Feline hyperthyroidism associated with chronic renal disease and diabetes mellitus after treatment with methimazole – A case study

Hipertiroidismul felin asociat cu boala renală cronică și diabet zaharat după inițierea tratamentului cu metimazol – Un studiu de caz

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Cuvinte cheie: hipertiroidism, boală renală cronică, diabet zaharat, metimazol.

Abstract

The association between hyperthyroidism and chronic kidney disease is often seen in geriatric cats making the therapeutic protocol of hyperthyroidism more difficult. A reversible therapy with methimazole like drugs is recommended when assessing the gravity of renal failure or other affection influenced by thyroid hormones. Chronic kidney disease and diabetes mellitus are common conditions knowns as co-existing affections in older cats that may be caused or cause hyperthyroidism. This case follows the evolution of a hyperthyroid cat whose therapeutic protocol undergoes repeated changes due to the presence of co-existing affections.

Rezumat

Asocierea hipertiroidismului cu boala renală cronică este frecvent observată la pisicile bătrâne făcând protocolul terapeutic anti-tiroidian dificil atunci când bolile concurente sunt prezente. Terapia reversibilă cu medicamente de tipul metimazolului este recomandată atunci când afecțiunea renală sau alte afecțiuni sunt suspectate. Acest caz urmărește evoluția unei pisici cu hipertiroidism a cărei protocol terapeutic suferă modificări repetate datorate afecțiunilor concurente dobândite. Insuficiența renală și diabetul zaharat sunt afecțiuni întâlnite frecvent la animalele bătrâne putând cauza sau fiind cauzate de hipertiroidism.

Introduction

Hyperthyroidism and feline diabetes mellitus are considered the most common affections encountered in domestic cats, with an incidence in 1 of 300, and 1 in 400 domestic cats respectively (11, 21, 30).

Hyperthyroidism is the result of excessive synthesis and secretion of thyroid hormones by the thyroid gland (26).

Diabetes mellitus is a condition characterized by alteration of the carbohydrates metabolism manifested by chronic hyperglycemia and is the result of acquired insulin resistance, poor insulin secretion or defective use of induline by target tissues (11, 21, 30).

Analogue to human type 2 diabetes mellitus, feline diabetes mellitus (FDM) represents 80-95% of diabetes cases, and is characterized by insulin resistance and malfunction of β-cells (25).

Frequent, an association between hyperthyroidism and chronic kidney disease (CKD) in geriatric cats is often observed and is believed to affect 5.8% of all cats, with a prevalence of 15.3% in cats older than 15 years old and because are considered "diseases of old age" their concomitant presence is expected (19).

The common symptomatology of these entities (polyuria, polydipsia, muscle waste, weight loss associated with polyphagia) makes

the diagnosis and the therapeutic protocol difficult (25, 31).

When the presence of CKD is suspected, a temporary medical protocol with methimazole is recommended because resolution of hyperthyroidism may reveal a pre-existent renal disease in literature, it was reported that 40% of cats with hyperthyroidism have developed azotemia after euthyroid state was reached (32).

This case describes the existence of three different pathological entities with similar symptoms, thus requiring the development of an adaptive therapeutic protocol in order to ensure a good metabolic stability and quality of life.

1. Case presentation

A nine year old European cat was brought to consultation because the owner reported atypical behavior for her age manifested by polyuria, polydipsia, hyper excitability and weight loss despite normal appetite.

The clinical examination revealed weight loss, tachycardia and strong cardiac shock (Figure 1).

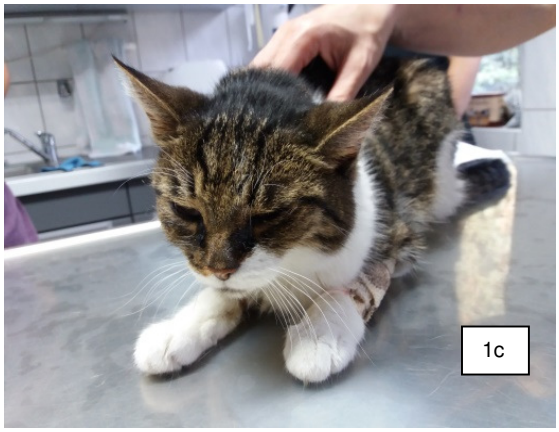

Figure 1. Examined cat with sad face, cachexia, un kept coat

2. Methodology

In order to establish a definitive diagnosis, blood samples were collected for laboratory analysis.

The blood samples were collected in microvette (500 µL) and used for biochemical and hormonal assays.

After collection, blood samples were kept at room temperature for 30 minutes to facilitate clot formation.

Blood samples were centrifuged at 6000 rpm for 3 minutes, and the serum obtained was used for biochemical testing of the following parameters:

- fructosamine (FR),
- creatinine (CREA),
- blood urea nitrogen (BUN),
- serum Cystatin C (sCysC) and
- total thyroxine (tT4).

Blood samples for sCysC assay was submitted to a private veterinary laboratory.

During a 3 year period (until present day) the cat was brought to the clinic 12 times during which the reassessment of the primordial parameters as well as the physical examination was carried out.

Laboratory tests of parameters: FR, CREA, BUN, GLU and tT4 were made using the previously described methodology. Biochemical assays and total thyroxine dosing were made using Fujifilm DRI-CHEM NX500i

biochemical analyzer (Figure 2) and EUROLyser solo analyzer (Figure 3).

The biochemical analyer used veterinary kits for the following parameters: TP, ALP, GPT / ALT, GLU, CRE and BUN.

Thyroxine dosing was performed with the EUROLyser solo analyzer using the T4 Vet kit based on the immunoenzymatic technique.

Figure 2. Fujifilm DRI-CHEM NX500i biochemical analyzer

Figure 3. Eurolyser solo automated analyzer

The therapeutic protocol was conducted using the following commercial products:

- Felimazole (methimazole) as tablets of 1.25 mg, 2.5 mg and 5 mg (Figure 4).
- Caninsulin 10 ml, 40 IU / ml (Figure 5).

Figure 4. Felimazole tablets

Figure 4. Caninsulin 10 mL, 40 UI / mL

3. Results

By correlating the anamnestic data, symptomatology and laboratory results, the cat was diagnosed with hyperthyroidism, and started the treatment with methimazole at a dose of 5 mg, divided into two administrations, morning and evening.

During the monitoring period, only certain parameters were taken into account, and based on serum glucose (71 - 148 mg/dL), CREA (<1.6 mg / dL), BUN (30 - 68 mg / dL), FR (<340 µmoll / L) and thyroxine (limits, 1-4 µg / dL), the therapeutic protocol underwent numerous changes (Table 1).

The diagnosis of hyperthyroidism was based on clinical signs of polyuria, polydipsia, polyphagia associated with weight loss and high total thyroxine (8.9 µg / dL).

Laboratory test results showed an increase in serum (2.4 mg / L) Cystatin C (normal <1.0 mg / L) but with normal creatinine (1.25 mg / dL) and BUN (62.4 mg / dL). Based on these results, a renal diet was recommended to protect kidney function.

On the second visit, sCysC value (1.3 mg/L) and tT4 level (4.4 µg / dL) were reduced but a rise in FR (547.7 µmoll / L) and BUN (80.4 mg / dL) was observed. Based on these results, the total dose of Felimazole was raised at 7.5 mg / day divided in a morning doze (5 mg) and an evening dose (2.5 mg).

Table 1.

Felimazole dosage based on tT4 values

Re-evaluation	tT4 µg/dL	Felimazole Dose/ day
Diagnostic	8.9	2 x 2.5 mg
R. I	4.4	1 x 5 mg, morning 1 x 2.5 mg, evening
R. II	1.6	1 x 5, morning 1 x 2.5, evening
R. III	4.6	2 x 5 mg
R. IV	0.9	1x 5 mg, 1 week 2 x 2.5 mg, 1 week 1 x 1, 25 mg
R. V	21.8	1 x 2.5 morning 1 x 1.25 mg evening
R. VI	11.4	2 x 2.5 mg
R. XII	9.4	2.5 mg, morning 2.5 + 1.25 mg, evening
R. XIII	6.1	2.5 mg, morning 5 mg, evening
R. IX	7.27	2 x 5 mg
R. X	2.19	2 x 2.5 mg
R. XI	15.74	1 x 2.5 mg, morning 1x 5 mg, evening
R. XII	27.88	1 x 2.5 mg, morning 1x 5 mg, evening

After one month, tT4 values showed a drastic decrease (1.6 µg/dL) falling within normal limits.

Serum fructosamine concentration maintained its high values (571.6 µmoll / L), but because we found a high blood glucose concentration (17.4 moll / L) the cat was suspected to be diabetic and started treatment with Caninsulin in dose of 1.5 IU twice daily.

Regarding the renal function, serum CREA (1.47 mg / dL) and BUN (68.4 mg / dL) concentrations decreased compared to the previous visit. After six weeks, the methimazole dosage consisted of consisted of 5 mg twice daily because the serum concentration of tT4 (4.6 µg / dL) exceeded the upper limit. FR (462 micromoll / L) and GLU concentrations (15.9 mmoll / L) did not show improvement and the dose of Caninsulin was increased to 2.0 IU twice daily. At re-control, after three months, tT4 values (0.9 µg / dL) decreased significantly but FR (460 µmoll / L), GLU (12.7 mmoll / L), CREA (2.0 mg / dL) and BUN (77.0 mg / dL) still exceeded the upper threshold.

At this point, the risk of developing hypothyroidism and azotemia was higher, hence the recommended therapy protocol was changed.

The treatment consisted of 5 mg one time daily for 1 week followed by another week in which the 5 mg would be divided in two administrations. For the next two weeks the dose was decreased to 1.25 mg one time daily.

Due to the reduction in methimazole dosage, the re-evaluation of thyroid function reported a significant increase in tT4 values (21.8 µg / dL) but with an improvement in GLU (3.2 mmoll / L), CREA (1.3 mg / and BUN (57.2 mg / dL).

Consequently, the dose of methimazole was increased to 3.75 mg divided into two administrations, one tablet of 2.5 mg in the morning and one tablet of 1.25 mg in the evening. Because after two months later, tT4 (11.4 µg / dL) continued to be high, the therapeutic dose of methimazole was increased to 2.5 mg twice daily.

The dose of methimazole was increased to 6.25 mg divided into 2.5 mg (morning) and 3.75 mg (evening) after four months of treatment because tT4 (9.4 µg / dL) values did not show improvement in thyroid function.

Three months later, the tT4 (6.1 µg / dL) value was slightly decreased and a higher dose of Felimazole was recommended (7.5 mg total dose), having as consequence increased serum CREA (1.9 mg/dL) concentration.

Because the thyroid function (tT4, 7.27 µg / dL) did not show improvements, the dose of methimazole was increased at 5 mg twice daily. After 9 months the cat was brought to the clinic because the clinical signs of polyuria and polydipsia have accentuated and renal parameters were evaluated.

The laboratory results revealed a higher CREA value (2.9 mg / dL) but with normal BUN (58.6 mg / dL) and tT4 (2.19 µg / dL) concentrations.

Because the risk of aggravating CKD was present, the methimazole dose was decreased at 2.5 mg twice daily.

Improvements in serum CREA (1.1 mg / dL) and BUN (36.5 mg / dL) worsened the thyroid function (tT4: 15.74 µg / dL). A 2.5 mg tablet of Felimazole in the morning and a 5 mg tablet in the evening was recommended.

Serum FR concentration (422.0 µmoll / L) registered a higher value and the dose recommended of Caninsulin was 3 IU twice daily.

Unfortunately, on the last visit, all parameters worsened. CREA (2.3 mg / dL), FR (424.8 µmoll / L) and tT4 (27.88 µg / dL) concentration exceeded the reference range, maintaining BUN values (38.3 mg / dL) within normal limits.

The treatment protocol changed and consisted of 4 IU Caninsulin twice daily. Because the renal function is compromised, the Felimazole dosage remained as previous.

4. Discutions

The thyroid hormones play an important role in the development and functioning of the kidney system and vice versa.

In hyperthyroidism, renal function undergoes hemodynamic, glomerular and tubular changes that play an important role when multiple concurrent diseases are suspected (17).

Polyuria, polydipsia and weight loss despite a good appetite are common clinical signs seen in hyperthyroidism and chronic kidney disease (28).

Due to the link between hyperthyroidism and CKD, a differential diagnosis was made based on laboratory findings of tT4, sCyst C, CREA and BUN. Because blood glucose and fructosamine concentration were not evaluated on the first visit we cannot say with certainty whether diabetes is a competitive or acquired disease during ant thyroid therapy.

An association between these pathologies is considered to be rare, but the presence of CKD and hyperthyroidism are known contributor factors in developing insulin resistant diabetes mellitus increasing the morbidity rate at 73 % (3, 25).

In order to establish a secured renal function, CKD diagnosis was made earlier than predicted, and was based on the serum Cystatin C values and not on the creatinine concentration, considered by some authors as instable because its values change as a result to the catabolic effect of thyroid hormones on the skeletal muscle (29, 33).

Cystatin C is a protein used for estimating the glomerular filtration rate (GFR) before the degradation of renal function, being superior to creatinine, parameter that detects renal alterations only after the loss of at least 50% of renal function (2, 7, 23).

Despite the fact that sCysC concentration was found significantly higher than creatinine in cats with chronic kidney failure (CKD) and even though its relevance is used worldwide in human medicine, some authors do not consider it accurate for staging CKD or consider that better results are obtained when both markers are taken into consideration (14, 18).

It was observed that sCysC concentration is altered by thyroid dysfunction, decreasing in hypothyroidism and increasing in hyperthyroidism (10, 12).

In our case, sCysC concentration was considered a marker for the development of CKD and as we predicted, the cat developed CKD after the euthyroid state was restored.

Using CREA and sCysC as markers in CKD staging is controversial.

An inverse process was observed after the initiation of the ant thyroid treatment, concluding that both sCysC production and the plasma concentration of CREA and sCysC are influenced by the effect of thyroid hormones on tubular renal metabolism, making sCysC values as inconsistent as those of CREA (6).

Similar findings have been observed in our case, sCysC values have decreased after initiation of ant thyroid therapy. Normalization of thyroid function with GFR reduction resulted in increased serum urea but maintaining creatinine serum concentration within the reference range.

The therapy protocol included a starting dose of 2.5 mg methimazole twice daily. Methimazole is considered the first choice when treating hyperthyroidism in cats due to the ease with which it is purchased and administered in most of the cases (26).

Throughout therapy, the dose of methimazole suffered numerous modifications according to laboratory findings of thyroid and renal function (Table 1).

With treatment, a strong link was seen between renal and thyroid function because serum TT4, CREA and BUN have changed.

Renal physiological values obtained in hyperthyroidism are due to the effect of thyroid hormones by GFR increase but with the restoration of thyroid function, the negative effect of thyroid hormones on renal function decreases with negative consequences on renal parameters, CREA and BUN (1, 17, 27, 34).

A clear example was observed when tT4 (0.9 µg / dL; 2.19 µg / dL) recorded the lowest values resulting in increased serum CREA (2.0 mg / dL; 2.9 mg / dL). The worsening of renal function with the occurrence of azotemia state is frequently observed in cases of iatrogenic hypothyroidism due to significant reductions in GFR (34).

When the methimazole dose was reduced, normalization of renal parameters (CREA: 1.3 mg / dL, BUN: 57.2 mg / dL) with negative effect on thyroid function (tT4: 21.8 µg / dL) occurred.

Based on these observations, we can say that a masked renal failure may have been present, situation well known when hyperthyroid state is seen in geriatric cats.

Even though the presence of CKD is not detected, it is well known that thyroid hyperfunction contributes to the development or progression of CKD by increasing systemic blood pressure favoring glomerular hyper filtration and glomerulosclerosis (5, 17, 19).

Unfortunately, in our case, the effects of thyroid hormones on renal function were permanetized because, despite the low dose of methimazole, CREA (2.3 mg / dL) and tT4 (27.88 µg / dL) increased significantly.

Both hyperthyroidism and CKD are considered favoring factors of insulin resistance by increasing insulin production and secretion in pancreatic islets, making difficult the assessment of the pancreatic function when based on serum glucose and fructosamine (24).

Reducing the half-life of insulin due to increased degradation rates but also increased intestinal absorption of thyroid hormone-mediated glucose are also responsible for the hyperglycemic state of hyperthyroidism (15).

Serum concentration of fructosamine is lower in cats with hyperthyroidism than in euthyroid cats and is considered to be the result of a quantitative increase in protein because, with the initiation of ant thyroid treatment, an increase in serum FR has been observed (22).

An important correlation was observed between FR and T4, T3 or even TSH values, and reduced FR values were considered a useful indicator of metabolic function in human hyperthyroidism (4).

However, evaluation of serum FR should not be considered an accurate parameter when a differential diagnosis between hyperthyroidism and DM or stress hyperglycemia is required.

It was found that serum FR concentration is significantly higher in non-treated or treated cats, changes that were not present in cats with stress-induced hyperglycemia (9).

Conversely, in our case, the serum concentration of FR was significantly increased with an average of 481.21 µmoll / L that did not respond to any insulin dosage. Finally, the insulin dose was increased to 4 IU twice a day.

Changing the insulin type was also recommended because longer action insulin is considered a good alternative when glucose control is not achieved with medium acting insulin even if is administered twice daily (20).

Taking into account that the cat had both hyperthyroidism and renal failure, acquired insulin resistance as well as a poor administration of insulin by the owner of the cat should be taken in consideration. Remission of diabetes mellitus is believed to be favored

when a high protein-low carbohydrate diet is fed (16).

In our case, due to the risk of acquiring CKD during methimazole therapy, the cat was fed a low protein – high carbohydrate diet, making the remission difficult, perhaps even exacerbating the insulin resistance.

5. Conclusions

Establishing a diagnosis and a therapeutic protocol in hyperthyroidism is difficult when the symptom presented are common to several conditions. Frequently, kidney failure is masked, and when associated with diabetes mellitus or hyperthyroidism, prognosis is reserved, and quality of life is questioned.

This case investigated the effects of thyroid hormones on renal function after initiation of methimazole treatment in a cat with hyperthyroidism, and an apparent correlation between serum tT4 concentration and renal function was observed after euthyroidism was reached.

When dealing with multiple pathological entities, the primary treatment must follow the affection that endangers the patient's life, but also the stabilization of competing disorders.

In our case, the main treatment focused hyperthyroidism and the maintenance of CKD at a masked level, situation that reversed once the CKD threatened the life of the patient.

Despite its measurements, fructosamine did not influence the effect of the existent treatment protocol of hyperthyroidism but at the same time, the administration of insulin had no significant effect on serum fructosamine concentration.

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