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Amyloidosis in Domestic Animals: Pathology, Pathogenesis, Gross and Microscopic Lesions and Clinical Findings

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1. Introduction

Amyloidosis refers to a group of protein misfolding diseases characterized by deposition of a particular amyloid protein in various organs and tissues of animals and humans. Although there are other components present in the deposit, the amyloid protein fibril is the main component of the amyloid substance. The amyloid substance differs in protein composition depending upon the types of amyloidosis (AA amyloidosis or AL amyloidosis) and the different clinical forms. Each clinical entity or form of amyloidosis may be manifested by a distinct clinical form with chemically specific amyloid fibril protein. This indicates that amyloid is a biochemically heterogeneous substance, although there are similarities in properties and staining characteristics.

Amyloidosis involving several tissues and organs throughout the body is referred to as systemic amyloidosis. This may be AA amyloidosis (including familial amyloidosis) or AL amyloidosis. Systemic amyloidosis can be deposited in several vital organs and tissues and may entail severe damage. Amyloid substance may be confined at a given area in the body in the form of localized amyloidosis.

The pathogenesis, pathology and clinical presentations of amyloidosis are protean consequent to the diverse underlying causes of its various forms, species of animals affected and the severity of functional disruption in different tissues and organs involved. The diagnosis of amyloidosis requires histopathologic identification of amyloid deposits in the affected tissues. This is confirmed by Congo red staining and green birefringence under polarized light.

In this chapter, the pathology, pathogenesis, lesions, and clinical syndromes encompassing various forms of amyloidosis in animals will be covered. Current knowledge available on amyloidosis in animals, which would be of importance as a reference for veterinary professionals and practitioners, and veterinary students will be elucidated in the chapter.

2. Pathology and pathogenesis

The pathology and pathogenesis of amyloidosis is a captivating enigma consequent to the diverse underlying causes of its various forms in different species affected. About 20-25

different types of proteins with the ability to aggregate, insolubilize, and deposit in tissue as amyloid have been identified (Murphy et al., 2001, Gruys, 2004). In animals, at least eight different amyloid precursors have been described (Ménsua et al., 2003). The precursor proteins in amyloid fibrils may be amyloidogenic mutants as in some familial amyloidosis, whereas other precursors are normal wild-type proteins (Westermark, 1998; Gruys, 2004). The exact mechanisms through which the proteins are converted into amyloid fibrils in vivo are not well known (Westermark, 1998). There are a number of divers conditions that can be associated with the formation of amyloid and each of these conditions are characterized by excessive production of amyloidogenic proteins that are prone to misfolding. Under normal conditions, the misfolded proteins are enzymatically degraded intracellularly within proteasomes or extracellularly by macrophages. In amyloidosis, these degradative processes are inadequate and may be responsible for the accumulation of misfolded protein extracellularly. The overproduction of precursor protein, although necessary, is not sufficient to result in the formation of amyloid by itself (Snyder, 2007). A single amyloidogenic protein may result in multiple forms of amyloid fibrils depending on their induction conditions. Multiple mechanisms for amyloidogenesis are expected to operate as witnessed with their fibrillar polymorphism (Bhak et al., 2009). Although there are divers proteins associated with the formation of amyloid, they are all characterized by misfolded proteins leading to the formation of fibrils that are unstable and self associated (Snyder, 2007). The protein fibril is the main component of the amyloid substance, however, there are other components present, the importance of which is yet not well established in the pathogenesis of amyloidosis. All forms of amyloid contain the pentraxin glycoprotein amyloid P-component (AP) that most probably is bound to the protein fibrils directly. The unique β-sheet fibril of amyloid is very resistant to physical agents and also gives the amyloid substance many of its characteristic properties, including affinity to the dye Congo red and green birefringence under polarized light after such staining (Westermark, 1998).

According to the WHO-IUIS Nomenclature Sub-Committee (1993) on the nomenclature of amyloid and amyloidosis, amyloid and amyloidosis are classified based on the amyloid fibril protein, followed by a designation of the fibril protein precursor. The capital letter A for amyloid is followed by the protein designation in abbreviated form. For example AL-amyloid refers to the amyloid derived from immunoglobulin light chain, whereas AA-amyloid refers to the amyloid derived from serum A-amyloid protein. Amyloid fibrils may be deposited locally in a given tissue (local amyloidosis) or it may be a systemic deposit (systemic amyloidosis) involving various tissues and organs in the body. Systemic deposits of amyloid are recognized as AL-amyloidosis (primary amyloidosis), AA-amyloidosis (secondary or reactive amyloidosis) or familial amyloidosis.

2.1 AA – Amyloidosis

AA-amyloidosis is described in literature as reactive or secondary amyloidosis. It is the most common form of amyloidosis in domestic animals. AA amyloidosis is associated with chronic inflammatory or neoplastic diseases (non-immunocyte dyscrasia) or it may be idiopathic, where no underlying disease is found (Kim et al., 2005**;** Snyder, 2007). In this form of amyloidosis, the deposited amyloid protein is derived from serum amyloid-A synthesized in the liver **(**Kim et al., 2005). Amyloid A is derived from the acute phase reactant, serum amyloid A (SAA) (Kisilevsky, 1990; Gruys, 2004), which is an apolipoprotein of high-density lipoproteins (HDL), classes 2 and 3. It is formed mainly in the liver upon

stimulation by pro-inflammatory cytokines (Gruys, 2004) and normally plays a role in cholesterol transport (Kisilevsky, 1990) and as a chemoattractant (Badolato et al., 1994) in the inflammatory processes. When the concentration of this molecule is increased, typically as a result of chronic inflammation, certain isoforms of SAA are partially cleaved into fragments that have an increased propensity to form fibrillar aggregates of amyloid that are deposited systemically, mainly in the kidney, liver, and spleen (Johnson et al., 1996). In systemic AA amyloidosis (reactive systemic amyloidosis), macrophages are known to be activated and elaborate endogenous pyrogens IL-1 and IL-6, which stimulate hepatocytes to synthesize and secrete SAA. During an inflammatory reaction, the quantity of SAA in the serum may increase several 100 times normal concentrations. However, not all systemic inflammatory reactions lead to the formation of AA amyloid; but only some of the inflammatory reactions lead to amyloidosis. Either an enzyme defect in the system that normally degrades SAA protein or the synthesis of abnormal SAA protein that is resistant to the enzymatic degradation is suggested to underlie production of insoluble AA molecules that form the amyloid fibrils (Snyder, 2007). Some species of animals appear to have genetic predisposition to the deposition of AA amyloidosis. Analysis of SAA cDNA sequences from several animals identified a distinct genetic dimorphism that may be relevant to the susceptibility to secondary amyloid disease. The duck genome contained a single copy of the SAA gene that was expressed in the liver and lung tissues of ducklings, even in the absence of induction of acute phase response (Guo et al., 1996). Siamese and Abyssinian cats and Shar Pei dogs appear to have familial predisposition of AA proteins with different primary sequence and pattern of deposition in the body (Boyce et al., 1984; DiBartola et al., 1986 & 1990). Amyloid resistant mouse strains were found to have a non-amyloidogenic acute phase SAA (Gonnerman et al., 1995; Liang et al., 1998). Rats were shown not to form acute phase SAA and AA-amyloid at all (Ren et al., 1999; Yu et al., 2000).

AA amyloidosis is the most common type of amyloid in mammals and birds (**Fig. 1**) and often results in hepatic or renal failure due to physical disruption of normal cellular and organ processes (Terio et al., 2008). It is a common disease of water fowl and is characterized by the deposition of extracellular fibrils of amyloid A (AA) protein in the liver and certain other organs in this species (Guo et al., 1996). AA amyloidosis is also reported in a wide variety of domestic animal species including canines, equines, bovines, avian species, porcines, felines, sheep and goats (Jakob, 1971; Johnson & Jamison, 1984; Hayden et al., 1988; Zschiesche & Jakob, 1989; DiBartola, et al., 1990; Blunden & Smith, 1992; Seifi et al., 1997; Landman, 1998; Ménsua et al., 2003). It is described in association with different chronic diseases, in captive cheetah (*Acinonyx jubatus*), Siberian tigers (*Panthera tigris altaica*), mink (*Mustela vison*), black-footed cats (*Felis nigripes*), black-footed ferrets (*Mustela nigripes*), Dorcas gazelle (*Gazella dorcas*), mountain gazelle (*Gazella gazella*), bighorn and Dall's sheep, free living lioness and in swans and other anatidae (*Panthera leo*) (Hadlow & Jellison, 1962; Sato et al., 1981; Kingston et al., 1982; Linke et al., 1986; Rideout et al., 1989; Munson, 1993; Nieto et al., 1995; Papendick et al., 1997; Schulze et al., 1998; Williams et al., 2005; Garner et al., 2007; Terio et al., 2008). It is reported in association with chronic lymphoplasmacytic gastritis in the cheetahs and as idiopathic in the Siberian tigers. In the cheetahs and the Siberian tigers, the deposits were primarily in the medullary interstitium, with minimal glomerular involvement (Papendick et al., 1997; Schulze at al., 1998). Deposition of the amyloid in renal amyloidosis reported in the Dorcas gazelle was also mainly in the renal medulla, sparing the glomeruli (Rideout et al., 1989).

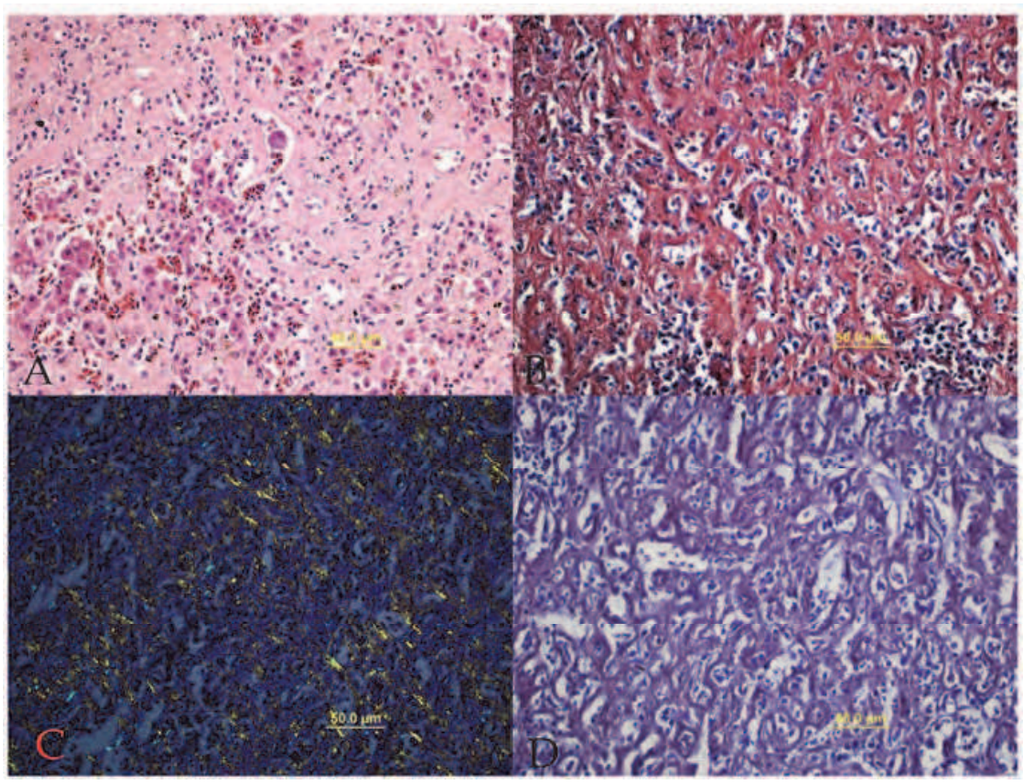


Fig. 1. A section of liver with hepatic amyloidosis in an American Coot with severe parasitism. (**A**) Light eosinophilic amorphous deposits disrupted the hepatic parenchyma (H&E stain). The deposit stained light red with Congo red stain (**B**) and exhibited green birefringens under polarized light (**C**). The amyloid deposit failed to stain with Congo red (**D**) after pretreatment with Potassium Permanganate solution, characteristic of AA-amyloid.

2.1.1 Familial forms of AA amyloidosis

Familial amyloidosis refers to the deposition of amyloid in tissues of animals in a given genetically associated family known to be prone to the deposition of amyloid fibrils. In veterinary medicine, it is reported in Siamese and Abyssinian cats (Boyce et al., 1984; DiBartola et al., 1986 & 1990) with the AA proteins differing in primary sequence and pattern of deposition in these cats (DiBartola et al., 1986 & 1990). Familial amyloidosis is also reported in Shar Pei dogs (DiBartola et al., 1990). The kidney is the main target organ for the deposition of amyloid in the Abyssinian cat, and Shar Pei dogs, while the amyloid protein is mainly deposited in the liver in Siamese cats (DiBartola et al., 1986 & 1990; Niewold et al., 1999). Furthermore, there are other animal species that appear to be prone to amyloid deposition. The high prevalence of amyloidosis in captive cheetahs is suggested to indicate some level of familial predisposition similar to the Abyssinian cats (Papendick et al., 1997). Amyloid arthropathy frequently occurred in brown layer chickens, but never in white layers. The suspected higher susceptibility of brown layers was confirmed experimentally by inducing amyloidosis with an arthropathic and amyloidogenic strain of *E. faecalis* (Ovelgönne et al., 2001). In the systemic amyloidosis reported in the black-footed cats, there was no association with concurrent chronic inflammatory conditions, indicating that the

amyloid deposit was not secondary to inflammation. Heritability estimation suggested that amyloidosis might be familial in this species. Additionally, tissues from a single free-ranging black-footed cat had small amounts of amyloid deposition, suggesting that there could be a predilection for amyloidosis in this species too (Terio et al., 2008). Therefore, in addition to Siamese and Abyssinian cats and Shar Pei dogs, in which familial amyloidosis is well-recognized in veterinary medicine, certain species such as cheetahs (*Acinonyx jubatus*), Dorcas gazelles (*Gazella dorcas*), black-footed cat and brown layer chickens appear to be genetically predisposed to amyloidosis.

2.2 AL – Amyloidosis

The AL amyloid type derived from immunoglobulin light chains is the most common form of systemic amyloidosis in humans (Picken, 2001). Small-sized bone marrow plasma cell clones are reported to produce toxic light chains that cause fibrillar deposits in multiple organs (Merlini & Stone, 2006). The amyloid fibrils are formed by the N-terminal fragment of a monoclonal immunoglobulin light chain comprising the variable region and a portion of the constant region. Only a small proportion of free monoclonal light chains form amyloid fibrils in vivo. Thus, the ability to form amyloid is probably related to individual structural characteristics of the light chain variable region. Unlike most other plasma cell dyscrasias, the λ light chain isotype is prevalent in AL (κ/λ ratio, 1:3), suggesting the existence of amyloid-associated Vλ germ line genes (Merlini & Stone, 2006).

AL amyloidosis is very rare in domestic animals **(**Kim et al., 2005**),** unlike in humans, in which it is a common form of systemic amyloidosis. Report on systemic AL amyloidosis in domestic animals is very rare. It is reported in a horse gelding with multiple myeloma **(**Kim et al., 2005**)**, a mare (Hawthorne et al., 1990) and in a cow with bovine leukocyte adhesion deficiency (Taniyama et al., 2000). Recently, non-AA amyloid is reported in two felines with thymomas (Burrough et al., 2011). In animals, the deposition of AL amyloid protein is generated following overproduction of monoclonal light chains associated with immunocyte dyscrasia**.** In this form of amyloidosis, plasma cells produce excessive quantities of immunoglobulin light chains that are resistant to complete enzymatic degradation and are susceptible to forming insoluble fibrils (Snyder, 2007). The most common immunocyte dyscrasia associated with AL amyloidosis in domestic animals is a neoplasm of plasma cell. The AL form of amyloid can contain complete immunoglobulin light chains, the NH_2-terminus portion of immunoglobulin light chains or both. Immunoglobulin secreting cells, B lymphocytes, and plasma cells are associated with the deposition of AL amyloid. In contrast to amyloidosis in humans, in which the majority of patients with AL do not have any overt B lymphocyte or plasma cell neoplasm, but do have monoclonal antibodies or light chains in their serum or urine, domestic species rarely have AL-type amyloid without evidence of an immune dyscrasia (Snyder , 2007).

2.3 Localized and other forms of amyloidosis

Localized amyloidosis refers to the deposition of amyloid fibrillar protein as a grossly visible mass or a microscopic deposit at a given site in an organ or tissue. Localized AL is an intriguing condition characterized by limited growth of monoclonal plasma cells and restriction of amyloid deposits to sites adjacent to those of the synthesis of the precursor (Merlini & Stone, 2006). In animals, localized amyloidosis is present in calcifying epithelial odontogenic tumors (amyloid producing odontogenic tumors) of the cat and dog and

pancreatic islets in cats (Gruys, 2004; Snyder, 2007). Aβ-amyloid and APrPsc-amyloid can be encountered in the brains of old dogs and sheep with scrapie, respectively (Prusiner et al., 1983; Gruys, 2004). Some forms of naturally occurring transmissible spongiform encephalopathies such as chronic wasting diseases (CWD), are characterized by amyloid plaques in the brain in addition to the intraneural vacuolation (Snyder, 2007). In horses, localized cutaneous amyloidosis is described in association with lymphoma (Gliatto & Alroy, 1995), extramedullary plasmacytoma (Linke et al., 1991) and liver amyloidosis in serum-producing horses (Abdelkadir, et al., 1991). Local amyloidosis associated with plasma cell dyscrasia or focal extramedullary plasmacytoma occurs on the skin and along intestinal tracts in dogs (**Fig. 2**).

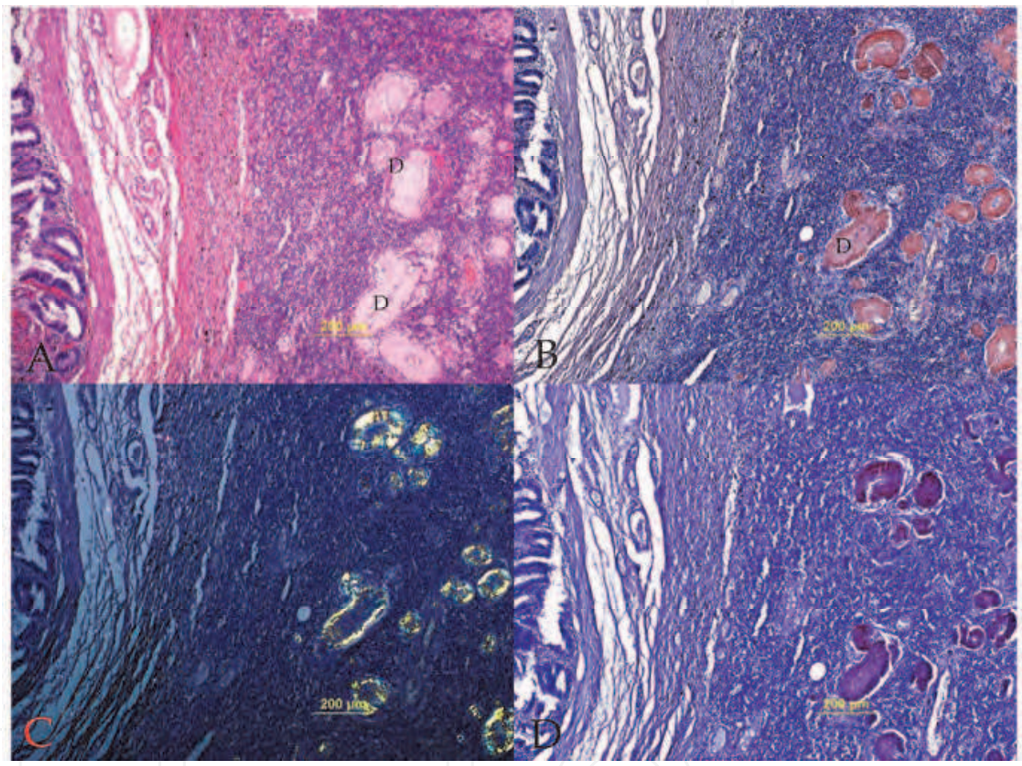


Fig. 2. A section of colon with amyloidosis in a dog with focal intestinal extramedullary plasma cell tumor. (**A**) Light eosinophilic amorphous deposits (D) surrounded by abundant plasmacytoid cells (H&E stain). The deposit stained light red with Congo red stain (**B**) and exhibited green birefringence under polarized light (**C**). The amyloid deposit stained with Congo red (**D**) after pretreatment with Potassium Permanganate solution, indicating that the amyloid is AL-amyloid.

Deposition of amyloid derived from islet amyloid polypeptide (IAPP), a normal protein secreted by the β cell of the pancreas, is reported in the pancreas of cats, and macaques. The mechanisms by which IAPP, a normal product of pancreatic islet beta cells, undergoes assembly and transformation into deposits of amyloid fibrils are not fully understood (O'Brien et al., 1996; Hoenig et al., 2000). However, the islet amyloid deposits in humans and feline and macaque animal models of type 2 diabetes mellitus are associated with significant loss of islet β cells (Hoenig et al., 2000). It is not known if the deposition of amyloid and the

development of clinical diabetes mellitus is the result of progressive loss of β cells from the amyloid deposit or if the deposition of the amyloid occurs as a result of prolonged stimulation of the β cells as a consequence of insulin resistance (Snyder, 2007).

Similar to human senile amyloidosis, old dogs develop neurodegenerative brain changes including cerebrovascular amyloidosis and senile plaques with amyloid deposition. The amyloid protein in the canine cerebrovascular amyloidosis is deposited in the medium- and small-caliber arterioles and capillaries of the leptomeninges and the brain parenchyma. Vascular or perivascular degeneration or cellular reactions were not detected in affected vessels (Borra's et al., 1999). Such amyloid deposits in the brain consist of a number of extracellular proteins, but most commonly contain Aβ type amyloid, which consists of a proteolytic fragment of the APP (Amyloid Precursor Protein). The Aβ form of amyloid is associated with the cerebral amyloid angiopathy of Alzheimer's disease in humans and with neurodegeneration in the canine brain (Snyder, 2007). In the brain tissue of aged dogs, Alzheimer-like pathology with lipofuscin being present in neurons and macrophages, Aβ-precursor protein in neurons, Aβ-positive plaques, 4-hydroxynonenal in neurons and macrophages, and limited intraneuronal accumulation of tau and advanced glycation end products increasing with longevity has been encountered (Gruys, 1995; Papaioannou et al., 2001; Rofina et al., 2001 & 2003). The amyloidosis which causes neurodegenerative disorders is almost always related to the intracerebral production of the pathogenic protein since most proteins, like immunoglobulins, do not cross the blood brain barrier. One exception may be the case of systemic amyloidosis related to transtiretin mutations, which produce peripheral neuropathy and cerebral changes in the white matter in some cases (Mena, 2009). Aβ-amyloid in the brain tissue of aged dogs showing signs of dementia forms a canine counterpart of senile dementia of the Alzheimer type (ccSDAT) in man. Other organ systems containing amyloid in the aged dog are the heart, gastrointestinal tract, and lungs. The deposition of amyloid in the pulmonary vasculature of the aged dogs was reported to be derived from apolipoprotein AI (Apo AI) (Snyder, 2007).

3. Clinical findings

Amyloidosis is a feature of several different pathologic mechanisms and as such should not be considered a single disease, but rather a group of diseases having in common the deposition of similar appearing proteins (Snyder, 2007). The animals affected with amyloidosis may show variable clinical signs due to the main underlying disease as commonly seen in AA amyloidosis (secondary amyloidosis) or those solely attributable to the deposition of amyloid in a given tissue or both. Some local amyloid depositions may be clinically non-significant incidental findings in certain tissues. In most cases, small local cutaneous amyloid masses pose no clinical problems. Therefore, the clinical finding of amyloidosis in affected animals is protean and reflects the extent of perturbed function of the predominantly affected organs and tissues due to the deposition of amyloid or may show variable clinical signs that may be associated to the underlying chronic disease and the concurrent amyloid deposit. For example, kidney is the main target organ for the deposition of amyloid in familial amyloidosis of the Abyssinian cat (glomerular deposit), and Shar Pei dogs (medullary deposit), while the amyloid is mainly deposited in the liver in Siamese cats (DiBartola et al., 1990; Niewold et al., 1999). Because amyloid deposit in the amyloidosis of the Abyssinian cat and Shar Pei dog is primarily a renal deposit, clinical signs associated with disrupted renal function will be seen in the affected

Abyssinian cats, and Shar Pei dogs, whereas clinical signs associated with derailed hepatic function may be manifested in Siamese cats. Deposition of amyloid in the pancreas of cats, non-human primates (macaques and baboons) and humans can lead to the development of type 2 diabetes mellitus (Hoenig et al., 2000; Snyder, 2007). Amyloid deposition can also occur in the cortex of the adrenal gland; however, it is not associated with any functional deficiencies (Snyder, 2007).

Reactive systemic amyloidosis secondary to chronic inflammatory conditions is often the most severe of the systemic forms. Liver, kidneys, spleen, lymph nodes, and adrenal glands are most commonly affected. Animals with renal amyloidosis frequently die from renal failure (Snyder, 2007). The clinical sign usually reflects the functional disruption and severity of the particular site of the kidney affected in renal amyloidosis. Progressive renal failure was the cause of death in Dorcas gazelles with renal medullary amyloidosis (Rideout et al., 1989). In contrast, renal medullary amyloidosis in cattle frequently occurs in conjunction with glomerular amyloidosis, and if the glomerular component is mild, it is usually a subclinical disease (Gruys, 1980, as cited by Rideout et al., 1989.) In Dorcas gazelle impairment of the renal function involved obstruction of the medullary tubules and collecting ducts, leading to atrophy and eventual loss of nephrons, with progressive interstitial fibrosis in the medulla and cortex (Rideout et al., 1989). Interstitial amyloidosis may also contribute to loss of concentrating ability and renal failure by interfering directly with maintenance of the medullary interstitial concentration gradient necessary for reabsorptive function in the renal tubules (Papendick et al., 1997). In 74% of the cheetahs with systemic amyloidosis associated with chronic gastritis, renal failure was determined to be the sole or partial cause of death (Papendick et al., 1997). Clinical signs including rapid weight loss, muscle atrophy, soft unformed stool, and ventral edema were noted in a horse gelding with multiple myeloma (Kim et al., 2005).

4. Gross and microscopic lesions

Several different pathologic mechanisms and conditions underlie various forms and types of amyloidosis, although abnormal proteins with similar staining characteristics are deposited in various organs and tissues of the affected animals. The gross feature of amyloidosis due to the deposited amyloid in these tissues and organs is not specific for amyloid. Grossly, the affected organs are often enlarged, moderately firm and abnormally discolored (Snyder, 2007). In AA-amyloidosis, the most frequently encountered amyloid type in veterinary medicine, the characteristic deposition pattern in most species is in the central organs such as spleen, liver, enteric mucosa and the arterial walls (Gruys, 1988 as cited by Gruys, 2004). Depending on the extent of the deposition, there may be splenomegaly, hepatomegaly and renomegaly as these organs are most commonly affected in systemic AA amyloidosis. Amyloid deposition was most severe in the renal medullary interstitium and glomeruli in systemic amyloidosis in black-footed cats (Terio et al., 2008). Renal lesions in AA amyloidosis in sheep and goats were characterized grossly by pale cortical surfaces with scattered, miliary, whitish-yellow foci and by straight, whitish-yellow striations on cut cortical surfaces **(**Ménsua et al., 2003**)**. However, experimentally induced AA Amyloidosis in sheep principally affected the gastrointestinal tract. Amyloid was present from the tongue to the rectum, but was most prominent in the duodenum where the deposits disrupted the normal mucosal architecture. Other body organs had only mild amyloid deposition (Biescas et al., 2009).

Diffuse gastrointestinal hemorrhage, markedly thickened jejunal mucosa, and splenomegaly were present in a horse with AL amyloidosis associated with multiple myeloma (Kim et al., 2005). In Gallinae, it may also be deposited in the joints. In felines, pancreatic insular amyloid (AIAPP) is rather common (Gruys, 1988, as cited by Gruys, 2004). Amyloid deposits are occasionally limited to a single organ or tissue and may be visible grossly as masses (Snyder, 2007). Local amyloid deposits associated with plasma cell dyscrasia may be seen as variably sized grossly visible skin granulomas in cutaneous nodular amyloidosis in various animals. Rowland et al., (1991) reported local cutaneous amyloidosis associated with plasmacytoma involving the digits, forelimbs, lips, and ears in dogs (**Fig. 3**).

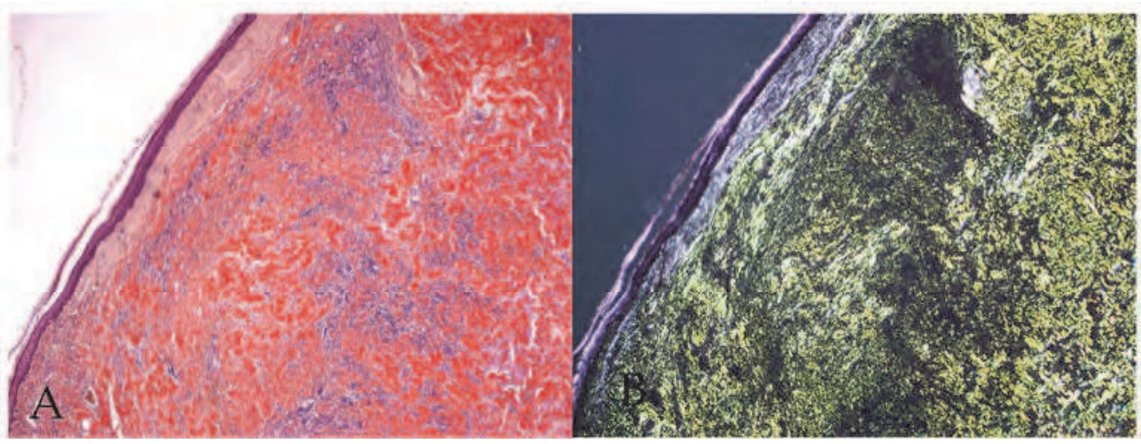


Fig. 3. Histological features of skin of a dog with nodular cutaneous amyloidosis, stained red with Congo red stain (left) and showed yellow-green birefringence (right) illuminated with polarized light, characteristic of amyloid deposits.

Microscopic findings of the deposition of amyloid protein may correspond to the grossly visible lesions, or it may be seen only after microscopic examination without distinct grossly discernible lesions. Amyloid should be differentiated from other similar-appearing extracellular deposits such as collagen and fibrin (Snyder, 2007). For a fibrillary protein to be considered amyloidogenic it should produce extracellular deposits with affinity for the red Congo dye and a green birefringence under polarized light. Congo red stain, which does not have chemical specificity for amyloid, but is dependent on the conformational property of being arranged in beta-pleated sheets, is the most commonly used stain for the identification of amyloid. Amyloid stains orange to red under light microscopy, which is seen under polarized light as an apple-green birefringent material (Ménsua et al., 2003**;** Snyder, 2007). Immunohistochemistry can also be used not only to identify amyloid deposits but also to identify the specific constituents composing the deposits such as the anti-β-light chain antibodies (Snyder, 2007). AA and AL amyloid deposits stain similar with Congo red stain. The identification of AA is usually based on its reactivity with specific anti-AA antibodies and sensitivity to permanganate pretreatment (Wright et al., 1977; Shtrasburg et al., 2005) (**Fig. 4**). The common ultra structure of amyloid proteins is made of some nonbranching, rigid fibrils, 7.5 to 10 nm wide and of variable length, which arrange themselves in anti-parallel sheets with β structure (Mena, 2009).

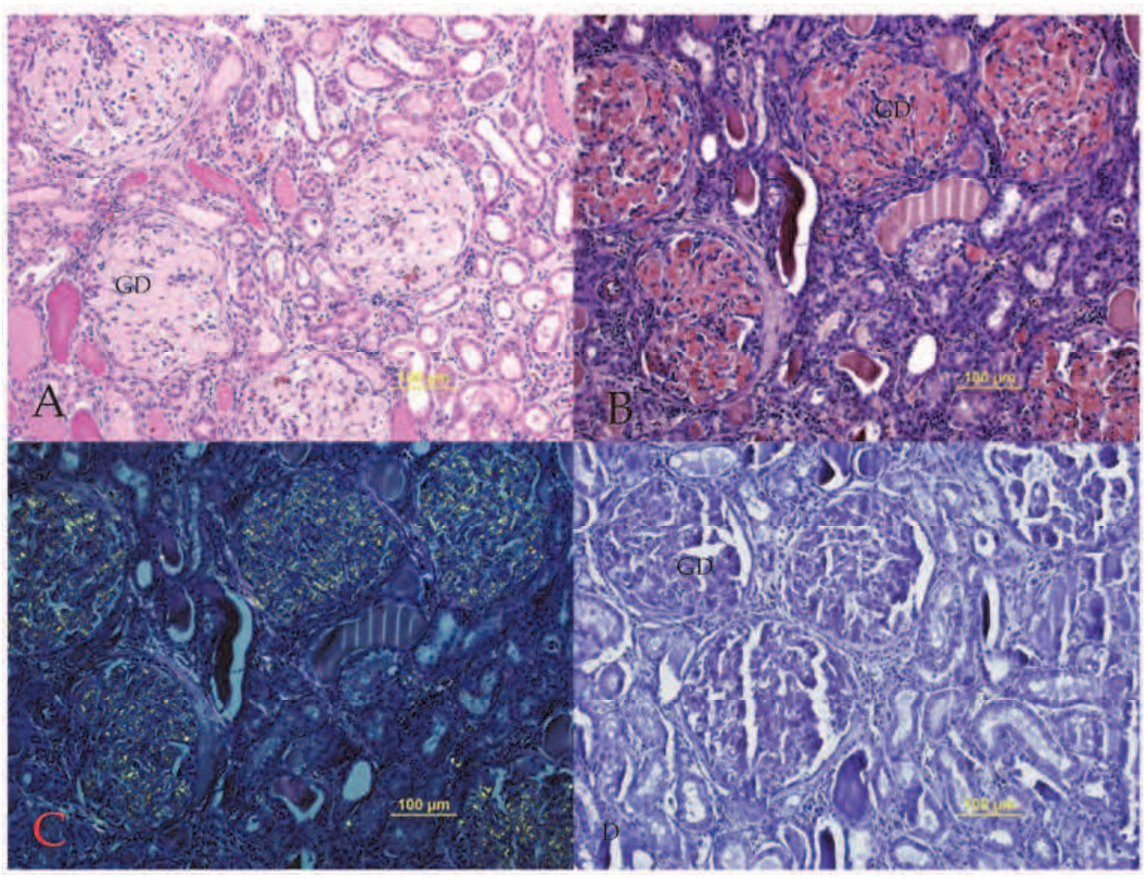


Fig. 4. A section of renal glomerular amyloidosis in a dog. (A) Light eosinophilic amorphous deposits partly effaced the glomerular architecture (H&E stain). The deposit stained light red with Congo red stain (**B**) and exhibited green birefringence under polarized light (**C**). The amyloid deposit failed to stain with Congo red (**D**) after pretreatment with Potassium Permanganate solution, indicating that the amyloid is AA-amyloid.

Microscopically, amyloid is deposited extracellularily in various affected tissues. Amyloid deposition was seen in the kidneys, blood vessels, spleen, liver, lymph nodes, gastrointestinal tract, and adrenal glands of sheep and goats with AA amyloidosis (Ménsua et al., 2003). There was widening of the medullary interstitium by eosinophilic homogeneous material, which encroached upon medullary tubules and collecting ducts with occasional renal papillary necrosis in Dorcas gazelle with medullary amyloidosis. The amyloid deposition significantly correlated with interstitial fibrosis, and tubular dilation and atrophy (Rideout, 1989).

In a horse with AL amyloidosis associated with multiple myeloma, diffuse severe extracellular amyloid deposits were present in the lamina propria of glandular stomach, duodenum, and jejunum. Much of the spleen and sternal bone marrow were replaced by neoplastic round cells, and multiple foci of amyloid were also present in the spleen and bone marrow. No significant microscopic changes were noted in the kidneys, liver, and lungs (Kim et al., 2005).

In a cow with systemic AL amyloidosis associated with bovine leukocyte adhesion deficiency, amyloid deposits immunohistochemically related to immunoglobulin kappa-

light chains of precursor protein were present in the perivascular and intercellular spaces of the visceral organs, such as the liver, kidneys, pancreas, adrenal glands, and upper alimentary tract (Taniyama et al., 2000).

5. Conclusion

In summary, the pathology and pathogenesis of amyloidosis in animals is diverse depending upon the underlying causes and species affected. Similarly, the clinical findings are quite variable consequent to the variation of the tissues and organs involved and the extent of functional disruption of the affected organs in various animal species. The affected organs may be enlarged and exhibit variable pallor or the amyloid deposit may not be grossly visible and may be discernible only after microscopic examination of the affected tissues. Amyloid appears as a pale eosinophilic homogenous extracellular deposit in tissues. However, microscopic examination and Congo red staining with green birefringence under polarized light are needed to confirm amyloid and differentiated it from other similar extracellular deposits such as collagen and fibrin. Pretreatment of the affected tissues using potassium permanganate solution before staining with Congo red helps to differentiate AA-amyloid from AL-amyloid deposit.

6. References

Abdelkader, SV., Gudding, R. & Nordstoga, K. (1991). Clinical chemical constituents in relation to liver amyloidosis in serum-producing horses. *Journal of Comparative Pathology,* 105 (2):203-11

Badolato, R., Ming Wang, J., Murphy, WJ., Lloyd, AR., Michiel, DF., Bausserman, LL., Kelvin, DJ. & Oppenheim, JJ. (1994). Serum amyloid A is a chemoattractant: induction of migration, adhesion, and tissue infiltration of monocytes and polymorphonuclear leukocytes. *Journal of Experimental* Medicine, 180:203–209

Bhak, G., Choe, Y-J. & Paik, SR. (2009). Mechanism of amyloidogenesis: nucleation-dependent fibrillation versus double-concerted fibrillation. *BMB reports*, 541-551

Biescas, E., Jirón, W., Climent, S., Fernández, A., Pérez, M., Weiss, D.T., Solomon, A. & Luján. L. (2009). AA Amyloidosis induced in sheep principally affects the gastrointestinal tract. *Journal of Comparative Pathology,* 140 (4):238-246 doi:10.1016/j.jcpa.2008.12.004

Blunden, AS. & Smith, KC. (1992). Generalised amyloidosis and acute liver haemorrhage in four cats. *Journal of Small Animal Practice,* 33:566–570

Borra's, D., Ferrer, I. & Pumarola, M. (1999). Age-related Changes in the Brain of the Dog. *Veterinary Pathology,* 36:202–211

Boyce, JT., DiBartola, SP., Chew, DJ. & Gasper, PW. (1984). Familial renal amyloidosis in Abyssinian cats. *Veterinary Pathology,* 21(1):33-8

Burrough, ER ., Myers, RK., Hostetter, SJ., Fox, LE., Bayer, BJ., Felz, C L., Waller, K R. & Whitley, E. M. (2011). Amyloid deposition in 2 feline thymomas. *Veterinary Pathology,* 10.1177/0300985811400442

DiBartola, SP., Tarr, MJ., & Benson, MD. (1986). Tissue distribution of amyloid deposits in Abyssinian cats with familial amyloidosis. *Joural of Comparative Pathology*, 96(4):387-98

DiBartola, SP., Tarr, MJ., Webb, DM., & Giger, U. (1990). Familial renal amyloidosis in Chinese Shar Pei dogs. Journal of the American Veterinary Medical Association, 197(4):483-7

Garner, MM., Raymond, JT., O'Brien, TD., Nordhausen, RW. & Russell, WC. (2007). Amyloidosis in the black-footed ferret (*Mustela nigripes*). *Journal of* Zoo *and* Wildlife Medicine, 38(1):32-41

Gliatto, JM., & Alroy, J. (1995). Cutaneous amyloidosis in a horse with lymphoma. *The Veterinary Record,* 137(3):68-69

Gonnerman, WA., Elliott-Bryant, R., Carreras, I., Sipe, JD., & Cathcart, ES., (1995). Linkage of protection against amyloid fibril formation in the mouse to a single, autosomal dominant gene. *Journal of Experimental* Medicine, 181:2249-2252

Gruys E. (2004): Protein folding pathology in domestic animals: A review. *Journal of Zhejiang University Science,* 5(10):1226-1238

Gruys, E. (1995). First workshop and clinic on neuropathology in geriatric dogs and cats. Wiesbaden, Germany, May 4-5, 1995. *Amyloid, International Journal of Experimental and Clinical Investigation*, 2:280-283

Guo Ju-Tao, Aldrich, C E., Mason, WS. & Pugh, JC. (1996): Characterization of serum amyloid A protein mRNA expression and secondary amyloidosis in the domestic duck. Cell Biology, *Proceedings of the National Academy of Science,* December 1996, *USA,* Vol. 93, pp. 14548–14553

Hadlow, WJ. & Jellison WL. (1962). Amyloidosis in rocky mountain bighorn sheep. Journal of the American Veterinary Medical Association, 141:243–247

Hawthorne, TB., Bolon, B. & Meyer, DJ. (1990). Systemic amyloidosis in a mare. Journal of the American Veterinary Medical Association, 196:323–325

Hayden, DW., Johnson, KH., Wolf, CB. & Westermark, P. (1988). AA Amyloid-associated gastroenteropathy in a horse. *Journal of Comparative Pathology,* 98:195–204

Hoenig, M ., Hall, G., Ferguson, D., Jordan, K., Henson, M., Johnson, K. & O'Brien, T. (2000). A Feline Model of Experimentally induced islet amyloidosis. *American Journal of Pathology, Vol. 157 (6)* 2143–2150

Jakob, W. (1971). Spontaneous amyloidosis of mammals. *Veterinary Pathology,* 8:292–306

Johnson, KH., Westermark, P., Sletten, K. & O'Brien, TD. (1996). Amyloid proteins and amyloidosis in domestic animals. *Amyloid, International Journal of Experimental and Clinical Investigation*, 3:270–289

Johnson, R. & Jamison, K. (1984). Amyloidosis in six dairy cows. Journal of the American Veterinary Medical Association, 185:1538–1543

Kim, DY., Taylor, HW., Eades, SC. & Cho, D.-Y. (2005): Systemic AL amyloidosis associated with Multiple Myeloma in a horse. *Veterinary Pathology,* 42:81–84

Kisilevsky, R. (1990). Heparan sulfate proteoglycans in amyloidogenesis: an epiphenomenon, a unique factor, or the tip of a more fundamental process? Laboratory Investigation, 63:589–591

Kingston, RS., Shih, M. & Snyder, SP. (1982). Secondary amyloidosis in Dall's sheep. *Journal of* Wildlife *Diseases*, 18:381–383

Landman WJM. (1998). Amyloid arthropathy in chickens. *Veterinary Quarterly,* 21:78–82

Liang, J., Elliott-Bryant, R., Hajri, T., Sipe, JD. & Cathcart, ES. (1998). A unique amyloidogenic apolipoprotein serum amyloid A (apoSAA) isoform expressed by the amyloid resistant CE/J mouse strain exhibits higher affinity for macrophages than apoSAA1 and apoSAA2 expressed by amyloid susceptible CBA/J mice. *Biochimica et Biophysica Acta,* 1394:121-126

Linke, RP., Geisel, O. & Mann, K. (1991). Equine cutaneous amyloidosis derived from an immunoglobulin lambda-light chain. Immunohistochemical, immunochemical and chemical results. *Biological* Chemistry Hoppe-Seyler, 372(9):835-43

Linke, RP., Hol, PR. & Geisel, O. (1986). Immunohistochemical identification of generalized AA-amyloidosis in a mountain gazelle (*Gazella gazella*). *Veterinary Pathology,* 23:63–67

Mena, MA., Rodríguez-Navarro, JA. & García de Yébenes, J. (2009): The multiple mechanisms of amyloid deposition. The role of parkin. Commentary & View. *Prion* 3:1, 5-11

Ménsua, C., Carrasco, L., Bautista, MJ., Biescas, E., Fernández, A., Murphy, CL., Weiss, DT., Solomon, A. & Luján, L. (2003). Pathology of AA Amyloidosis in Domestic Sheep and Goats. *Veterinary Pathology,* 40: 71-81

Merlini, G. &. Stone, MJ. (2006). Dangerous small B-cell clones. *Blood,* 108, (8):2520-2530

Munson, L. (1993). Diseases of captive cheetahs (*Acinonyx jubatus*): results of the Cheetah Research Council pathology survey, 1989–1992. *Zoo Biology,* 12:105–124

Murphy, CL., Eulitz, M., Hrncic, R., Sletten, K., Westermark, P., Williams, T., Macy, SD., Wooliver, C., Wall, J., Weiss. DT. & Solomon, A. (2001). Chemical typing of amyloid protein contained in formalin-fixed paraffin-embedded biopsy specimens. *American Journal of Clinical Pathology,*116:135–142

Nieto, JM., Va´zquez, S., Quiroga, MI., Lo´pez-Pen˜a, M., Guerrero, F. & Gruys ,E. (1995). Spontaneous AA-amyloidosis in mink (*Mustela vison*). Description of eight cases, one of which exhibited intracellular amyloid deposits in lymph node macrophages. *European Journal of Veterinary Pathology,* 1 : 99–103

Niewold ,TA., van der Linde-Sipman, JS., Murphy, C., Tooten, PC. & Gruys, E. (1999). Familial amyloidosis in cats: Siamese and Abyssinian AA proteins differ in primary sequence and pattern of deposition. *Amyloid,* 6 (3):205-9

O'Brien, TD., Wagner, JD., Litwak, KN., Carlson, CS., Cefalu, WT., Jordan, K., Johnson, KH. & Butler, PC. (1996). Islet amyloid and islet amyloid polypeptide in Cynomolgus Macaques *(Macaca fascicularis):* An animal model of human non-insulin-dependent Diabetes Mellitus. *Veterinary Pathology,* 33 : 479-485

Ovelgönne, JH., Landman, WJ., Gruys, E., Gielkens , AL. & Peeters, BP. (2001). Identical amyloid precursor proteins in two breeds of chickens which differ in susceptibility to develop amyloid arthropathy. *Amyloid,* 8(1) : 41-51

Papaioannou, N., Tooten, PCJ., Van Ederen, AM., Bohl, JRE., Rofina, J., Tsangaris, T. & Gruys, E. (2001). Immunohistochemical investigation of the brain of aged dogs. I. Detection of neurofibrillary tangles and of 4-hydroxynonenal protein, an oxidative damage product, in senile plaques. *Amyloid Journal of Protein Folding Disorders*, 8:11-21

Papendick, RE., Munson, L., O'Brien, TD. & Johnson, KH. (1997). Systemic AA amyloidosis in captive cheetah (*Acinonyx jubatus*). *Veterinary Pathology,* 34:549-556

Picken MM. (2001). The changing concepts of amyloid. *Archives of* Pathology *& Laboratory* Medicine, 125:38–43

Prusiner, SB., McKinley, MP., Bowman, KA., Bolton, DC., Bendheim, PE., Groth, DF., & Glenner, GG. (1983). Scrapie prions aggregate to form amyloid-like birefringent rods. *Cell*, 35:349-358

Ren, Y., Reddy, SA. & Liao, WS. (1999). Purification and identification of a tissue-specific repressor involved in serum amyloid A1 gene expression. *Journal of Biological Chemistry*, 274:37154-37160

Rideout,BA., Montali, RJ., Wallace, RS., Bush, M., Phillips, LG., Antonovych, TT. & Sabnis, SG. (1989). Renal medullary amyloidosis in Dorcas Gazelles. *Veterinary Pathology*, 26:129–135

Rofina, JE., Papaioannou, N., Van Andel, I., Van Ederen, AM., Gossens, M., Secreve, M., Van der Meer, I., Toussaint, MJM., Terlou, M. & Gruys, E. (2001). Cerebrovascular amyloidosis may cause a decrease of blood supply leading to oxidative damage and formation of amyloid plaques in the aged canine brain. *In*: Bely, M., Apathy, A. (Eds.), *Amyloid and Amyloidosis* IX. Apathy, Budapest, Hungary, p.445-447

Rofina, JE., Van Andel, I., Van Ederen, AM., Papaioannou, N., Yamaguchi, H. & Gruys, E. (2003). Canine counterpart of senile plaques near capillaries but lack of spatial relationship with activated microglia and macrophages. *Amyloid Journal of Protein Folding Disorders,Dis* 10:86-96

Rowland, PH., Valentine, BA., Stebbins, KE. & Smith, CA. (1991). Cutaneous plasmacytomas with amyloid in six dogs. *Veterinary Pathology,* 28 (2): 125-130

Sato, A., Koga, T., Inoue, M. & Goto, N. (1981). Pathological observations of amyloidosis in swans and other anatidae. Japanese journal *of veterinary* science, 43:509–519

Seifi, HA., Karimi, K. & Movasseghi, R. (1997). Renal amyloidosis in cattle: a case report in Iran. *Journal of Veterinary Medicine,* 44:631–633

Shtrasburg, S., Gal, R., Gruys, E., Perl, S., Martin, BM., Artin, B., Kaplan, R., Koren, A., Nyska, A.,Pras, M. & Livneh, A. (2005). An ancillary tool for the diagnosis of amyloid A amyloidosis in a variety of domestic and wild animals. *Veterinary Pathology,* 42:132–139

Schulze, C., Brügmann, M., Bo¨er, M., Brandt, HP., Pohlenz, J. & Linke, RP. (1998). Generalized AA-amyloidosis in Siberian tigers (*Panthera tigris altaica*) with predominant renal medullary amyloid deposition. *Veterinary Pathology,* 35:70–74

Snyder, P.W. (2007). Diseases of Immunity: Amyloidosis . *In Pathologic basis of veterinary diseases, 4th edition. Editors,* McGavin, M.D, & Zachary, JF. Pp 246-251. Mosby Elsevier, ISBN-13:978-0-323-02870-7. St Lois Missouri

Taniyama, H., Yamamoto, S., Sako, T., Hirayama, K., Higuchi, H. & Nagahata H. (2000). Systemic κAL amyloidosis associated with bovine leukocyte adhesion deficiency. *Veterinary Pathology,* 37:98–100

Terio, KA., O'brien, T., Lamberski, N., Famula, TR. & Munson L. (2008). Amyloidosis in Black-footed Cats (*Felis nigripes*). *Veterinary Pathology,* 45:393–400

Westermark, P. (1998). The pathogenesis of amyloidosis. Understanding general principles. *American Journal of Pathology,* 152(5):1125-1127

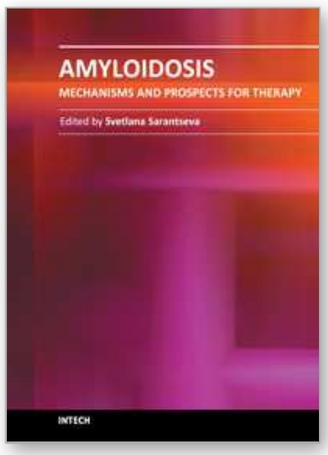
WHO-IUIS, Nomenclature Sub-Committee. (1993). Nomenclature of amyloid and amyloidosis. *Bulletin of the World Health Organization,* 71(1): 105–112

Williams, JH., Van Wilpe, E. & Momberg, M. (2005). Renal medullary AA amyloidosis, hepatocyte dissociation and multinucleated hepatocytes in a 14-year-old free-ranging lioness (*Panthera leo*). *Journal of South African Veterinary Association,* 76(2):90-98

Wright, JR., Calkins, E. & Humphrey, RL. (1977). Potassium permanganate reaction in amyloidosis. *Laboratory Investigation*, 36:274-281

Yu, J., Guo, JT., Zhu, H. & Kindy, MS. (2000). Amyloid formation in the rat: adenoviral expression of mouse serum amyloid A proteins. *Amyloid International Journal of Experimental and Clinical Investigation*, 7:32-40

Zschiesche, W. & Jakob, W. (1989). Pathology of animal amyloidoses. *Pharmacology and Therapeutics,* 41:49–93



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Amyloidoses are a heterogeneous group of diverse etiology diseases. They are characterized by an endogenous production of abnormal proteins called amyloid proteins, which are not hydrosoluble, form depots in various organs and tissue of animals and humans and cause dysfunctions. Despite many decades of research, the origin of the pathogenesis and the molecular determinants involved in amyloid diseases has remained elusive. At present, there is not an effective treatment to prevent protein misfolding in these amyloid diseases. The aim of this book is to present an overview of different aspects of amyloidoses from basic mechanisms and diagnosis to latest advancements in treatment.

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