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The nephrotic syndrome

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The nephrotic syndrome (NS) is characterized by the association of 3 purely biological anomalies:

- A proteinuria.
- A hypoalbuminemia.
- A hypoproteinemia.

To these biological signs are associated inconsistent clinical signs:

- Effusions, edema, thrombosis, etc.

Pathophysiology

The NS is the consequence of a glomerular renal lesion that results in proteinuria.

Protein leakage primarily concerns low molecular weight proteins:

- Albuminuria is constant.
- Globulinuria only appears in the case of more significant lesions.

When protein leakage exceeds hepatic synthesis capacity;

- Hypoalbuminemia appears.

Hypoalbuminemia causes a drop in oncotic pressure leading to the formation of effusions and/or edema.

This phenomenon is only observed when albuminemia becomes < 20 g/l.

The effusions occur passively: they are pure transudates.

Protein leakage leads to certain complications observed in this syndrome:

- Weight loss related to protein deficiency.
- State of hypercoagulability related to the leakage of antithrombin III.
- Increase in infections related to the leakage of immunoglobulins, etc.

Etiology

The NS is related to a disorder of glomerular capillary permeability.

Massive proteinuria (> 3 g/l) is pathognomonic of glomerular damage.

Only chronic phenomena can lead to the onset of nephrotic syndrome.

In carnivores, 2 glomerulopathies are particularly responsible for massive proteinuria:

- Renal amyloidosis.
- Glomerulonephritis (GN).

Amyloidosis

Renal amyloidosis results from the deposition of amyloid substance at the level of the glomerular mesangium.

This phenomenon can be:

- Primary (idiopathic).
- Secondary to another condition (infection,

The amyloid substance is highlighted due to its staining properties:

- Macroscopically by a Lugol's staining.
- Microscopically by a Congo red test.

NB:

Glomerular lesions that do not contain amyloid substance are classified among the GN.

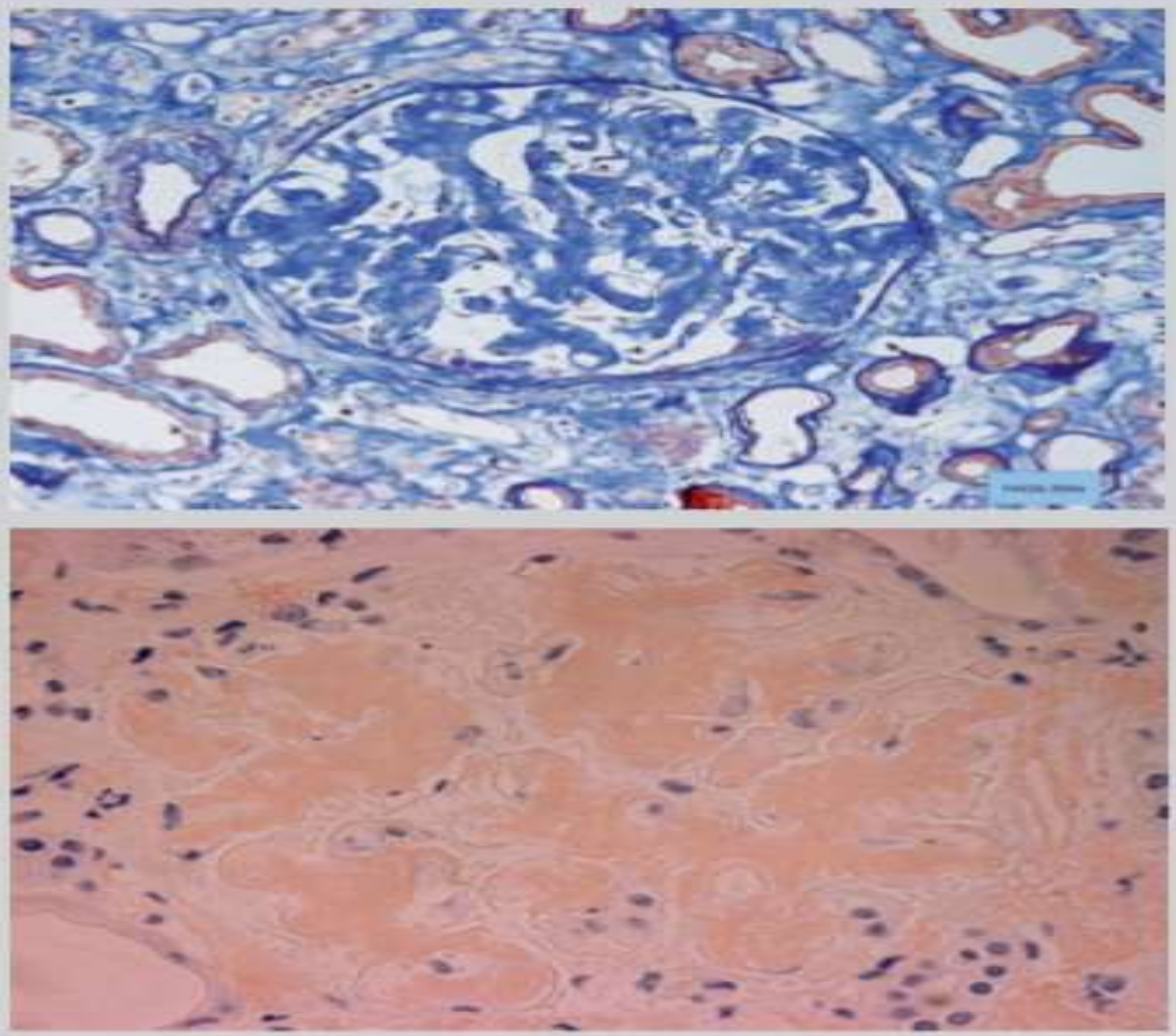


Figure 1. A. Dépôts d'amyloïde dans un glomérule rénal
B. Coloration au rouge Congo

Les dépôts d'amyloïde sont colorés en bleu pâle au trichrome FAOG. Ces dépôts sont positifs pour le rouge Congo **(B)**. Ils sont présents dans le mésangium et la paroi des capillaires glomérulaires, dans l'interstice et dans la paroi des artérioles.

Glomerulonephritis

Glomerulonephritis is mainly the result of immune phenomena (deposits of immune complexes, anti-basement membrane antibodies).

They are:

- Primary (idiopathic).
- Secondary, meaning associated with an intercurrent condition: lupus, leishmaniasis, babesiosis, dirofilariasis, etc.

Epidemiology

Frequency

SN is exceptional in cats.

Rare in dogs: isolated cases.

SN is probably underdiagnosed:

- Diagnosis is often limited to the accompanying chronic kidney disease.

Nature of lesions

In dogs:

- *In the USA:*

The SN is rare in the United States; it is the lesions of GN that are more often responsible.

- *In France (West):*

The SN is not so rare (520 cases over a period of years) and it is predominantly the result of renal amyloidosis.

- In Algeria: No data

Breeds

A hereditary origin of renal amyloidosis is established in Shar Pei and Abyssinian cats.

Shar Pei, a dog of Chinese origin

Chat Abyssin

Dogs belonging to breeds known as "hunting breeds" are predisposed to renal amyloidosis lesions:

- Brittany Spaniels, Beagles, Jura Hounds, Brittany Ferreting Dogs, German Shorthaired Pointers, Jagd Terriers, Vendéen Griffons.

Épagneul breton.

Beagle tricolore

Terrier de chasse allemand

Jagdterrier

Braque allemand

Braque allemand à poil court

Lifestyle

The reasons for the predisposition of hunting dogs to amyloidosis lesions are not elucidated.

However, some authors believe that in hunting dogs (and those who hunt), renal amyloidosis could be secondary to:

- A chronic infection
- Repeated infections by leptospires.

Clinical

Reason for consultation

Astenia and weight loss are the most consistent reasons for consultation.

Effusions, edema, and polyuria-polydipsia are reported less frequently.

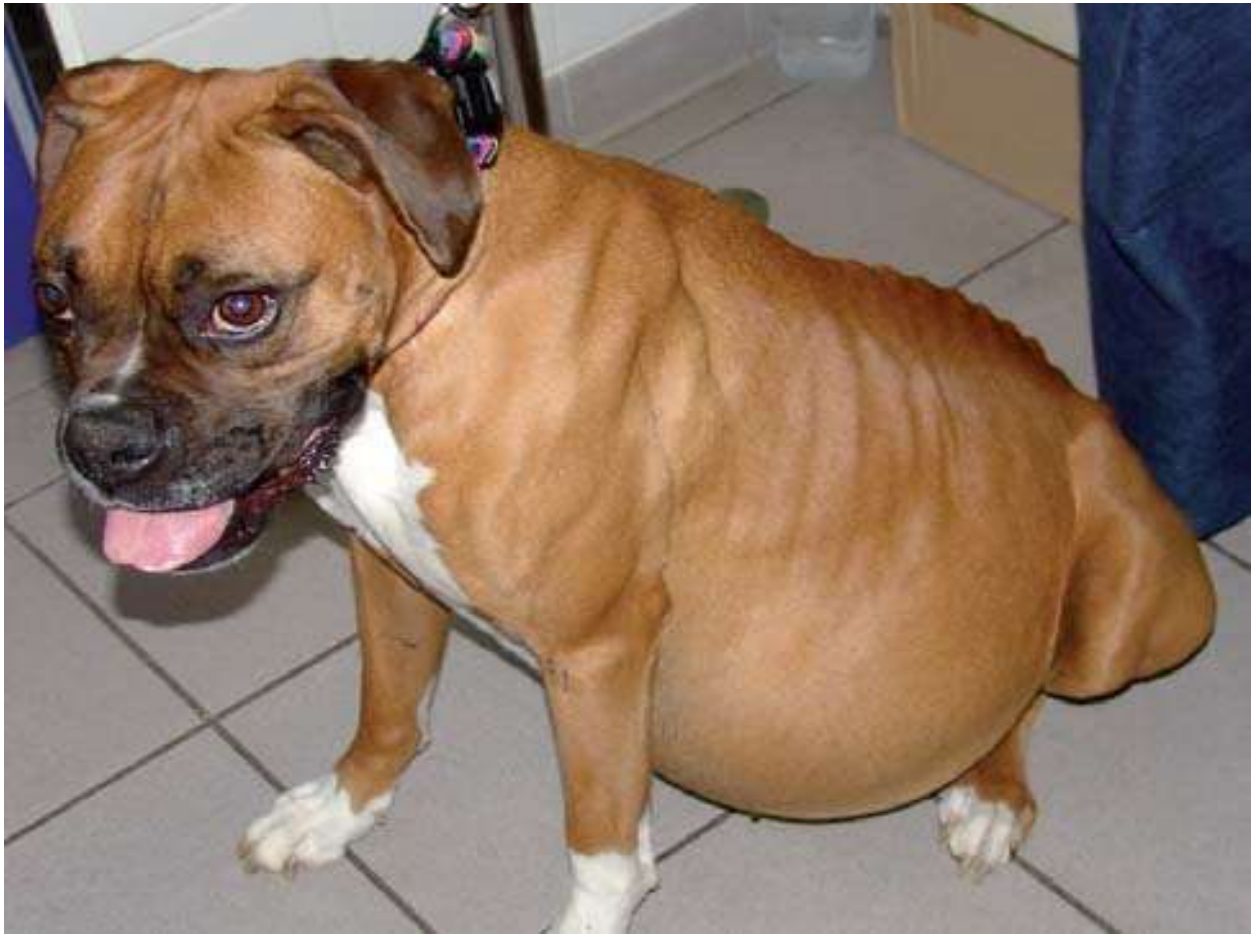
Clinical signs

Cavitary effusions

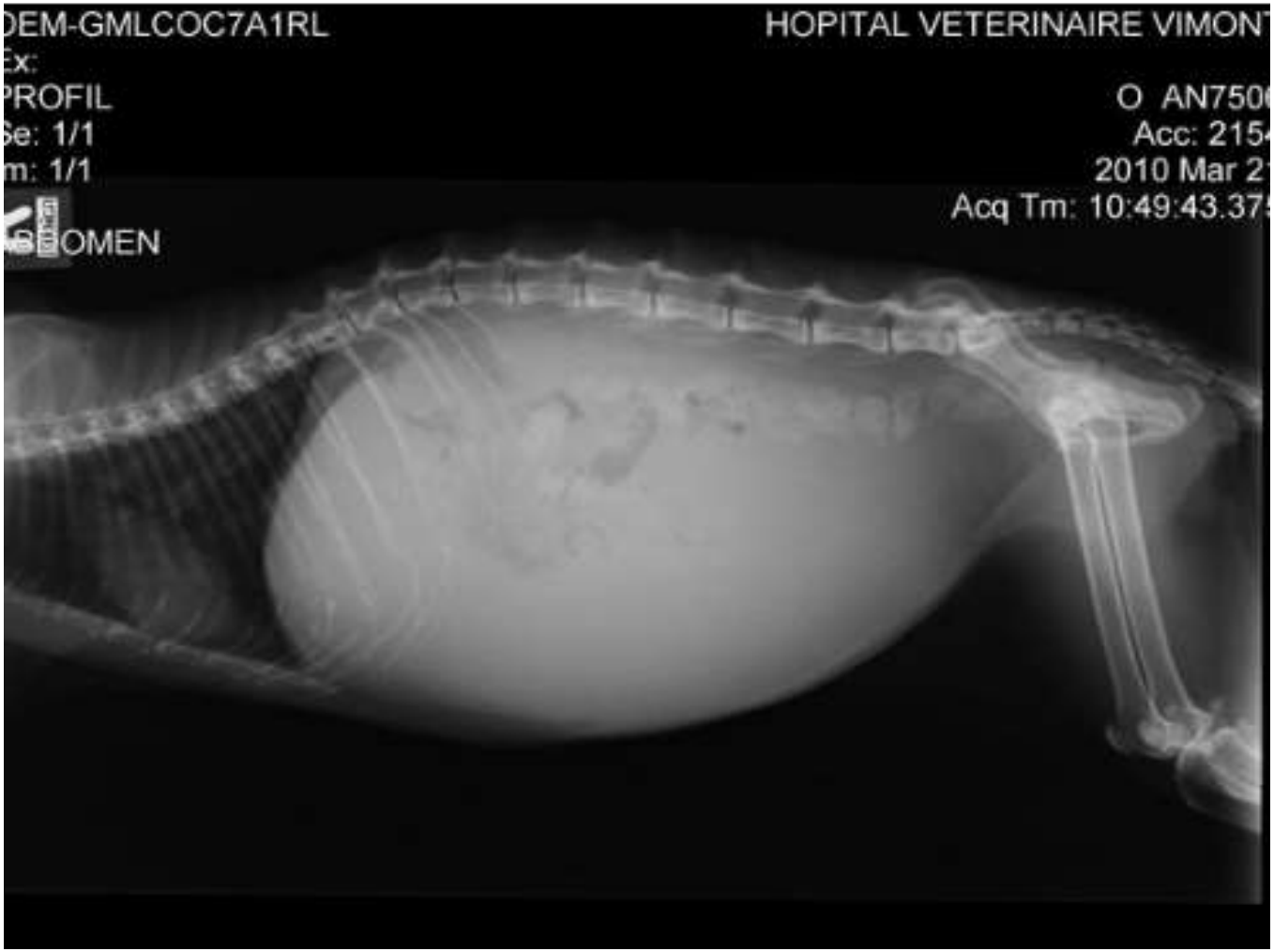
The drop in oncotic pressure classically manifests as cavitary effusions.

These are mainly abdominal effusions (ascites), less often thoracic effusions.

Ascites



Ascite (liquide dans l'abdomen) chez un chat



The effusion is a pure transudate.

- Its characteristics are close to those of water: Clear appearance (rock water color).
- Density near 1.000, <1.020.
- Very low cellularity < 4000 nucleated cells per mm3.
- Low protein content, < 30 g/l.

This transudate remains pure for a long time:

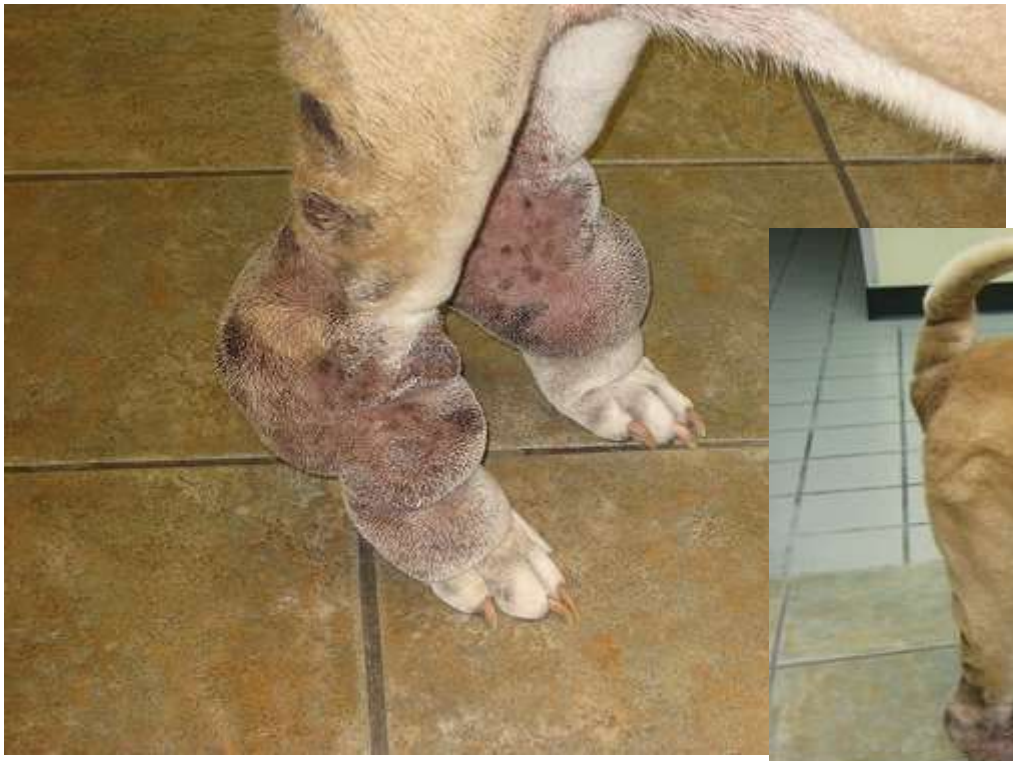
it can maintain a clear appearance for months;

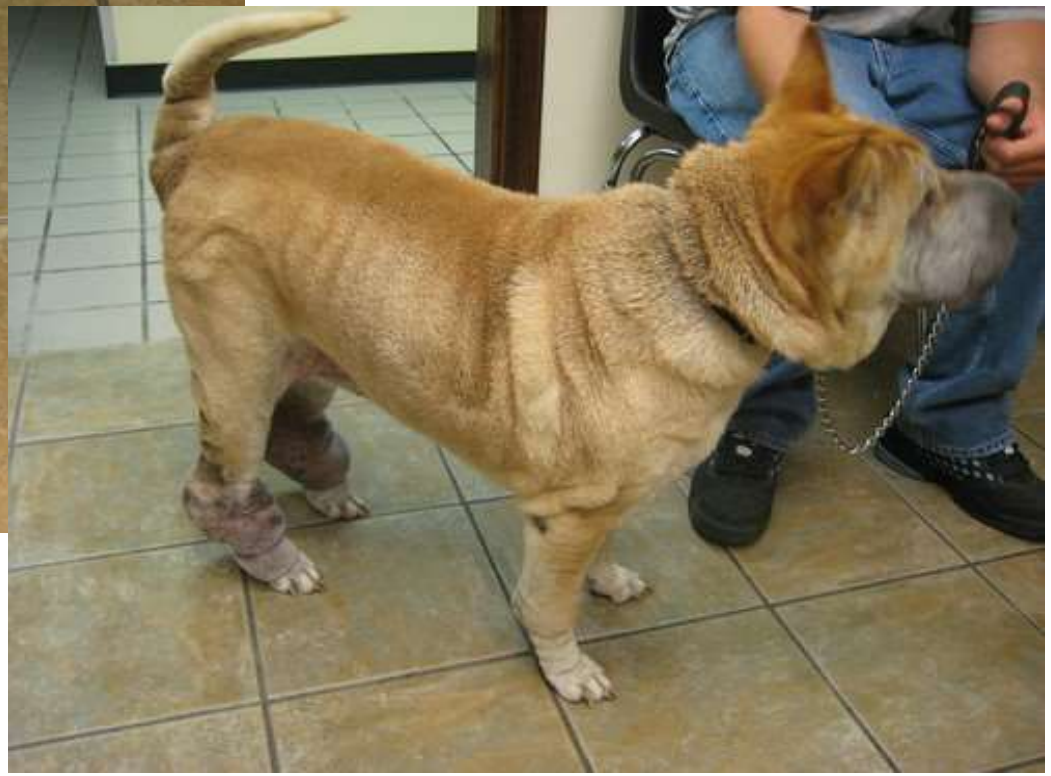
more rarely, it changes slightly and becomes slightly cloudy and pink.

Edema of dependent parts

The drop in oncotic pressure can also manifest as edema of dependent parts (extremities of the limbs, sheath or vulva, lips, tips of drooping ears, etc.).

edema of the extremities of the limbs





Edemas are less frequent than effusions.

Pulmonary edemas are not reported.

Kidney failure

The renal lesions responsible for protein leakage can also lead to the onset of CRF: this is referred to as "impure NS".

In the absence of kidney failure: this is referred to as "pure NS".

In the most common case of impure NS, polyuria-polydipsia is noted along with the array of symptoms encountered in chronic kidney failure.

*Renal amyloidosis and CRF

Amyloidosis is a slowly progressive condition.

After several months or even years without clinical expression.

Massive proteinuria appears, signaling glomerular involvement.

This proteinuria goes unnoticed until it leads to hypoalbuminemia and the accompanying symptoms.

The decrease in urinary density indicates the onset of CRF.

Triggered by a triggering factor: physical fatigue (hunting season, for example) the state phase of IRC settles in

It is often the symptoms of renal insufficiency that alert the owners, which explains the higher proportion of impure SN at the time of the first consultation.

Thromboses

Thromboses can complicate an SN.

Their incidence is 25% in dogs autopsied showing severe proteinuria.

This phenomenon is the consequence of a state of hypercoagulability mainly resulting from a deficiency in antithrombin III, a low molecular weight protein that leaks systematically from the early stages of the disease.

Moreover, hypoalbuminemia facilitates platelet aggregation.

Thromboses preferentially localize in the pulmonary artery and manifest as a sudden onset dyspnea associated with intense pain.

Thromboses less frequently involve the aorta and even more rarely other vessels.

Biological signs

The nephrotic syndrome is associated with massive proteinuria and hypoalbuminemia.

Clinical signs are only observed for one:

- Proteinuria > 3g/l (normal values < 1 g/l).
- Albuminemia <20 g/l (normal values around 30 g/l).
- Total protein level is < 50 g/l (normal values around 60 g/l).

In strict terms:

- Hypoproteinemia must be present for the diagnosis of nephrotic syndrome to be established.
- However, this hypoproteinemia is a consequence of hypoalbuminemia; it is not an additional

- When an elevation of globulins (especially alpha 2) compensates for the decrease in albumins, the total protein level measured in grams per liter may appear normal even though characteristic symptoms are present.

- At equal molecular weight, albumin having a stronger oncotic power than globulins, the decrease in albuminemia may suffice to allow for the appearance of effusions or edema without hypoproteinemia.
- The dosage of albumins is always preferable to that of total proteins.

- The presence of proteins in the urine leads to osmotic diuresis, resulting in polyuria associated with a decrease in urinary density:

- This is observed even when tubular function remains intact.

- A hypercholesterolemia > 3 g/l is classic in dogs as well as in humans, but it does not have clinical repercussions in carnivores.

- In the case of impure SN:

Uremia and creatininemia are elevated, and one observes other biological changes associated with chronic renal failure.

- In the case of pure SN:

It is classic to identify a slight increase in uremia without any anomaly in creatininemia.

This phenomenon indicates a pre-renal kidney failure related to the state of dehydration.

Diagnosis

Signs of call

3 circumstances are particularly responsible for the diagnosis of SN:

- The detection of proteinuria during a routine urine examination in an animal presented for asthenia or weight loss.
- A clear abdominal effusion.
- Dependent edema.

Considering the aforementioned epidemiological data, the detection of massive proteinuria in a hunting dog is a major sign of SN.

The identification of thrombosis in a carnivore should lead to the search for SN.

Certain diagnosis

The joint existence of massive proteinuria and hypoalbuminemia is necessary for the diagnosis.

Hypoproteinemia is required to conclude the diagnosis (hypoproteinemia is mainly the consequence of hypoalbuminemia).

Proteinuria

Proteinuria is first sought through urine testing with a dipstick.

This test being sensitive, a negative diagnosis excludes nephrotic syndrome (NS).

A positive reaction leads to the implementation of the Heller reaction which allows a semi-quantitative assessment of proteinuria:

- The thickness of the white halo is proportional to the extent of proteinuria.

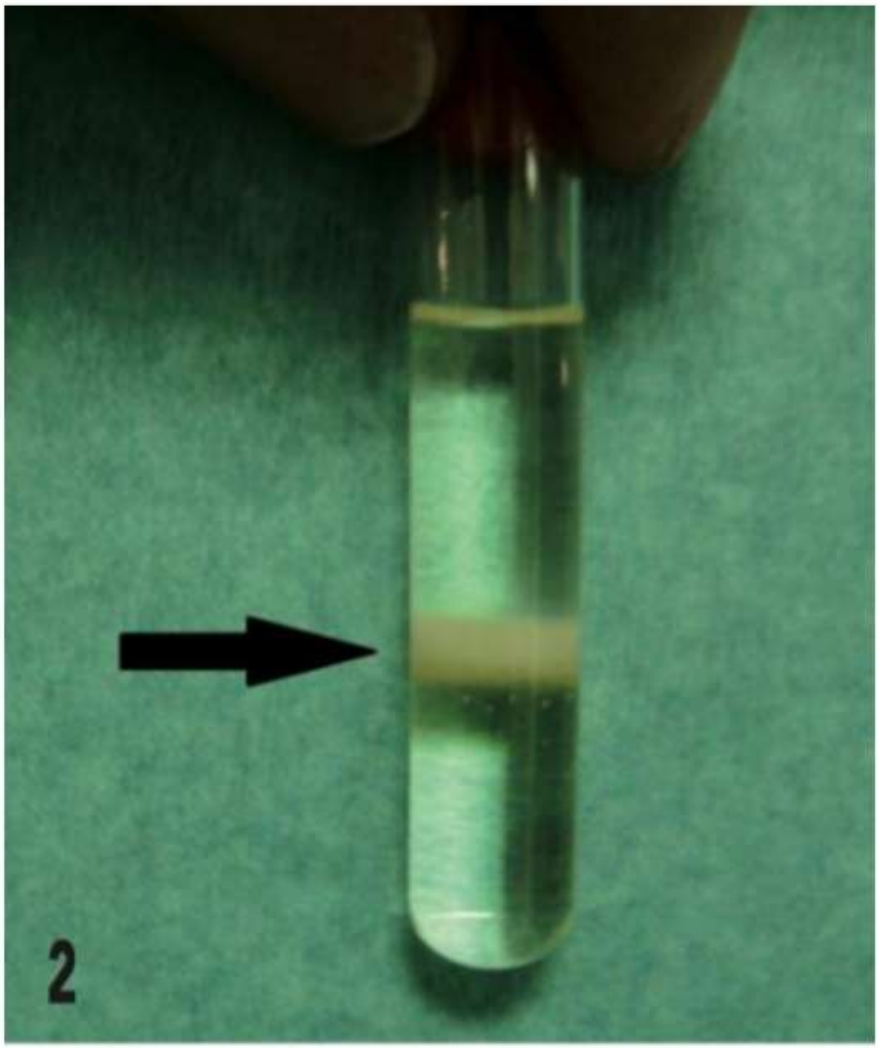
*Implementation of the Heller reaction

Heller test: gently place urine on the surface of an equal volume of nitric acid.

In the presence of proteins, a white halo forms at the interface between the acid and the urine.

Its thickness is proportional to the amount of protein.

: Résultat positif au test de Heller (FINE et MAHINC, 2014)



The urinary protein/creatinine ratio > 1 indicates abnormal proteinuria.

The measurement of urinary proteins is too imprecise; it is the electrophoresis of urinary proteins that provides the missing quantitative and qualitative information:

- A proteinuria > 1 g/L is abnormal.

- In the case of nephrotic syndrome:

Proteinuria > 3 g/L (values of 20 g/L are not exceptional).

Hypoalbuminemia

The refractometer gives a correct value of the protein level.

An analyzer allows the measurement of serum proteins and provides a good approach to the disorder.

Proteinuria and hypoalbuminemia:

Electrophoresis of serum proteins and urinary proteins is the appropriate complementary examination in case of suspicion of nephrotic syndrome.

Differential diagnosis

Protéinurie

L'existence d'une protéinurie ne signifie pas SN.

Une hypoalbuminémie doit être associée pour que le SN soit confirmé.

Épanchements

En présence d'un signe du flot, une centèse abdominale permet l'analyse de l'épanchement.

Même ancien, le transsudat observé dans le SN reste longtemps pur (limpide), c'est-à-dire non-inflammatoire.

Un épanchement limpide:

"eau de roche", est quasiment pathognomonique d'une hypoalbuminémie.

Face à un épanchement de cette nature, une fuite rénale des protéines doit être recherchée en priorité.

Si elle est présente (protéinurie) , le diagnostic de SN sera confirmé par le dosage de l'albuminémie.

In the absence of SN, exudative enteritis or shunt hypotheses should be prioritized.

Dependent edema

Dependent edema is also observed in right or global heart failure (cardiomyopathies, tamponade, rhythm disorders, etc.).

A careful auscultation is often sufficient for differential diagnosis.

Edema of the limbs should also suggest Cadiot-Ball syndrome (hypertrophic osteopathy).

If an effusion is associated with edema, its characteristics are crucial in the differential diagnosis:

- in heart failure, the abdominal effusion is almost always: a modified transudate, pinkish in appearance.

Etiological diagnosis

Diagnosis of renal lesion

The etiological diagnosis involves the identification of the renal lesion through a histological examination performed after kidney biopsy.

A urinary protein / urinary creatinine ratio very high > 4 is indicative of amyloidosis damage.

Diagnosis of the cause of kidney damage

➢ ***In glomerulonephritis***

The investigation of the cause will take into account epidemiological data (race for lupus, place of residence for leishmaniasis, etc.) and associated symptoms.

➢ ***In amyloidosis***

The identification of the origin of the disorder is exceptional and often illusory.

Its relevance is limited for the animal due to the irreversible nature of the damage.

Leptospirosis has been identified several times in hunting dogs affected by SN:

- The systematic search for leptospire infection in hunting dogs.

Prognosis

Nature of renal lesion

The dog's ARF always progresses towards the impure form, and the prognosis of ARF follows that of renal failure.

The prognosis is often poor due to the irreversible and progressive nature of the lesions.

Renal amyloidosis is a slowly progressive but irreversible disease: significant glomerular lesions without specific treatment.

Importance of proteinuria

The importance of proteinuria conditions the organism's adaptive capacities and consequently the vital prognosis.

Worsening proteinuria is a heralding sign of the onset of renal failure.

Thromboses

Thromboses quickly lead to death:

- Their appearance should lead to proposing euthanasia due to the associated pain and lack of therapeutic hope.

Life expectancy

The survival of dogs affected by SN:

- generally does not exceed a few months;
- only a few weeks after the onset of renal failure.

Treatment

Etiological treatment

There is no etiological treatment for renal amyloidosis.

An etiological treatment is only feasible for glomerulonephritis.

Even if the cause is eradicated, the lesion often persists.

The effectiveness of corticosteroids is inconsistent.

The treatment of SN is almost always palliative:

- The goal is to improve quality of life by limiting effusions and edema and to prolong survival by slowing the progression of renal lesions.

Hygienic treatment

Hygienic treatment involves rest which excludes any hunting activity.

Intercurrent conditions will be treated without delay.

Drainage puncture

The drainage puncture of effusions is of no interest as it does not restore oncotic pressure, causing the effusion to reform and worsening hypovolemia.

Drainage puncture is justified only in the rare cases where the effusion threatens vital prognosis (in cases of respiratory discord, for example).

Dietary treatment

There is a contradiction between the need for a high-protein diet to compensate for urinary losses and the risk of developing chronic kidney disease (CKD) due to excessive protein intake.

Protein restriction does not limit proteinuria and promotes malnutrition.

The compromise lies in the choice of a diet containing high biological value proteins.

Sodium restriction will limit edema.

The palatability of the diet remains a determining factor in the choice of nutrition.

Medical treatment

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors are indicated in the treatment of SN.

In addition to their hemodynamic effects, they reduce proteinuria and combat hypertension.

They break the vicious cycle responsible for the formation of effusions and edema.

Their antiproteinuric effect is potentiated by diuretics.

Diuretics

Furosemide, DIMAZON, FUROZENOL, is effective in the fight against effusions and edema at a dose of 1 to 4 mg/kg/day in two doses.

It is unnecessary and even dangerous to exceed 4 mg/kg/day.

Corticosteroids

Corticosteroids precipitate the onset of renal failure and are therefore not recommended in the treatment of nephrotic syndrome associated with renal amyloidosis.

Their indication is limited to the treatment of glomerulonephritis responding to corticosteroid therapy.

Infusions

The role of fluid resuscitation in the treatment of nephrotic syndrome is the same as in the treatment of renal failure.

Although they restore oncotic pressure, colloid solutions have no interest in the treatment of effusions or edema due to their too brief effects (12 to 24 hours).

Anabolic steroids

By their stimulating effect on protein synthesis, anabolic steroids are recommended in the treatment of SN even though their effectiveness is not documented.

Anticoagulants

Some authors recommend the prescription of aspirin at a dose of 0.5 to 5 mg/kg twice a day in the preventive treatment of vascular thromboses.

If thrombosis is confirmed, heparin is recommended at a dose of 100 UI/kg by SC route three times a day.

The treatment seems unreasonable in a context of severity and intense pain in an animal whose life expectancy is very limited due to renal lesions.

Colchicine

Colchicine is recommended in the treatment of humans for a form of congenital amyloidosis called 'familial Mediterranean fever.'

There is a comparable pathological entity of genetic origin, associating renal amyloidosis and fever in Shar Peis and Abyssinian cats, but the effectiveness of colchicine has not been demonstrated in these animal models.

This molecule primarily having a preventive role, it has no interest in the treatment of declared amyloidoses.

In summary:

- Dietary management and the prescription of an angiotensin-converting enzyme inhibitor and furosemide are the pillars of palliative treatment for heart failure.