**Journal of Veterinary Science and Public Health**

***J. Vet. Sc. Public Health, v. 8, n. 2, p. 115-125, 2021***

# SKIN FRAGILITY SYNDROME IN A CAT WITH MULTICENTRIC LYMPHOMA

## *SÍNDROME DA FRAGILIDADE CUTÂNEA EM UM GATO COM LINFOMA MULTICÊNTRICO*

Lucas Alécio Gomes[1*], Giorgio Queiroz Pereira[2], Jéssica Chagas Domingues Menck[2], Jéssica Regina Moreira[3], Selwyn Arlington Headley[3]

[1]Small Animal Internal Medicine, Department of Veterinary Clinics, Universidade Estadual de Londrina, Paraná, Brazil.
[2]Small Animal Internal Medicine, Universidade Filadelfia, Paraná, Brazil.
[3]Laboratory of Animal Pathology, Department of Veterinary Preventive Medicine, Universidade Estadual de Londrina, Paraná, Brazil.
*Corresponding author: E-mail: lagomes@uel.br
DOI: 10.4025/revcivet.v8i2.53938

## ABSTRACT

The feline skin fragility syndrome (FSFS) is a unique disease entity of unknown aetiology that is frequently associated with tumors or disease processes. This report describes the clinical and pathological findings of FSFS observed in a cat associated with multicentric lymphoma and hepatic diseases. A 13-year-old female cat with a history of apathy was treated at a Veterinary School Hospital and the animal's physical examination revealed a traumatic lacerating lesion of the skin showing cutaneous fragility. Laboratory tests were requested, in which leukocytosis due to neutrophilia and lymphocytosis was detected, as well as marked elevation of alkaline phosphatase and gamma-glutamyl transferase. Abdominal US revealed nodules in the pancreas and liver, and enlargement of some lymph nodes. Necropsy revealed nodules at the pancreas and liver with enlarged mesenteric lymph nodes. Histopathology of the skin revealed dermal atrophy and loosely arranged and ruptured collagenous tissue. Small cell lymphoma was diagnosed in mediastinal and peripancreatic lymph nodes; neoplastic lymphocytes were observed in the pancreas, thyroid gland, spleen, lung, liver, kidney, brain, and duodenum. In addition, there was chronic hepatitis and hepatocelular degeneration. A diagnosis of FSFS was confirmed due to the combined clinical and pathologic findings. This unusual syndrome may be associated with severe hepatic disease or be the manifestation of a paraneoplastic syndrome in cats.

**Keywords**: feline; histopathology; disseminated neoplasm; chronic hepatitis.

**RESUMO**

A síndrome da fragilidade cutânea felina (SFCF) é uma doença de etiologia desconhecida, que está frequentemente associada a tumores ou enfermidades. Este relato descreve os achados clínicos e patológicos da SFCF observados em um gato, os quais estão associados a linfoma multicêntrico e alterações hepáticas. Uma gata de 13 anos de idade, sem raça definida, com histórico de apatia foi atendida em um Hospital Veterinário Escola. Na contenção do animal, para o exame físico ocorreu lesão lacerante traumática da pele evidenciando-se fragilidade cutânea. Foram solicitados exame laboratoriais e detectou-se leucocitose por neutrofilia e linfocitose, elevação acentuada de fosfatase alcalina e gama-glutamil transferase. A ultrassonografia (US) abdominal revelou nódulos no pâncreas, fígado e aumento de alguns linfonodos. A necropsia revelou nódulos no pâncreas e no fígado com linfonodos mesentéricos aumentados. A histopatologia da pele revelou atrofia dérmica e tecido colágeno frouxamente organizado. Linfoma de pequenas células foi diagnosticado nos linfonodos mediastinal e peripancreáticos; linfócitos neoplásicos foram observados no pâncreas, glândula tireoide, baço, pulmão, fígado, rim, cérebro e duodeno. Além disso, havia hepatite crônica e degeneração hepatocelular. Um diagnóstico de SFCF foi confirmado devido aos achados clínicos e patológicos combinados. Essa síndrome incomum pode estar associada a doença hepática grave ou ser a manifestação de uma síndrome paraneoplásica em gatos.

**Palavras-chave:** felino; histopatologia; neoplasia disseminada; hepatite crônica.

## INTRODUCTION

Acquired feline skin fragility syndrome (FSFS) is a remarkably rare disease of multifactorial aetiology that is characterized by a severely fragile and thin skin in the absence of hyperextensibility (GROSS et al., 2005). Since the early description of this unusual syndrome (BARTHOLD et al., 1980), FSFS has been associated with several disease conditions including cholangiohepatitis (DANIEL et al., 2010), hepatic lipidosis (TROTMAN et al., 2007; DANIEL et al., 2010), cholangiocarcinoma (REGNIER & PIERAGGI, 1989), histoplasmosis (TAMULEVICUS et al., 2011), multicentric lymphoma (CROSAZ et al., 2013), and feline infectious peritonitis (TROTMAN et al., 2007). Regarding to this, the aim of this article is to describes the clinical and pathological findings observed in a cat with FSFS associated with multicentric small cell lymphoma and chronic hepatitis.

## DEVELOPMENT

### Case report

A 13-year-old, mixed breed, female cat, with a history of intermittent vomiting for approximately 12 months, was admitted at a Veterinary Teaching Hospital in Southern Brazil. During the clinical examination severe dehydration, mild icterus of mucous membranes, ulcerations at the upper lip, cachexia, and depression of consciousness were observed. However, during routine manipulation and smooth restraint of the cat, the skin at the dorsal cervical region was easily detached without bleeding. Skin detachment also occurred at the left thoracic limb and at the flank. Moreover, abdominal palpation detected nodules at the cranial abdominal region. The FSFS was suspected due to the unusual skin detachment and the possible tumorous growths. A complete blood count (CBC), serum biochemistry, and abdominal ultrasound evaluations were solicited.

The most significant haematological findings were leukocytosis (78,100 $mm^3$; normal limits 5,500 -19,500 $mm^3$) due to neutrophilia (40,612 $mm^3$; normal limits 2,500 -15,500 $mm^3$) and lymphocytosis (35,145 $mm^3$; normal limits 1,500 – 7,000 $mm^3$). Serum biochemistry revealed marked elevations in the activity of the hepatic enzymes alkaline phosphatase, ALP (514 U/L; normal limits 12 - 110 U/L) and gamma-glutamyl transferase, GGT (21 U/L; normal limits 1-11 U/L), with a slight increase in urea (77 mg/dL; normal limits 21.4 – 60 mg/dL). Abdominal ultrasound revealed nodules in the pancreas and liver, and enlargement of the mesenteric lymph nodes.

The cat was hospitalized; maintained on fentanyl on a continuous infusion rate (1µ/kg/hour/IV). The wound was washed with a sterile sodium chloride solution, a commercial ointment was than applied, and the patient was then wrapped and bandaged. However, in the following day the clinical status of the cat worsened, and due to a poor prognosis associated with a possible neoplasm, the owner elected for euthanasia. Euthanasia was performed with the anesthetic propofol being injected intravenously at a higher dose than the anesthetic, and then potassium chloride was performed intravenously. Absence of chest movements and signs of breathing, absence of heartbeat and pulse, loss of mucous color and loss of corneal reflex confirmed the patient's death. A routine necropsy was performed soon after death; fragments of the skin from the cervical and abdominal regions and the limb, as well as other selected organs (lymph nodes, brain, liver, kidney, lungs, pancreas, and the adrenal, pituitary, thyroid, and parathyroid glands), were fixed by immersion in 10% buffered formalin solution and routinely processed for histopathologic evaluation with the Haematoxylin and Eosin stain. In addition, duplicate fragments of the skin were stained with

the Masson Trichrome histochemical technique and compared with that of the skin from a normal cat with similar age as that of this case.

At necropsy, there was absence of the skin (Figure 1) without evidence of bleeding at the dorsal cervical region (20 cm x 16 cm), at the left thoracic limb (3 cm x 3 cm), and at the flank (6 cm x 2 cm); these corresponded to the areas gently manipulated during the clinical evaluation. Further, the skin at the dorsal region was very thin, extremely fragile, lacerated easily without any extra effort, and became twisted and curled as the skin was removed from the carcass.

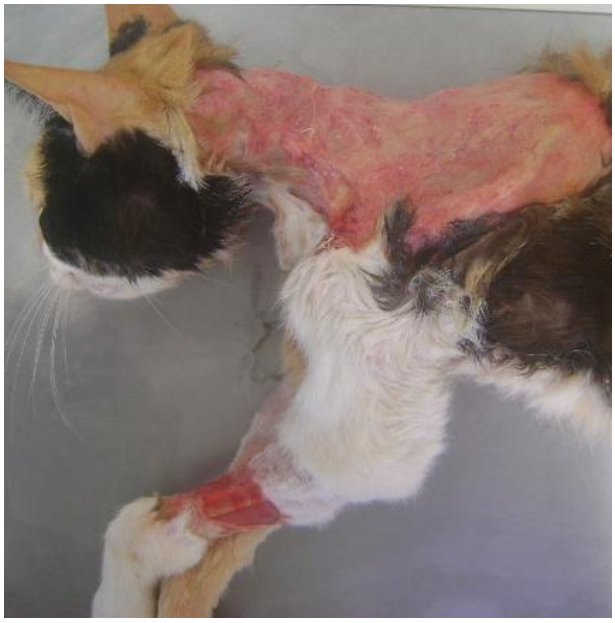

Figure 1. Feline during necropsy: observe the extensive loss of skin at the cervical region and the left hind limb of the cat that occurred during clinical restraint.

The peripancreatic, mesenteric, and mediastinal lymph nodes were enlarged and oedematous, with several white (0.2 – 0.3 cm in diameter) nodules at the sectioned surfaces. There were several white, firm, elevated, 0.2 – 3 cm in diameter, randomly distributed nodules at the pancreas; The liver was pale, enlarged with prominent lobular pattern and several randomly white areas at the capsular surface of the medial lobe; similar white nodules were also observed at the sectioned surface of this lobe. Other significant pathologic alterations included severe hydrothorax (90 ml), moderate pulmonary edema, moderate ascites (40 ml), and mild hydropericardium (7 ml). However, pathologic alterations were not observed at the adrenal, pituitary, thyroid, and parathyroid glands.

The histopathologic alterations in all cutaneous fragments were similar between the different anatomical locations (abdominal and cervical regions) evaluated, showing the same type of histopathological alterations. The epidermis was extremely thin and formed by a single layer of epithelial cells (Figure 2).

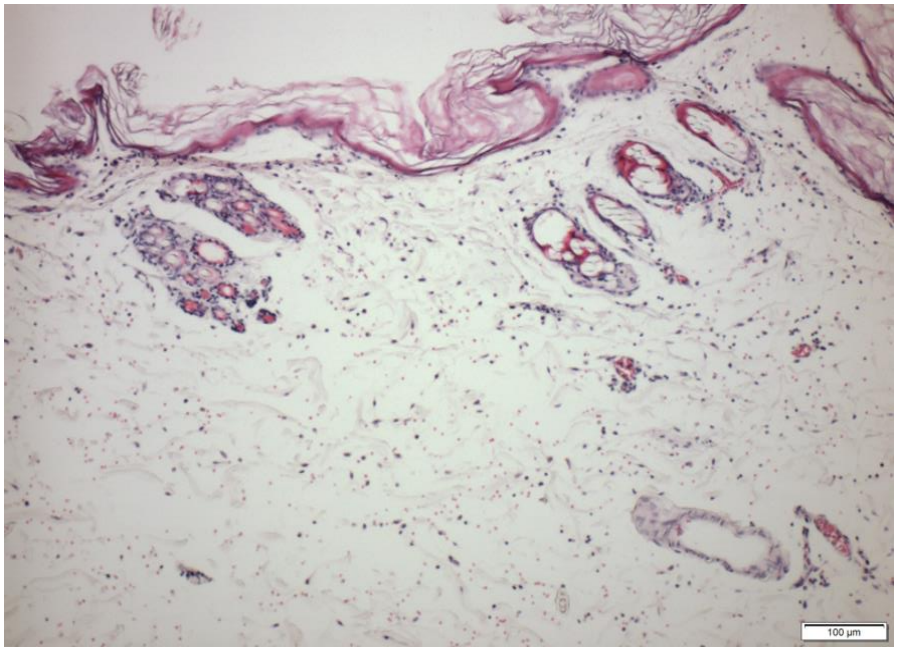


Figure 2. Feline; skin abdominal region; observe that the epidermis is formed by a single layer of cells and there is atrophy of hair follicles. Haematoxylin and Eosin stain; bar, 100 µm

Furthermore, there was diffused, moderate orthokeratotic hyperkeratosis, severe atrophy of the sebaceous and apocrine glands, and hair follicles were in telogen arrest. The collagenous fibers at the dermis were loosely arranged and severely disrupted (Figure 3) and were relatively reduced when compared with those from a normal cat by the Masson Trichrome stain.

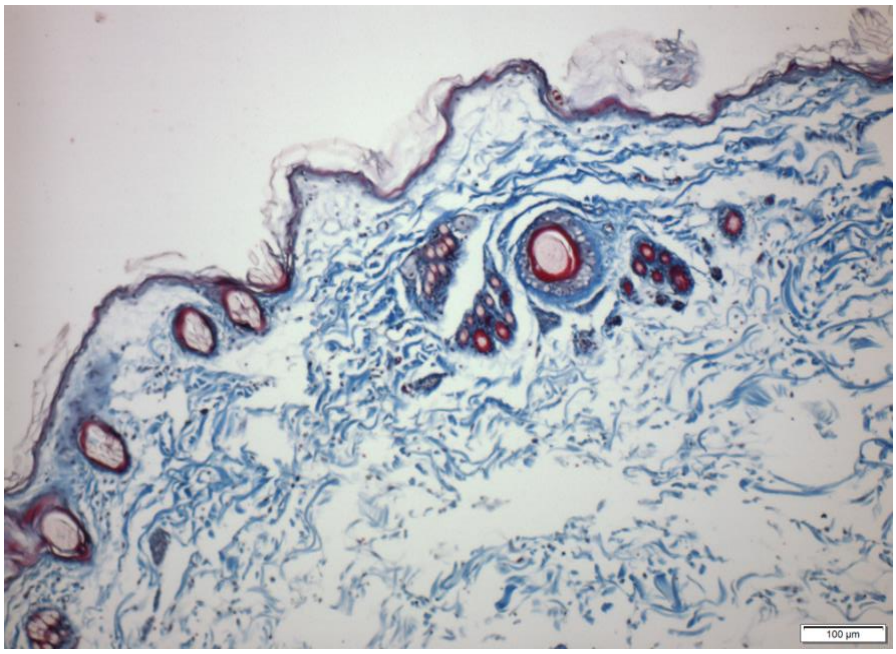

Figure 3. Cat; skin abdominal region; observe the reduced quantity of disrupted collagenous tissue at the dermis. Masson Trichome stain; bar, 100 µm

Histopathology of the mediastinal and peripancreatic lymph nodes revealed a tumour formed by the proliferation of neoplastic lymphocytes, which resulted in complete disorganization of the normal architecture of the lymph nodes. Within this neoplastic growth there were several blood-filled vascular structures, many of these contained accumulations of neoplastic lymphocytes. The neoplastic nodules consisted primarily of small lymphocytes that demonstrated scant eosinophilic cytoplasm with undefined celular margins, moderate anisocytosis, mild anisokaryosis, nuclei were rounded, conspicuous and with condensed chromatin. Similar populations of neoplastic lymphocytes were observed at the pancreas, spleen, lung, liver, kidney, brain (Figure 4), duodenum, and within the adipose tissue adjacent to the adrenal gland.

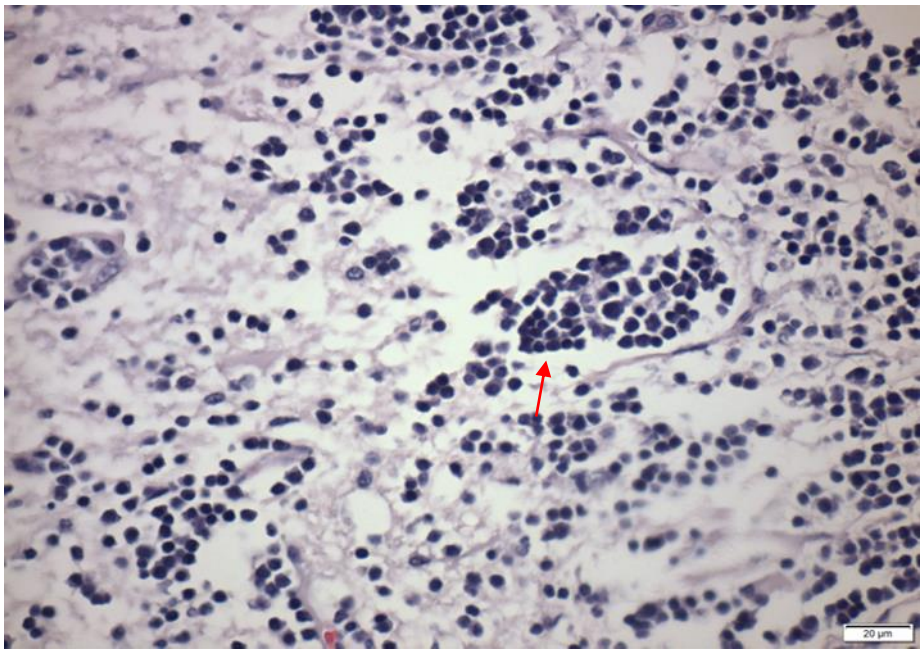


Figure 4. Brain, histopathologic characterization of lymphoma. Note a marked amount of atypical lymphocytes intermingled with the neuropile. Haematoxylin and Eosin stain; bar, 20 µm

Additional significant histopathologic alterations were observed in the liver, being characterized as severe hepatocelular degeneration; moderate dissociation, atrophy and loss of hepatic cords; moderate biliary canicular and ductal stasis; severe proliferation of bile duct epithelial cells; and mild to moderate portal fibrosis. Furthermore, histopathologic alterations were not observed in any of the endocrine glands evaluated.

## DISCUSSION

A diagnosis of feline skin fragility syndrome (FSFS) was confirmed due to the clinical alterations of severe skin fragility observed during manipulation and smooth restraint of the cat associated with the characteristic histopathologic and histochemical findings. Similar reports were described (REGNIER & PIERAGGI, 1989; TROTMAN et al., 2007; DANIEL et al., 2010; TAMULEVICUS et al., 2011; CROSAZ et al., 2013). The absence of lesions within the adrenal, pituitary, thyroid, and parathyroid glands suggest that an endocrine-related disorder was not associated with the clinical manifestations herein described. In addition, the animal's age and the inexistence of hyperextensibility in this case excluded the Ehlers–Danlos syndrome as a possible cause (GROSS et al., 2005). Further, the histochemical analysis was important to confirm the reduced concentration of collagenous tissue as compared with a healthy cat; these findings are in accordance with previous reports of FSFS (FERNANDEZ et al., 1998; DANIEL et al., 2010).

The disseminated neoplastic disease observed in this cat is consistent with multicentric small cell lymphoma (VALLI et al., 2000). Although there is a previous description of a cat with FSFS and concomitant multicentric lymphoma (CROSAZ et al., 2013), this is the first description of simultaneous hepatic diseases and a neoplastic growth in a cat with FSFS. Other cases of FSFS were associated with neoplasms (REGNIER & PIERAGGI, 1989; CROSAZ et al., 2013), hepatic disease processes (TROTMAN et al., 2007; DANIEL et al., 2010), and systemic histoplasmosis (TAMULEVICUS et al., 2011). Common to all cases of FSFS thus far described, including the present, was hepatic involvement as either a neoplastic, inflammatory or infectious disease process. Therefore, it is questioned whether hepatic disease is necessary for the development of FSFS or the simultaneous occurrence of hepatic disease with FSFS is just a simple coincidence. The patient had two important underlying diseases, but alternatively, FSFS might be a paraneoplastic syndrome in which skin fragility is the predominant clinical feature, as previously suggested (ROCCABIANCA et al., 2006; TAMULEVICUS et al., 2011). In addition, FSFS is more frequently associated with iatrogenic or spontaneous hyperglucocorticoidism (HOENIG, 2002; GROSS et al., 2005; McKNIGHT et al., 2018), but in this case there is no history of glucocorticoid administration. Nevertheless, more cases as well as detailed investigations are needed to fully understand the occurrence, aetiology and pathogenesis associated with FSFS. The FSFS is frequently associated with normal hematological and biochemical profiles (GROSS et al., 2005), but in this case there were alterations to both profiles, probably due to the severe liver diseases and the disseminated tumor herein described.

## CONCLUSION

The feline skin fragility syndrome should be considered an important differential diagnosis in cats with ulcerations/rupture in the skin after a little handling, mainly when associated to abdominal mass detected in the physical examination and/or by abdominal images.

## REFERENCES

BARTHOLD, S.W.; KAPLAN, D, B. J.; SCHWARTZ, A. Reversible dermal atrophy in a cat treated with phenytoin. **Veterinary Pathology,** v.17**,** p.469-476, 1980. Available from: <http://journals.sagepub.com/doi/pdf/10.1177/030098588001700408>. Accessed: Aug. 19, 2020.

CROSAZ, O.; VILAPLANA-GROSSO, F.; ALLEAUME, C.; CORDONNIER, N.; BEDU-LEPERLIER, A.; MARIGNAC, G.; HUBERT, B.; ROSENBERG, D. Skin fragility syndrome in a cat with multicentric follicular lymphoma. **Journal of Feline Medicine and Surgery**, v.15**,** p.953-958, 2013. Available from: <http://journals.sagepub.com/doi/10.1177/1098612X13483460>. Accessed: Aug. 19, 2020. doi: 10.1177/1098612X13483460.

DANIEL, A.G.; LUCAS, S. R. R.; JÚNIRO, A. R.; MONTEIRO, P. R. G.; RAMOS, D. PIRES, C. G.; SINHORINI, I. L. Skin fragility syndrome in a cat with cholangiohepatitis and hepatic lipidosis. **Journal of Feline Medicine and Surgery**, v.12, p.151-155, 2010. Available from: < http://www.producao.usp.br/handle/BDPI/1758>. Accessed: Aug. 19, 2020. doi:10.1016/j.jfms.2009.07.006.

FERNANDEZ, C.J.; SCOTT, D. W.; ERB, H. N.; MINOR, R. R. Staining abnormalities of dermal collagen in cats with cutaneous asthenia or acquired skin fragility as demonstrated with Masson's trichrome stain. **Veterinary Dermatology**, v.9, p.49-54, 1998. Available from: < https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1365-3164.1998.00074.x>. Accessed: Aug. 19, 2018. doi: 10.1046/j.1365-3164.1998.00074.x.

GROSS, T.L.; IHRKE, E, J.; WALDER, E. J.; AFFOLTER, V. K. Degenerative, dysplastic and depositional diseases of dermal connective tissue. In: _____. **Skin Diseases of the Dog and Cat: Clinical and Histopathologic Diagnosis.** Oxford : Blackwell Science, 2005, p. 373-403.

HOENIG, M. Feline hyperadrenocorticism-where are we now? **Journal of Feline Medicine and Surgery**, v.4**,** p.171-174, 2002. Available from: < http://journals.sagepub.com/doi/abs/10.1053/jfms.2002.0178?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed>. Accessed: Aug. 19, 2020. doi: 10.1053/jfms.2002.0178.

McKNIGHT, C.N.; LEW, L.J.; GAMBLE, D.A. Management and closure of multiple large cutaneous lesions in a juvenile cat with severe acquired skin fragility syndrome secondary to iatrogenic hyperadrenocorticism. **Journal of the American Veterinary Medical Association,** v.252, p.210-214, 2018. Available from: <https://avmajournals.avma.org/doi/pdf/10.2460/javma.252.2.210>. Accessed: Aug. 31, 2020. doi:10.2460/javma.252.2.210

REGNIER, A.; PIERAGGI, M.T. Abnormal skin fragility in a cat with cholangiocarcinoma. **Journal of Small Animal Practice**, v.30**,** p.419-423, 1989. Available from: < https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1748-5827.1989.tb01597.x>. Accessed: Aug. 19, 2020. doi:

10.1111/j.1748-5827.1989.tb01597.x.

ROCCABIANCA, P.; RONDENA,; M. PALTRINIERI, S.; POCACQUA, V.; SCARPA, P. FAVERZANI, S.; SCANZIANI, E; CANIATTI, M. Multiple endocrine neoplasia type-I-like syndrome in two cats. **Veterinary Pathology**, v.43, p.345-352, 2006. Available from: < http://journals.sagepub.com/doi/abs/10.1354/vp.43-3-345?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed#>. Accessed: Aug. 19, 2020. doi: 10.1354/vp.43-3-345.

TAMULEVICUS, A.M.; HARKIN, K.; JANARDHAN, K.; DEBEY, B. M. Disseminated histoplasmosis accompanied by cutaneous fragility in a cat. **Journal of the American Animal Hospital Association**, v.47**,** p.e36-41, 2011. Available from: <http://jaaha.org/doi/10.5326/JAAHA-MS-5517?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed&code=amah-site>. Accessed: Aug. 19, 2020. doi: 10.5326/JAAHA-MS-5517.

TROTMAN, T.K.; MAULDIN, E.; HOFFMANN, V.; DEL PIERO, F. HESS, R. S. Skin fragility syndrome in a cat with feline infectious peritonitis and hepatic lipidosis. **Veterinary Dermatology**, v.18**,** p.365-369, 2007. Available from: < https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-3164.2007.00613.x>. Accessed: Aug. 19, 2020. doi: 10.1111/j.1365-3164.2007.00613.x.

VALLI, V.E.; JACOBS, R. M.; NORRIS, A.; COUTO, C. G.; MORRISON, W. B.; MCCAW, D.; COTTER, S.; OGILVIE, G.; MOORE, A. The histologic classification of 602 cases of feline lymphoproliferative disease using the National Cancer Institute working formulation. **Journal of Veterinary Diagnostic investigation**, v.12**,** p.295-306, 2000. Available from: < http://journals.sagepub.com/doi/abs/10.1177/104063870001200401?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed>. Accessed: Aug. 16, 2018. doi: 10.1177/104063870001200401.