casus beschreven en besproken. In felien astma is er een chronische ontsteking van de luchtwegen. Terugkerende aanvallen van hoest, piepende ademhaling en dyspnee veroorzaakt door bronchoconstrictie zijn kenmerkend voor deze ziekte. De aanvallen kunnen mogelijks dodelijk zijn maar normalerwijze gaan ze vanzelf over en reageren ze goed op gebruik van bronchodilatoren. De diagnose is dan ook hoofdzakelijk gebaseerd op de klinische symptomen en de respons op bronchodilatoren. Felien astma is het resultaat van een type I hypersensitiviteit veroorzaakt door bronchoconstrictie aan aeroallergenen. De hoofdkenmerken van felien astma, chronische ontsteking, vernauwing van de luchtwegen en hyperresponsiviteit, komen overeen met deze van humaan astma. Bij hyperresponsiviteit kunnen verschillende irriterende stoffen bronchoconstrictie uitlokken. Histologisch wordt felien astma vooral gekarakteriseerd door hypertrofie van de bronchiale gladde spiercellen, hyperplasie van de bronchiale klieren, oedeem en infiltratie van ontstekingscellen. Vaak zijn deze bevindingen afkomstig van studies met katten waarbij astma kunstmatig werd geïnduceerd. Dezelfde pathologische veranderingen werden ook in deze casus van spontaan asthma terug gevonden.

Trefwoorden: Allergie - Astma - Kat - Longen - Pathologie
INTRODUCTION

Asthma is a common disease of the lower airways in humans and cats (Padrid 2009). In humans, it is on the rise, especially in developed countries where a correlation has been noticed between prevalence and evolution in the way people live (Busse et al. 2007).

In cats, one of the first descriptions of what is now called feline asthma dates back to 1906. Hill described cats with clinical signs of labored breathing and wheezing whose airways were inflamed and filled with copious amounts of mucus (Padrid 2000). In the past feline asthma and related syndromes were referred to in a number of ways, and there was no consensus in the veterinary community. The disease has been referred to, and sometimes still is, as feline lower airway disease, feline allergic bronchitis, chronic pulmonary disease, eosinophilic bronchitis and chronic bronchitis. This shows the widespread confusion within the veterinary community in regards to feline respiratory disorders (Padrid 2000).

Interestingly, cats are the only species, besides humans, where naturally occurring asthma has been observed (Padrid et al. 1995). Additionally, feline asthma shares many of its core features with human asthma. Therefore, cats are important objects of study in order to understand further the pathology of asthma and to develop new treatments for the condition.

In this case review and literature review, the clinical and pathological aspects of feline asthma will be discussed as well as some treatment options and differential diagnoses. In the discussion, the findings in this specific case will be compared to the lesions described in the literature.
LITERATURE REVIEW

1. DEFINITION
In humans, asthma has been defined as "a common chronic disorder of the airways that involves a complex interaction of airflow obstruction, bronchial hyperresponsiveness and an underlying inflammation" (Busse et al. 2007). In most cases the airway obstruction is reversible and resolves either spontaneously or after treatment. The disease is further characterized by the many cells and cellular elements that are involved. Particularly mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, epithelial cells and smooth muscle cells play a role in the pathogenesis of asthma (Busse et al. 2007).

As mentioned earlier, there was a lack of consensus on what constituted feline asthma within the veterinary community, and many studies did not differentiate between the different respiratory diseases, especially between asthma and chronic bronchitis. This even led to the hindrance of clinical trials of new therapeutics (Trzil & Reinero 2014).

Most recent contributions to the topic agree that feline asthma is a common, naturally occurring condition in cats that shares important hallmark features with, or even mimics, human asthma (Trzil & Reinero 2014; Dye et al. 1996; Norris et al. 2003). These hallmark features are airway inflammation, airway hyperresponsiveness, airway constriction and airway remodeling (Trzil & Reinero 2014). The disease is further characterized by its typical clinical signs of recurrent coughing, wheezing, and dyspnea, as well as its responsiveness to glucocorticoid therapy (Corcoran et al. 1995).

2. OCCURRENCE
Feline asthma is one of the most frequently diagnosed respiratory diseases in cats (Venema & Patterson 2010). The data on the incidence and prevalence of feline asthma is uncertain, but the prevalence of lower airway disease is estimated to be around 1% in adult cats. The prevalence is higher in the Siamese breed where it may be 5% or even more. The Siamese breed may also be overrepresented in the number of feline asthma cases as a poll of owners suggests (Padrid 2009). Gender has no influence on the occurrence of the disease. The mean age of cats diagnosed with feline asthma is 4 years – ranging from 1 to 15 years (Venema & Patterson 2010).

3. CLINICAL PRESENTATION
The two major clinical presentations of feline asthma are the acute asthmatic crisis, or status asthmaticus, on the one hand, and the chronic presentation on the other hand. Typical signs of cats in an asthmatic crisis are: open mouth breathing, tachypnea, and increased abdominal effort during expiration (Trzil & Reinero 2014). Outside of an asthmatic crisis, patients are usually presented with recurrent complaints of coughing, wheezing, dyspnea and exercise intolerance (Corcoran et al. 1995; Padrid 2009). Corcoran et al. (1995) found chronic coughing to be the most common symptom being present in 25 out of 29 studied cats. Respiratory distress occurs primarily during expiration (Padrid 2009).

The waxing and waning nature of asthma is typical and the episodes usually resolve spontaneous or
respond well to glucocorticoid treatment (Corcoran et al. 1995; Caswell & Williams 2015). In resting cats, there are often no symptoms present during examination, but coughing can usually be prompted by palpating the trachea (Padrid 2000).

On auscultation, rhonchi, wheezes or crackles can be heard, with inspiratory and expiratory rhonchi predominating (Corcoran et al. 1995). Padrid (2009a) notes that while crackles can be heard in both chronic bronchitis and asthma, wheezes are more characteristic of feline asthma.

A certain amount of patients may present without signs of respiratory distress but rather with complaints of vomiting, paroxysmal hacking, or hacking up hairballs. This may mistakenly result in a gastrointestinal workup (Trzil & Reinero 2014). Based on the severity and frequency of the symptoms, feline asthma can be classified to be intermittent, mild, moderate or severe (see Treatment) (Padrid 2000).

4. PATHOPHYSIOLOGY AND PATHOGENESIS

The recurrent and reversible airflow limitation is central to asthma and is responsible for most symptoms. A couple of different mechanisms are responsible for the airflow reduction in human asthma. Among others, the most important factors are 1) bronchoconstriction, 2) airway edema, 3) mucus hypersecretion, 4) airway hyperresponsiveness and 5) airway remodeling (Busse et al. 2007). All these features have also been observed in cats suffering from asthma and are a consequence of type I hypersensitivity and chronic lower airway inflammation (Padrid 2000; Venema & Patterson 2010; Corcoran et al. 1995; Dye et al. 1996).

Bronchoconstriction is caused by allergens or irritants. Allergens may cause a type I allergic reaction (see Immunopathogenesis) resulting in the release of mast cell mediators, such as histamine, leukotrienes and prostaglandin, that cause bronchial smooth muscle contraction (Busse et al. 2007). In humans, aspirin or physical stimuli like exercise and cold air can also cause bronchoconstriction (Busse et al. 2007). In cats, administration of bromide, used to treat seizures, may induce asthma like symptoms (Boothe et al. 2002).

Additionally the airways of asthmatic patients become hyperresponsive, characterized by "an exaggerated bronchoconstrictor response to a wide variety of stimuli" (Busse et al. 2007). This hyperreactivity is measured as an increased response to low levels of methacholine and has also been observed in cats (Dye et al. 1996). The mechanisms behind airway hyperresponsiveness in humans are "inflammation, dysfunctional neuroregulation, and structural changes" (Busse et al. 2007).

Airway edema is the result of increased vascular permeability due to the vasoactive properties of mast cell mediators and infiltration of mucosa and submucosa by inflammatory cells (Padrid 2000). The released leukotrienes also increase mucus production and contribute to smooth muscle constriction.

In some patients the structural changes become irreversible and are grouped under the term airway remodeling. Possible changes include: airway smooth muscle hypertrophy, subepithelial fibrosis, bronchial gland hyperplasia and angiogenesis (Busse et al. 2007).
Padrid (2000) notes that there are a limited number of ways how the airways can react to a chronic stimulus. The different layers may react as follows:

- The airway epithelium may become hypertrophic, metaplastic or eroded.
- The mucus producing goblet cells and submucosal glands may become hyperplastic and produce increased amounts of thick mucus.
- Smooth muscle may spasm and eventually become hypertrophic.

All of the above mentioned processes contribute to airway narrowing and become clinically visible as labored breathing and exercise intolerance. A relatively small decrease in airway radius may lead to a significant airflow reduction. When the airway radius is decreased by 50% the result is a 16-fold reduction of the airflow (Padrid 2000). This does not only explain the symptoms but also the marked effect that bronchodilators can have.

5.1. FACTORS CONTRIBUTING TO THE DEVELOPMENT OF FELINE ASTHMA

EXPOSURE TO ALLERGENS

Feline asthma is assumed to be triggered by aeroallergens (Reinero 2011). Some sensitizing allergens have already been identified, for example human dander, house dust mite antigen (HDMA), cockroach antigen, and Bermuda grass antigen (BGA) (Corcoran et al. 1995; Prost 2004; Norris Reinero et al. 2004). Of these, HDMA and BGA have successfully been used to experimentally induce asthma in cats as well as to experimentally treat these cats by means of allergen specific immunotherapy (Norris Reinero et al. 2004; Reinero et al. 2012).

GENETICS

In human asthma, various genes have been identified that play a role in the development of the disease (Busse et al. 2007). In cats, overrepresentation of the Siamese breed in the number of cases may hint in the direction of a genetic predisposition (Padrid 2009).

HYGIENE HYPOTHESIS

In human medicine there seems to be an inverse relationship between viral and other infections during childhood and the occurrence of asthma. This so-called "hygiene hypothesis" is based on the assumption that the immune system of the neonate is more skewed towards T helper 2 (Th2) cytokine production. During childhood exposure to pathogens will lead to a balancing between Th1 and Th2 response. This may explain the increased prevalence of asthma in western countries and urban environments (Busse et al. 2007).

Other environmental factors such as tobacco smoke, air pollution, diet, and exercise contribute to the development of asthma in humans (Busse et al. 2007). In cats, exposure to dust, unusual scents and smoke may exacerbate symptoms (Dye et al. 1996).

5.2. IMMUNOPATHOGENESIS

The pathological changes in feline asthma are mostly the result of type I hypersensitivity (Padrid 2009; Corcoran et al. 1995). The induction of a type I hypersensitivity is generally dependent on the type of antigen, the dose and route of exposure, as well as genetic factors (Janeway et al. 2001).
During the induction of type I hypersensitivity, inhaled antigen is presented to naïve CD4+ T cells that are activated and become, under the influence of IL-4, T\(_h\)2 cells. T\(_h\)2 cells secrete interleukins (IL) 4, 5 and 13. IL-4 induces class switching of B lymphocytes, that than produce allergen specific immunoglobulin E (IgE). The produced IgE is bound by high affinity receptors (Fc\(_{RI}\)) on mast cells. When the airways are subsequently exposed to the sensitizing allergen, the antigen is bound by multiple IgE molecules on the mast cell surface. This causes cross-linking of IgE, ultimately resulting in mast cell degranulation. Mast cell degranulation releases histamine and leukotrienes causing increased vascular permeability, smooth muscle contraction and mucus secretion (Venema & Patterson 2010; Janeway et al. 2001). After this acute phase of allergic reaction, activated mast cells keep on synthesizing and releasing leukotrienes, chemokines and cytokines, leading to the late response. This late response is characterized by recruitment of T\(_h\)2 lymphocytes, eosinophils and basophils from the circulation. Released IL-4 and IL-13 further perpetuate the T\(_h\)2 response and leukotrienes act to sustain the inflammatory response (Janeway et al. 2001). IL-4 and IL-5 cause differentiation and prolonged survival of eosinophils (Busse et al. 2007). Eosinophil activation and degranulation is initiated by T\(_h\)2 cells together with activated mast cells. The activated eosinophils release cationic and basic protein as well as free radicals causing tissue damage. The release of granular proteins, for instance cationic and basic protein, and free radicals by activated eosinophils results in tissue damage. The release of granular proteins and mast cell mediators results in second wave of smooth muscle contraction and edema (Janeway et al. 2001). Additionally they contribute to hyperresponsiveness by making smooth muscle more excitable (Padrid 2000). In humans airway hyperreactivity is also associated with mast cell infiltration into airway smooth muscle tissue (Brightling et al. 2002). When airways have become hyperreactive, other substances than the allergen can trigger asthmatic attacks (Janeway et al. 2001). Irritants, like cigarette smoke, can be triggers (Janeway et al. 2001). The degree of hyperresponsiveness can be determined with methacholine challenges and correlates with the clinical severity of asthma (Busse et al. 2007).

IgE antibodies and type I hypersensitivity are central to the pathogenesis of asthma, but other immunoglobulins such IgG and IgA also play a role. Following antigen sensitization IgA and IgG were found to be increased in serum and BALF (Norris et al. 2003). These immunoglobulins may have a protective function by capturing antigen, but in humans IgG4 has been shown to aggravate allergic attacks and IgA can mediate eosinophil degranulation. (Norris et al. 2003; Venema & Patterson 2010).
5. **Pathological Presentation**

Various microscopic lesions are described in cats but many descriptions are derived from experimental studies. Because mortality is not so common, histopathologic changes in naturally occurring cases of feline asthma are described less frequently in the literature (Caswell & Williams 2015).

In an experimental study Padrid et al. (1995) sensitized cats to Ascaris suum antigen. Afterwards the cats were repeatedly exposed to nebulized Ascaris suum antigen. This induced hyperresponsiveness and lesions that are comparable to those seen in chronic human bronchial asthma. On necropsy these cats showed bronchoconstriction and narrowing of the airway lumen. The smooth-muscle-layers were significantly thickened (29%). Furthermore, hypertrophy and hyperplasia of goblet cells and submucosal glands was described. In the sensitized cats submucosal glands were distributed over the whole circumference of the airway and there were often four or more layers of glands, compared to one to three glands in the reference group. There was eosinophilic infiltration and erosion of the epithelium. In this experimental study there was also 11-fold increase of the number of eosinophils in bronchoalveolar lavage fluid (Padrid et al. 1995). Smooth muscle hypertrophy was described in most articles and Norris Reinero et al. (2004) found smooth muscle hypertrophy to be the most consistent histological deviation and being more pronounced in the distal airways. The airway lumen can be plugged with mucus and inflammatory cells (Corcoran et al. 1995; Caswell & Williams 2015). Other lesions described are epithelial hyperplasia, thickening of the basement membrane, submucosal edema and lymphoplasmatic infiltration with forming of lymphoid follicles (see Table 1) (Johnson 2013; Caswell & Williams 2015; Corcoran et al. 1995; Dye et al. 1996).

Macroscopic lesions were not specifically described in the reviewed literature, bronchoscopic findings give an impression of the macroscopic lesions that may be expected during necropsy. During bronchoscopy mucosal erythema, edema and airway narrowing as well as excessive amounts of mucus can be observed (Byers & Dhupa 2005).

<table>
<thead>
<tr>
<th>Histopathological features of feline asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoconstriction / Airway narrowing⁴, ⁴</td>
</tr>
<tr>
<td>Intraluminal plugs/mucus and inflammatory cells⁵, ³, ⁵</td>
</tr>
<tr>
<td>Infiltration of inflammatory cells (especially eosinophils)⁴</td>
</tr>
<tr>
<td>Epithelial hyperplasia¹, ³, ⁶</td>
</tr>
<tr>
<td>Epithelial erosions³, ⁴</td>
</tr>
<tr>
<td>Hypertrophy and hyperplasia of mucous glands¹, ⁴</td>
</tr>
<tr>
<td>Thickened basement membrane²</td>
</tr>
<tr>
<td>Hyperplasia of submucosal glands¹, ⁴</td>
</tr>
<tr>
<td>Smooth muscle hypertrophy¹, ², ³, ⁴</td>
</tr>
<tr>
<td>Lymphoplasmatic infiltrate with lymphoid follicles³</td>
</tr>
</tbody>
</table>


Table 1: Common histopathological features of feline asthma.
6. DIFFERENTIAL DIAGNOSES

There are a couple of diseases that can mimic feline asthma. Most notably, chronic bronchitis that is not easily differentiated from feline asthma, especially in cases where chronic coughing is the only clinical sign (Padrid 2000). Additionally, both chronic bronchitis and feline asthma display a bronchial pattern on radiographs. Signs that help to differentiate chronic bronchitis from asthma are: the absence of spontaneous bronchoconstriction, irreversible airway obstruction, and the typical non-degenerative neutrophilic inflammation seen in bronchoalveolar lavage fluid (BALF) (Trzil & Reinero 2014). A range of parasitoses can mimic feline asthma, including: heartworm disease, aelurostrongylosis, and *Toxocara cati* infection (Trzil & Reinero 2014). They have in common that they can cause respiratory symptoms as well as a eosinophilic inflammation of the lungs resulting in eosinophilia observed in BALF (Ware 2014; Trzil & Reinero 2014). Aelurostrongylosis and *Toxocara* infection can additionally cause a bronchointerstitial lung pattern on radiographs. In order to differentiate, one must take a closer look at previous preventive treatments, endemicity of the disease in that region or further parasitological examination (for an overview see Table 2) (Trzil & Reinero 2014). Other pathologies that may also cause asthma-like respiratory symptoms are heart failure, pulmonary malignancy and inhaled foreign objects (Padrid 2000)
The diagnosis of feline asthma is challenging at times because its clinical and pathological features overlap with other diseases of the lower airways as described above. Nonetheless, it is important to differentiate it from other similar diseases because of the different pathogenesis, prognosis and treatments (Trzil & Reinero 2014). Fortunately, most of the above mentioned disorders do not cause asthma-like symptoms in otherwise healthy cats, with the exception of chronic bronchitis (Padrid 2000). But at the same time, there is no single clinical sign that is pathognomonic for feline asthma (Padrid 2000). A tentative diagnosis can often be made based on the history, physical examination and the results of thorax radiography. An additional positive response to therapy is usually sufficient for a diagnosis (Padrid 2009). According to (Corcoran et al. 1995) the benefit of further testing seems to be limited. But in some cases, other causes of respiratory symptoms need to be excluded, or further tests are needed to specify the responsible antigen in order to institute allergen specific immunotherapy (ASIT).

The most important finding on radiographs of asthmatic cats is bronchial wall thickening. This becomes radiographically apparent as doughnuts and tramlines (bronchial pattern). Additionally flattening of the diaphragm may indicate air trapping due to airway constriction (Padrid 2000). Bronchoscopy is seldom necessary to make a diagnosis of asthma in cats. Padrid (2009a) proposes its use only when clinical signs do not improve after about one week of aggressive treatment with

### Differential diagnoses of feline asthma

<table>
<thead>
<tr>
<th>Disease</th>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic bronchitis</td>
<td>chronic coughing</td>
<td>no spontaneous broncho-constriction</td>
</tr>
<tr>
<td></td>
<td>bronchial pattern</td>
<td>not reversible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BALF neutrophilia</td>
</tr>
<tr>
<td>Aelurostrongylosis</td>
<td>BALF eosinophilia</td>
<td>larvae in BALF or Baermann</td>
</tr>
<tr>
<td></td>
<td>bronchial to bronchointerstitial pattern</td>
<td>Empiric treatment with fenbendazole</td>
</tr>
<tr>
<td>Heartworm associated respiratory disease</td>
<td>BALF eosinophilia</td>
<td>Endemic in certain regions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can be excluded when preventive medication is taken</td>
</tr>
<tr>
<td>Toxocariasis</td>
<td>bronchointerstitial pattern</td>
<td>asymptomatic</td>
</tr>
<tr>
<td></td>
<td>BALF eosinophilia</td>
<td>no hyperresponsiveness</td>
</tr>
<tr>
<td>Other airway infections (pneumonia)</td>
<td>Similar complaints and radiographic findings</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Differential diagnosis of feline asthma and their similarities and differences with feline asthma. Based on Trzil & Reinero (2014)
corticosteroids. This cautious use of bronchoscopy is also indicated because bronchoscopy comes with a certain risk, especially in cats with respiratory problems (Padrid 2009).

Even though asthma consists of an eosinophilic inflammation, finding large numbers of eosinophils in a bronchoalveolar lavage specimen is not specific for feline asthma as this is also commonly found in other diseases and in many healthy cats (Padrid 2000; Padrid et al. 1991). Even in asthmatic cats, eosinophils are not always found in BALF, nor are they regularly the predominant cell type (Corcoran et al. 1995). The fact that neutrophils are the predominant type of inflammatory cell in chronic bronchitis may help to differentiate between the two disorders (Padrid 2000).

As neither the lower airways nor the lung parenchyma are sterile, a mixed population of bacteria is expected to be found (Padrid 2009; Dye et al. 1996). Even bacteria that are considered pathogens may be found but are often not of clinical relevance (Padrid 2009). A notable exception may be Mycoplasma, that has been found in 25% of cats with lower airway diseases and that may contribute to spontaneous bronchoconstriction and cause structural damage to the airway epithelium (Padrid 2009; Padrid 2000). In these cases antimicrobial treatment may be warranted (Padrid 2000).

Intradermal testing is not done routinely but may help to identify allergens that play a role in feline asthma. Knowledge about the kind of allergen may help in the avoidance of such an allergen and the development and implementation of allergen specific immunotherapy (Corcoran et al. 1995; Prost 2004; Reiner et al. 2006; Trzil & Reiner 2014).

Other tests like CT scans and pulmonary function testing are used predominantly in research but may help in the differentiation of feline asthma from other lower airway diseases (Trzil & Reiner 2014).

8. **TREATMENT**

Even in asymptomatic cats a chronic underlying inflammation is suspected, as has been shown in human asthma patients. Therefore treatment should not only be aimed at alleviating the symptoms but also aim to decrease the “underlying inflammatory component” (Padrid 2009). Unfortunately, conventional treatments are not capable of changing the abnormal immune response and cannot prevent or revoke chronic airway remodeling in the long run (Trzil & Reiner 2014).

**CLASSICAL APPROACH**

Feline asthma is commonly treated with glucocorticoids, bronchodilators, or a combination of both. These treatments are effective in most cats, but some cats either remain unresponsive or are not suited for treatments with glucocorticoids because of a simultaneous disease like diabetes mellitus (Trzil & Reiner 2014).

Before treatment is initiated the diagnosis of feline asthma should be certain. Patients who experience symptoms less than once a week, are not necessarily considered to have chronically inflamed airways and may be treated with bronchodilators as needed (Padrid 2009). Even patients with intermittent episodes and no daily symptoms can be treated this way. In the case of daily occurring symptoms, Padrid (2000) suggests a classification based on the severity of the symptoms and proposes a standard of treatment. Feline asthma with daily occurring episodes can be classified as mild, moderate.
or severe. The classification is mainly based on the evaluation of the quality of life, the frequency of symptoms and the presence of symptoms at rest (see Table 3). For the treatment of intermittent occurring acute episodes a $\beta_2$-adrenergic bronchodilator such as salbutamol (=albuterol) can be administered with a metered dose inhaler as needed. When symptoms occur daily the treatment is supplemented with an inhaled glucocorticoid, for example fluticasone, two times a day. The effects of fluticasone may not be notable during the first 7 to 10 days. Therefore, moderate cases initially require an additional treatment with prednisolone (1mg/kg) every 12 hours for the first 10 days. In severe cases an initial treatment with dexamethasone, salbutamol every 30 minutes and up to 4 times, and oxygen therapy may be indicated to stabilize the patient. Once the patient is stabilized treatment is continued similarly as in moderate cases (Padrid 2000).

### Classification of feline asthma and proposed treatment

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent No daily symptoms Acute episodes</td>
<td>Albuterol as needed (inhaler)</td>
</tr>
<tr>
<td>Mild Quality of life not affected Normal behavior in between episodes</td>
<td>220µg fluticasone (inhaler) BID Albuterol (inhaler) as needed</td>
</tr>
<tr>
<td>Moderate Quality of life is sometimes affected Symptoms not present continuously No difficulty breathing during most of the day</td>
<td>220µg fluticasone (inhaler) BID Albuterol (inhaler) as needed 1mg/kg prednisolone p.o. BID for 10 days</td>
</tr>
<tr>
<td>Severe Continuous asthmatic condition Quality of life is noticeably reduced Cat is not comfortable at rest Symptoms are present most of the day</td>
<td>Initially: 2mg/kg dexamethasone Albuterol every 30 min up to 4 times 40-100% oxygen After patient is stabilized: 220µg fluticasone (inhaler) BID Albuterol (inhaler) QID/as needed + eventually intermittent low doses of prednisolone</td>
</tr>
</tbody>
</table>

Table 3: Classification and treatment options for asthmatic cats as proposed by (Padrid 2000)
Exclusive treatment with prednisolone has also been shown to be an effective treatment (Corcoran et al. 1995). In cats with symptoms more than once a week prednisolone (1-2mg/kg) can be administered twice daily for five to seven days with a subsequent dose reduction over two to three months. Low-dose alternate day therapy with corticosteroids has also been shown to effectively control symptoms of feline asthma (Cohn et al. 2010; Padrid 2009). For patients that require higher and consistently administrated doses, inhaled corticosteroids should be suggested in order to reduce adverse effects (Padrid 2009; Cohn et al. 2010). When it is not possible to use oral or inhaled corticosteroids, injectable long acting corticosteroids (e.g. methylprednisolone) can be used but will regularly cause serious adverse effects (Padrid 2009). For the above mentioned fluticasone, Cohn et al. (2010) showed that a dose of 44µg showed a similar effect in reducing eosinophilic airway inflammation as a dose of 220µg. Therefore, the dose may be reduced in the future. The administration of inhalable drugs is best done using a metered dose inhaler in combination with a spacer and facemask (see Figure 3). This assures that the whole dose is inhaled, because deliberate synchronization of inspiration and drug administration is not possible in feline patients (Padrid 2000).

![Figure 3: Use of a metered dose inhaler in combination with an aerosol chamber(AEROKAT ®). © Trudell Medical International. Retrieved from https://www.trudellmed.com/animal-health/aerokat. on 10.08.2016](attachment:image)

Antibiotic therapy is usually not warranted as there is no objective evidence for bacteria being involved in the pathogenesis of feline asthma. Only when there is evidence for a secondary bacterial infection is the use of antibiotics indicated (Padrid 2000). The only exceptions to this are *Mycoplasma* species, which have been isolated from cats with lower airway disease and are usually not cultured from healthy cats. As *Mycoplasma* can significantly damage airway epithelium, appropriate antibiotic therapy may be warranted in these cases (Padrid 2000). Corcoran et al. (1995) found antibiotics to be effective in some cats but suggest that this could also be misinterpretation of the waxing and waning nature of asthma.
ALLERGEN AVOIDANCE AND ALLERGEN-SPECIFIC IMMUNOTHERAPY

The first step, before treating asthmatic cats, is the identification of the sensitizing allergen (Trzil & Reinero 2014). Possible allergens can be identified by intradermal skin tests and IgE ELISA (Prost 2004; Norris Reinero et al. 2004).

Corcoran et al. (1995) and Prost (2004) found allergen avoidance to be effective in some cats, leading to remission of respiratory symptoms. For example, some cats having shown a reaction to human dander improved when access to the owners’ bedroom was restricted (Corcoran et al. 1995).

Antigen specific immunotherapy (ASIT) and a modification of it, rapid immunotherapy (RIT), where studied in cats with naturally occurring (Prost 2004) and experimentally induced asthma (Reinero et al. 2006; Reinero et al. 2008; Reinero et al. 2012) with promising results. ASIT first emerged in human medicine and it is proposed to attenuate the T helper 2 mediated allergic response and to induce immunologic tolerance (Trzil & Reinero 2014).

Example of a RIT protocol in an experimental feline asthma model

<table>
<thead>
<tr>
<th>Day</th>
<th>Time</th>
<th>Dose of BGA (µg)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 a.m.</td>
<td>10</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>1</td>
<td>10 a.m.</td>
<td>20</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>1</td>
<td>12 p.m.</td>
<td>40</td>
<td>Intranodal</td>
</tr>
<tr>
<td>1</td>
<td>2 p.m.</td>
<td>80</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>1</td>
<td>4 p.m.</td>
<td>100</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>1</td>
<td>6 p.m.</td>
<td>200</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>2</td>
<td>8 a.m.</td>
<td>200</td>
<td>Subcutaneous</td>
</tr>
</tbody>
</table>

Table 4: Example of a RIT protocol used by Reinero et al. (2006). Published in Veterinary Immunology and Immunopathology. © Elsevier

RIT led to a significant reduction of eosinophilic inflammation in cats with experimentally induced asthma but had some adverse effects (Reinero et al. 2006). Adjuvant RIT using CpG oligodeoxynucleotides also reduced eosinophilic inflammation but with fewer adverse effects (Reinero et al. 2008). Interestingly, the allergens used for hyposensibilization do not have to be identical to the sensitizing allergen and will still have an effect (Reinero et al. 2012). But according to Reinero et al. (2012) there are two different mechanisms at play. RIT with matched allergen induces hypoproliferation of allergen specific lymphocytes and increases the amount of IL-10 producing cells as well as CD4+ CD 25+ FoxP3 lymphocytes. This may allow discontinuation of therapy as opposed to treatment with non-specific allergen that does not change the numbers of IL-10 producing cells (Reinero et al. 2012). In another study with experimentally sensitized cats, Lee-Fowler et al. (2009) found that intranasal administration of RIT also led to the elimination of clinical signs. Furthermore RIT did not induce asthma in non-asthmatics cats, making accidental administration, for example to cats with chronic bronchitis, in a clinical setting less dangerous (Reinero et al. 2012).

OTHER TREATMENTS

Omega-3 fatty acids in combinations with luteolin may have a positive effect in decreasing airway responsiveness as has been suggested in a study with cats with experimentally induced asthma
(Leemans et al. 2010). Other treatments targeting different players in the inflammatory reaction have been studied. These include among other things the antiserotonergic, antihistamine, and antileuktriene drugs cyproheptadine, cetirizine, and zafirkulast. These drugs are used in human medicine in combination with glucocorticoid therapy. In cats, they had insufficient effect as monotherapies and their use cannot be advocated yet (Venema & Patterson 2010). The long term use of racemic albuterol may be detrimental in feline asthma, as the S-enantiomer may exacerbate inflammation (see Table 5) (Venema & Patterson 2010).

<table>
<thead>
<tr>
<th>Pharmaceutical Class</th>
<th>Dose</th>
<th>Outcome</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyproheptadine</td>
<td>Antiserotonergic</td>
<td>2–8 mg PO q12h</td>
<td>No difference in functional or inflammatory parameters compared with placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Antihistamine</td>
<td>5 mg PO q12h</td>
<td>No difference in inflammatory parameters compared with placebo</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Antileuktriene</td>
<td>10 mg PO q12h</td>
<td>No difference in inflammatory parameters compared with placebo</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>T cell and mast cell inhibitor</td>
<td>10 mg/kg PO q12h</td>
<td>Inhibition of airway hyperresponsiveness and cytological and histological alterations but not mast cell degranulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol/fluticasone</td>
<td>LABA/glucocorticoid</td>
<td>100/500 µg via inhalation q12h</td>
<td>Significant decrease in functional and inflammatory parameters compared with pretreatment</td>
</tr>
<tr>
<td>Racemic albuterol</td>
<td>Short-acting β&lt;sub&gt;2&lt;/sub&gt;-adrenergic agonist</td>
<td>2 mg/kg via inhalation q12h</td>
<td>Significant increase in inflammatory parameters compared with placebo</td>
</tr>
</tbody>
</table>

Table 5: Pharmaceuticals that have been evaluated for management of feline asthma. From Venema & Patterson (2010), published in Journal of Feline Medicine and Surgery, © SAGE Publications

9. PROGNOSIS
When the disease is controlled with medication the prognosis is good, but in most cases lifelong treatment is necessary. Severe bronchoconstrictive attacks have the potential to be fatal. High costs for treatment and repeated veterinary visits may increase the risk of euthanasia (Johnson 2013).
CLINICAL CASE

1. SIGNALMENT
A female spayed cat of unknown age was submitted for pathological examination to the department of pathology, Faculty of Veterinary Medicine, Ghent University.

2. CASE HISTORY
The cat was found dead and initially intoxication was suspected.

3. NECROPSY
At the time of necropsy the cat weighed 3.45 kg and beginning post mortal decay was noted. The cat was well nourished but dehydrated. The mucosal surfaces and conjunctiva were pale.

The heart weighed 10 g. Left and right ventricular wall were respectively 7 and 2 mm thick. The ventricular septum was 8 mm thick. There was a pale area at the height of the apex. The lumen of the left ventricle was narrowed due to prominent concentric thickening of the ventricular wall.

There was a large quantity of frothy fluid within the larynx and trachea. The lungs showed a patchy pattern with alternating emphysematous and hyperemic zones. Rib impressions were notable. Furthermore, the lungs were edematous and there was unilateral consolidation of a caudal lung lobe.

The liver weighed 114 g and was congested. Bilateral, there were several very small cysts on the kidneys. The thymus was present and the mesenteric lymph nodes were markedly enlarged.

4. HISTOPATHOLOGY
Tissue from lungs spleen, heart and liver was fixed in buffered formalin, embedded in paraffin and subsequently stained with haematoxylin and eosin.

4.1. LUNGS
There is marked hyperplasia of the bronchial glands and bronchial smooth muscle. The lungs are moderately congested and there is diffuse edema. There is multifocal infiltration of limited number of

Figure 4: HE stain of lung tissue. The alveolar walls appear to be thickened. Capillaries are dilated and there is transudate within alveolar spaces.
eosinophils. Peribronchial, there are multiple vast aggregates of follicular lymphocytes. The arterial walls are remarkably thickened with hypertrophic small muscle cells. There is deposition of extracellular matrix indicating atherosclerosis.

Figure 5: HE stain. Transverse section of a bronchus. The bronchial wall is markedly thickened due to bronchial gland hyperplasia and lymphocyte infiltration.

Figure 6: Magnification from Figure 7. Submucosal glands are hyperplastic and there is lymphocytic infiltration.

Figure 7: Magnification from Figure 7. Bronchial gland hyperplasia (and smooth muscle)
Figure 8: Magnification from Figure 7. Peribronchial aggregate of lymphocytes. Some eosinophils.

Figure 9: HE stain of lung tissue. Transversal section of a bronchiole. There is marked hypertrophy of smooth muscle cells.

Figure 10: HE stain of lung tissue. Transverse section of an arteriole. Smooth muscle hyperplasia of the arterial wall. Atherosclerosis.
4.2. Spleen
In the spleen multifocal hemosiderin-laden macrophages were observed.

4.3. Heart
Cardiac myocytes of the left ventricle have a hypertrophic appearance, characterized by myocytic disarray.

![Figure 11: HE stain of the left ventricle. There is marked myocytic disarrays with loss of the parallel architecture of cardiomyocytes and many fibres that are perpendicular to the normal direction.](image1)

4.4. Liver
There is marked centrilobular vacuolar degeneration of hepatocytes. This is compatible with a cardiac pathology. A large amount of hepatocytes contain granular yellow-brown pigment that is most likely bile pigment. Furthermore the abundance of erythrocytes indicates hyperemia.

![Figure 12: HE stain of the liver. Many hepatocytes contain a granular brown pigment.](image2)
5. PATHOLOGIC DIAGNOSIS

The prominent bronchial gland hypertrophy, lymphocytic and eosinophilic infiltration as well as bronchial smooth muscle hyperplasia led to the diagnosis of feline asthma. The macroscopically obvious concentric thickenings of the ventricular wall, as well as the microscopic signs of hypertrophy are indicative of hypertrophic cardiomyopathy. The congested liver and signs of degeneration (vacuolated hepatocytes) are compatible with a cardiac disease. In this case, death most likely occurred due to a combination of feline asthma, hypertrophic cardiomyopathy and atherosclerosis. The significance of the other abnormalities (bilateral renal cysts, anemia and mesenteric lymphadenopathy) is unclear.

Figure 13: HE stain of the liver. Centrilobular, there is vacuolization of the hepatocytes.
**DISCUSSION**

The histological lesions reported in this case of naturally occurring asthma match the lesions that have been described in the literature. Bronchial smooth muscle hypertrophy that has been described as one of the most consistent lesions in feline asthma (Norris Reiner et al. 2004) was distinct in this case. The other pulmonary lesions (edema, eosinophilic inflammation and lymphocytic aggregates) have also already been described in the literature. This indicates that the lesions described in cats with experimentally induced asthma match the lesions in naturally occurring asthma. In addition to pulmonary changes, cardiovascular pathologies such as hypertrophic cardiomyopathy and atherosclerosis were found. A connection between these pathologies and asthma has not been established in cats. In humans on the other hand, asthma may be a risk factor in cardiovascular diseases such as stroke (Schanen et al. 2005). Unfortunately, the lack of a clinical history in this case make a comparison of the clinical signs of asthma with the literature impossible. When the cat was found dead, intoxication was suspected. The chronic lesions in this case do not support this initial suspicion.

The fact that feline asthma mimics asthma in humans so well, hast led to the establishment of the cat as model organism for human asthma. This contributes to a better understanding of feline asthma. The rise in prevalence in human asthma coincides with a change in living conditions. This raises the question if this may also play a role in cats as they live in close proximity with their owner and are therefore also affected by the changing conditions. In the future, it would be interesting to find out if the hygiene hypothesis can be extrapolated to cats and other companion animals. If this is the case, the shared living conditions and improved medical care could turn out to put cats at higher risk of getting asthma.
RESOURCES


Norris Reiner, C.R. et al., 2004. An experimental model of allergic asthma in cats sensitized to house dust mite or Bermuda grass allergen. *International Archives of Allergy and Immunology*, 135(2),


