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CLINICAL CASE

Unusual presentation of systemic coronavirus in a ferret[☆]



Présentation atypique d'une coronavirose systémique chez un furet

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KEYWORDS

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Summary A young ferret was presented for a posterior paresis, urinary and fecal incontinence, weight loss, anorexia and lethargy. Biochemichemistry and hematology revealed hyperproteinemia with hyperglobulinemia and anemia. Abdominal ultrasonography showed splenomegaly, adenomegaly and nephromegaly with abnormal echogenicity of the abdominal organs, compatible with a diagnosis of systemic coronaviriosis. The ferret was humanely euthanized. On histopathology, a severe pyogranulomatous inflammation with neutrophilic vasculitis was seen in several organs (kidney, liver, lung, spleen and lymph node). Immunochemistry with FIPV3-70 antibody revealed the presence of coronaviral antigen within the lesions, confirming the diagnosis of Feline Infectious Peritonitis-like disease. A slight mononuclear radiculoneuritis was also present in the sciatic nerve, possibly explaining the peripheral neuropathy observed in this ferret. Whereas posterior paresis is common and non-specific in ferrets, fecal and urinary incontinence are rarely described. Radiculoneuritis caused by systemic coronavirus should be considered in young patients presenting these symptoms.

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MOTS CLÉS

Furet ;
Coronavirose
systémique ;

Résumé Un jeune furet est présenté pour une parésie postérieure, une incontinence fécale et urinaire ainsi qu'une perte de poids, une anorexie et de la léthargie. Des examens biochimiques et hématologiques révèlent une hyperprotéïnémie, hyperglobulinémie, et une anémie. Après la réalisation d'une échographie abdominale et de cytoponctions, le diagnostic de

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Parésie ;
Hyperglobulinémie ;
Neuropathie

coronavirose systémique est confirmé post-mortem à l'histologie. Une inflammation pyogranulomateuse et des lésions de vascularité neutrophilique sont présentes sur différents organes (rein, foie, poumon, rate et nœud lymphatique). L'immuno-histochimie réalisée avec les anticorps FIPV3-70 est positive. Les nerfs périphériques sont également infiltrés par une inflammation pyogranulomateuse. Une radiculonévrite semble expliquer la neuropathie périphérique observée chez ce furet. La parésie postérieure est fréquente et non-spécifique chez le furet. À l'inverse, l'incontinence fécale et urinaire est rarement décrite dans cette espèce. Une radiculonévrite provoquée par le coronavirus systémique devrait être évoquée dans le diagnostic différentiel de ces incontinences et parésie chez le jeune furet.

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A one-year-old ferret was referred for posterior paresis and fecal and urinary incontinence. The ferret was adopted in a French pet-shop 2 months before. He was correctly vaccinated and dewormed. His food was composed of ferret kibble and snacks. Since his adoption, the owners had always observed a very quiet pet, sleeping almost continuously. According to the owners, fecal and urinary losses during walking or sleeping began 2 weeks ago. Anal glands emptying increased in frequency, without previous excitation or relaxation.

The ferret was thin and dehydrated. He lost 150 g in 2 months (from 900 to 750 g). His rectal temperature was normal (38.4 °C/101.1 °F) [1]. Abdominal palpation was painful and a splenomegaly was found. The bladder was not painful or indurated. It was half-filled and soft with a normal size. The cardiorespiratory examination was within normal limits.

Exploratory behavior was preserved but slightly diminished. Hind limbs weakness was observed. No proprioceptive defects or gait anomalies were noticed during examination, but this is difficult to assess in this species. The ferret interacted and responded normally to various stimuli. Bone and muscle palpation were not painful. Postural reactions and spinal reflexes were normal. The perineal reflex was present and the anus was reactive (correct anal contraction after needle stimulation). At this stage, the neurological examination did not explain the urinary and anal incontinence. The presence of a normal sized bladder and intermittent leakage of urine and stools can evoke a mild peripheral nerve disease or clinical signs linked to abdominal pain.

Following physical examination, remarkable findings included abdominal pain, anorexia, weakness, hindlimb paresis and fecal and urinary incontinence.

A complete blood count pointed out a moderate anemia with neutrophilic leukocytosis (Table 1), compatible with an infectious or an inflammatory process. Biochemistry results revealed a severe hyperproteinemia with severe hyperglobulinemia. A moderate increase of urea was also noticed, most likely related to dehydration.

These findings, particularly hyperglobulinemia, were compatible with an infectious disease (aleutian mink disease, systemic coronavirus, mycobacteriosis, helicobacteriosis), a chronic digestive inflammation or a neoplastic process (lymphoma, multiple myeloma).

Abdominal pain was compatible with all these hypotheses, but less probably with multiple myeloma.

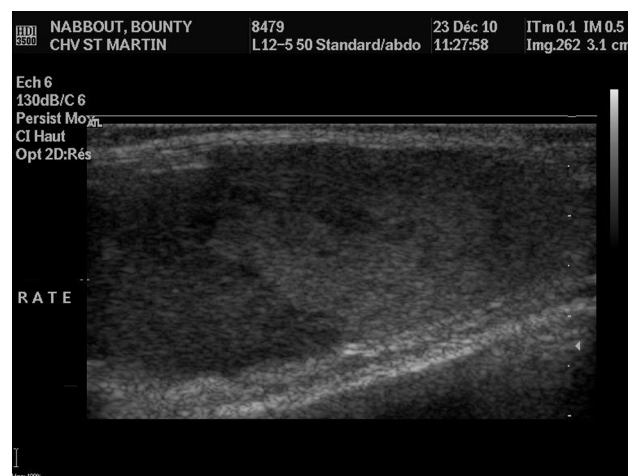


Figure 1. Spleen ultrasonography showing a mixed echoic parenchyma compatible with inflammation and cellular infiltration. From CHVSM.

Abdominal ultrasonography revealed splenomegaly with a heterogeneous parenchyma (Fig. 1), reactive mesenteric lymph nodes measuring up to 1 cm diameter (Fig. 2), a hypoechoic liver (Fig. 3) and irregular kidneys with hypoechoic areas in the parenchyma (Fig. 4). Following the



Figure 2. Mesenteric adenomegaly and inflammation are seen on ultrasonography. From CHVSM.

Table 1 Blood results – hemogram and biochemistry.

	Patient	Reference range ([Carpenter])
Hemogram		
Red blood cells ($10^6/\mu\text{L}$)	5.2	7.1–13.2
Hemoglobin (g/dL)	8	7.1–13.2
Hematocrit (%)	25.2	33.6–61
White blood cells ($10^3/\mu\text{L}$)	20.66	4.4–19.1
Platelets ($10^3/\mu\text{L}$)	272	297–730
Biochemistry		
ALKP (U/L)	39	11–120
ALT (U/L)	168	54–289
Urea (g/L)	0.695	0.1–0.42
Creatinine (mg/L)	2.5	2–10
Total protein (g/L)	117	53–74
Albumin (g/L)	28	28–42
Globulins (g/L)	88	20–40

**Figure 3.** Liver ultrasonography showing hypoechoic areas. From CHVSM.**Figure 4.** Kidney ultrasonography showing irregular form and hypoechoic areas. From CHVSM.

abdominal ultrasonography, systemic coronaviriosis was privileged.

Fine-needle aspirations of the spleen, the liver and the mesenteric lymph nodes were performed but were non-diagnostic because of blood contamination.

A polymerase chain reaction for Epizootic Catarrhal Enteritis was performed on blood and fine-needle aspirates and came back negative.

Protein electrophoresis and exploratory laparotomy were declined by the owner.

A palliative treatment was prescribed. NSAIDs (meloxicam: 0.2 mg/kg SID *per os*. Metacam, Boehringer Ingelheim, France) was used to control inflammation and pain, but opioids could have been chosen. Large-spectrum antibiotic therapy (amoxicillin – clavulanate: 12.5 mg/kg BID. Synulox gouttes, Pfizer, France) was initiated to prevent secondary opportunistic infections. Digestive protectant (sucralfate: 25 mg/kg TID. Ulcar, Sanofi-Aventis, France) was added because of the NSAIDs treatment and force-feeding with an appetent food (Oxbow Carnivore Care. Oxbow, USA). After a short period of improvement, signs worsened and the ferret was humanely euthanized.

Owner accepted necropsy but declined brain withdrawal. On necropsy, large white and tan coalescing nodules were observed on all abdominal organs (Fig. 5) including the kidneys, the liver (Fig. 6), the mesenteric lymph node (Fig. 7), the spleen (Fig. 8), the lungs, mesentery and intestinal serosa. Samples of abdominal organs, lungs and the two sciatic nerves were fixed in 4% buffered formalin and processed for histology with hematoxylin and eosin.

Severe pyogranulomatous inflammation with neutrophilic vasculitis, suggestive of systemic coronaviriosis was seen in all the samples (liver, spleen, lung, kidney, mesenteric lymph nodes and abdominal serosa) (Fig. 9). Multifocal minimal mononuclear radiculoneuritis was present in the sciatic nerves.

Gomori-Grocott and Ziehl-Nielsen stains were negative, excluding a fungal infection and a mycobacteriosis.

Immunohistochemistry using FIPV3-70 antibody recommended to detect FRSCV antigen, was performed, including positive and negative controls [1] used for feline infectious



Figure 5. General necropsy view with numerous white coalescent nodules seen on all the abdominal organs. From Adeline Linsart.

peritonitis, confirmed the presence of coronavirus antigens within the pyogranulomatous lesions. Immunohistochemistry was not performed positive on the sciatic nerve.

Discussion

Systemic coronaviriosis is an emerging disease, first diagnosed by Garner et al. in the United States and by Perpignan et al. in Spain in 2008 [2,3]. Pathogeny and epidemiology seem to be similar to those of feline infectious peritonitis' dry form (dry FIP). Coronaviruses are well known as enteric viruses causing benign enteritis in young carnivorous species. However, a recent study on feline coronaviruses

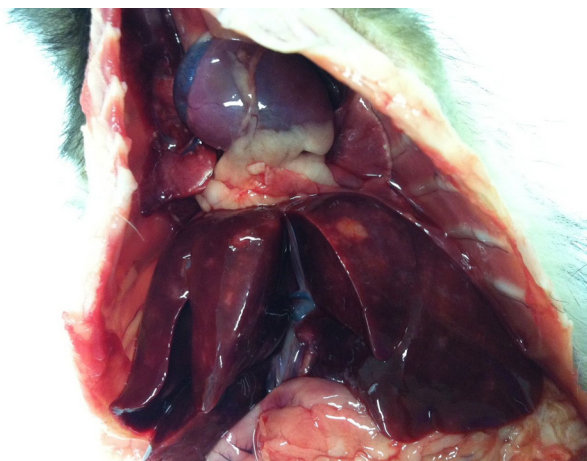


Figure 6. White foci distributed on all liver parenchyma. From Adeline Linsart.

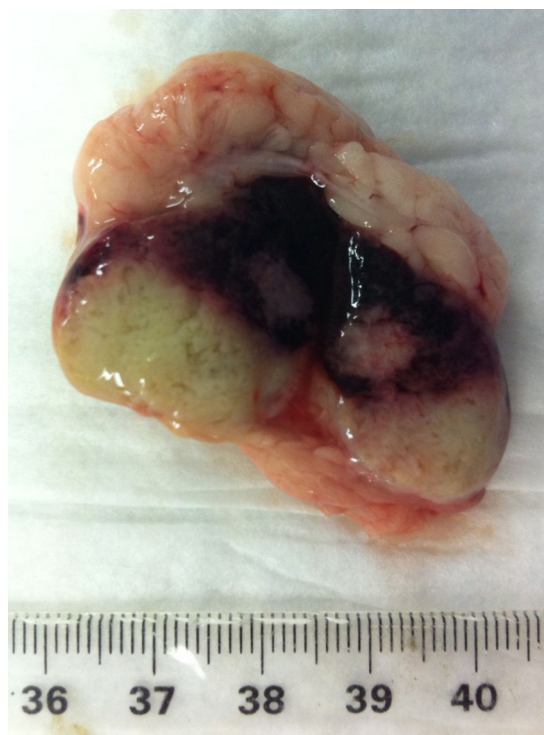


Figure 7. Reactive mesenteric lymph node with white coalescent nodule. From Adeline Linsart.

showed that persistent infection provokes a strong immune reaction and coronavirus can be detected in various organs following viraemia (lung, spleen, kidney, brain, liver...), independently of enterocytes and monocytes dissemination [4].

Until now, three coronaviruses have been identified in ferrets [5]. The Ferret Enteric Coronavirus (FRECv) is responsible of Epizootic Catarrhal Enteritis (ECE). The ferret coronavirus (FRCov) has been reported in fecal samples in healthy ferrets and is closely related to the Ferret Systemic Coronavirus (FRSCv), responsible for the systemic coronaviriosis in the ferret. As for the dry form of FIP in cats, different theories are explored to explain a relationship between the enteric and the systemic strains: a genetic mutation of the enteric strain in the body, a recombination between different strains, a highly virulent strain or an abnormal immune



Figure 8. Presence of numerous white coalescent nodules on the spleen. From Adeline Linsart.

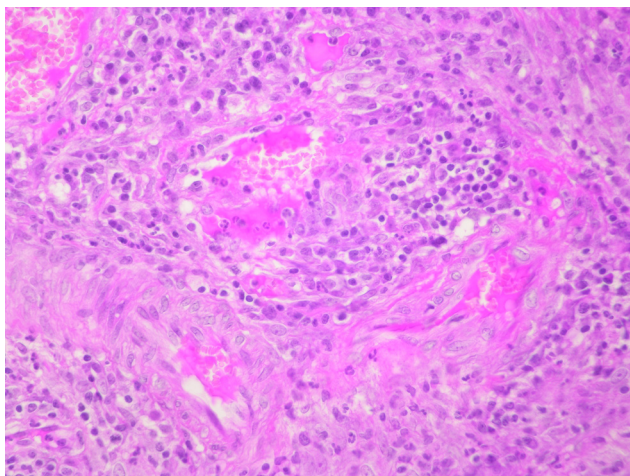


Figure 9. Histopathological picture of a vasculitis showing the destruction of a vessel wall by neutrophils and macrophages. Hematoxylin and eosin $\times 400$. From Alexandra Nicolier.

response of the organism. However, to date, none of these hypotheses has been validated [5–8].

Although coronaviruses are common in ferrets, systemic coronaviriosis is an occasional disease. It occurs more frequently in young ferrets, usually less than 18-months-old, living in community. Facilitating factors, such as young age, weak immune response, elevated density of animals, infections, stress, social or food competition or lack of hygiene are suspected in the development of systemic coronaviriosis. No sex predisposition has been clearly identified even if bibliographic data tend to show that males are more affected than females [2,5,9,10].

Clinical signs are non-specific (weight loss, lethargy, mesenteric masses, anorexia, diarrhea) but the presence of a mesenteric mass in a young ferret coming from a pet-shop is highly suggestive [2,3]. Hyperglobulinemia is an important finding [2,3]. Differential diagnosis with infectious and neoplastic causes is necessary [2,3]. Protein electrophoresis can reveal monoclonal or polyclonal gammopathy [11]. Ultrasonography and fine-needle aspirations are easily and rapidly performed but results could be non-specific and frustrating (authors' observations). Macroscopic lesions seen during exploratory laparotomy or necropsy are typical and are characterized by white to tan coalescent nodules disseminated in the abdominal organs. On histopathology, the nodules consist of a pyogranulomatous inflammation with a neutrophilic vasculitis similar to the one observed in FIP in cats. The presence of coronavirus antigen within the lesions could be confirmed by immunochemistry using the same antibody FIPV3-70 employed for FIP in cats [5].

To date, PCR tests commercially available for coronaviriosis in ferret are able to detect FRECV but not FRSCV. Detection of FRECV in the blood of a ferret cannot be considered diagnostic of a systemic coronaviriosis. Indeed, the link between the two strains is not well established, and it has been shown that some healthy cats could have enteric coronavirus in their blood, without developing a FIP later [12].

Fecal and urinary incontinence are a rare complaint in ferrets whereas posterior paresis is frequently seen [3]. This

last symptom is generally observed in sick ferrets with various problems: weakness due to cardiac disease, metabolic disturbance or abdominal pain are the more probable causes in a young ferret, rather than real neurological deficiency [13]. In our case, it seems that peripheral neuropathy was more likely responsible of the clinical presentation. The clinical signs were mild and of relatively short duration. No central signs were observed and neurological examination was within normal limits. We should definitely have examined the brain and spinal cord but the owner refused for personal reasons.

Central nervous system can be affected by systemic coronaviriosis: leptomeningitis, choroiditis, ependymitis and pyogranulomatous encephalomyelitis have all been described [5]. In these animals, neurological signs were, however, more important and generalized than in our case (which was only suffering of posterior paresis and incontinence). Pyogranulomatous inflammation of peripheral nerve (minimal sciatic radiculoneuritis) can explain our clinical signs even if we cannot show neurological anomalies. Fecal and urinary incontinence are sometimes associated with weakness or pain signs [2,3]. In our case, it seems less probable that pain caused the incontinence because it was observed at rest, during sleeping and in activity. Other peripheral nerves could have been affected by radiculoneuritis.

Conclusion

Systemic coronaviriosis can be associated with various clinical signs. To our knowledge, this case is the first description of an urinary and fecal incontinence linked to this emerging disease. Palliative treatment is unrewarding and until now, diagnosed ferrets cannot be treated efficiently.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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