CLINICAL REPORT

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Hepatocellular carcinoma associated with hepatocutaneous syndrome in a feline

Carcinoma hepatocelular associado a síndrome hepatocutânea em felino

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ABSTRACT: Hepatocellular carcinoma (HCC) is a primary hepatobiliary neoplasm (PHN) originating in hepatocytes. It is rarely described in felines and represents 27% of the species' liver neoplasms. Patients may present emesis, anorexia, lethargy, weight loss, jaundice, coagulopathy, and hepatomegaly. This article aimed to report the case of a cat of no defined breed, approximately seven years old, with a crusted and hemorrhagic nasal injury, apathy, mild dehydration, a 2/9 body score, and mean systolic blood pressure of 187 mmHg. Abdominal ultrasound suggested renal senility and hepatomegaly, serum biochemistry indicated hyperphosphatemia and azotemia, and there was low urinary density with increased UPro/UCr. Amlodipine besylate was prescribed to control hypertension, and only after two months did the patient return, presenting cushion hyperkeratosis and a clot in the right nostril. The lesions were biopsied. The patient died three days after the procedure, and, at necropsy and histopathological analysis, there was a definitive diagnosis of HCC, presenting vacuolation in neoplastic hepatocytes under microscopy, superficial necrotic dermatitis (SND) in the nostril and cushions by parakeratotic hyperkeratosis on microscopy, and chronic kidney disease as comorbidity. The patient's clinical manifestation was consistent with that described in the literature. HCC is associated with an SND framework, a rare condition in cats.

KEYWORDS: neoplasia; liver; cat; hepatobiliary; superficial necrotic dermatitis.

RESUMO: O carcinoma hepatocelular (CHC) é uma neoplasia hepatobiliar primária (NHP) originada em hepatócitos, raramente descrita em felinos, representando 27% das neoplasias hepáticas da espécie. Os pacientes podem apresentar êmese, anorexia, letargia, perda de peso, icterícia, coagulopatia e hepatomegalia. Objetivou-se com este artigo relatar o caso de uma gata sem raça definida, com aproximadamente 7 anos de idade, com lesão nasal crostosa e hemorrágica, apatia, desidratação leve, escore corporal 2/9 e pressão arterial sistólica média de 187 mmHg. O exame ultrassonográfico abdominal sugeriu senilidade renal e hepatomegalia, a bioquímica sérica indicou hiperfosfatemia e azotemia, e houve baixa densidade urinária com RPCU aumentada. Prescreveu-se besilato de anlodipino para controle de hipertensão arterial e somente após dois meses a paciente retornou, apresentando hiperqueratose de coxins e coágulo em narina direita, tendo sido feito biópsia das lesões. Três dias após o procedimento, a paciente veio a óbito e, à necropsia e análise histopatológica, teve-se diagnóstico definitivo de CHC, apresentando vacuolização em hepatócitos neoplásicos à microscopia, dermatite necrótica superficial (DNS) em narina e coxins pela hiperqueratose paraqueratótica na microscopia, e doença renal crônica como comorbidade. A manifestação clínica da paciente foi condizente com a descrita na literatura. O CHC está associado ao quadro de DNS, uma condição rara em gatos.

PALAVRAS-CHAVE: neoplasia; fígado; gato; hepatobiliar; dermatite necrótica superficial.

INTRODUCTION

Primary hepatobiliary neoplasms (PHN) originate in hepatocytes, bile duct cells (intra and extrahepatic), mesenchymal cells, and neuroendocrine origin being classified, according to their origin, into hepatocellular tumors, bile duct tumors, sarcomas, and neuro-endocrinological tumors (Johnson; Sherding, 2006). Morphologically, they are presented in massive, nodular, and diffuse forms. The massive form affects only one hepatic lobe, the nodular form is multifocal, and the diffuse form spreads to all lobes (Liptak, 2019).

PHNs are uncommon in cats (Cullen; Stalker, 2016). Hepatocellular carcinoma (HCC), a PHN originating in hepatocytes, accounts for 27% of feline liver neoplasms (Bayton *et al.*, 2018). According to Post *et al.* (2021), the disease may be caused by hepadnaviruses of domestic cats. Its low frequency

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occurs due to the difference in hepatic cell ploidy of the species compared to humans and rats.

Clinical signs of PHN can be nonspecific, which makes diagnosis difficult and includes emesis, anorexia, lethargy, and weight loss (Barros, 2016). Liver-related signs include jaundice, coagulopathy, and hepatomegaly identified on abdominal palpation. The results of hematological laboratory tests can also be nonspecific and include leukocytosis, thrombocytosis, and anemia. As for biochemicals, there may be elevated alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (Balkman, 2009; Goussev *et al.*, 2016). The abdominal ultrasound (US) helps diagnose, allowing us to identify changes in size, echogenicity, and hepatic vascular architecture. However, the ultrasound appearance of HCC is highly variable, ranging from diffuse changes in echogenicity to focal or multifocal masses and nodules (Griffin, 2019).

The histological evaluation of liver fragments is considered the gold standard for diagnosing PHNs, essential for the definitive diagnosis of HCC (Brandstetter *et al.*, 2023). The primary therapeutic method in cases of PHN is surgical resection (partial or total liver lobectomy) (Johnson; Sherding, 2006; Liptak, 2019). In cats with HCC, according to Brandstetter *et al.* (2023), there is a relationship between surgical interventions and prolonged survival time (compared to those who did not undergo surgery) and a low incidence of metastases.

The present case report is valuable due to the scarce literature on PHN and, consequently, HCC associated with hepatocutaneous syndrome in domestic cats.

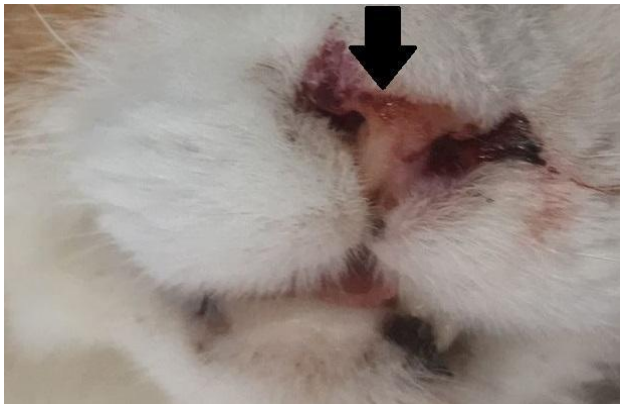
CASE REPORT

A female cat with no defined breed, long fur, approximately seven years old, 3.150 kg, neutered, with a complaint of polyuria, hypoxia, sneezing, recurrent epistaxis, hyperkeratosis, and nasal injury was serviced, presenting such clinical signs since her rescue (approximately two months before the consultation). She had a quadruple and anti-rabies polyvalent vaccination and a negative result for FIV/FeLV through a rapid test. On physical examination, she was apathetic, slightly dehydrated (7%), with a body score of 2 (on a scale of 1 to 9), a muscle mass index of 1 (on a scale of 0 to 3), and a capillary filling time of over two seconds. Systolic blood pressure (SBP) was measured by Doppler, resulting in 187 mmHg, with a calm patient.

Hydration was performed through subcutaneous fluid therapy (200 mL of Ringer-lactate solution). Due to the low score and body muscle mass, it was indicated to provide hypercaloric pasty feed at a daily total of 220 kcal (metabolizable energy of 1,183 kcal/kg), equivalent to 186g/day every six hours, with supplementation of amino acids in a paste. During the consultation, an *imprint* was done of the nasal lesion for cytology and complementary tests of urinalysis, protein/urinary creatinine ratio (UPC), abdominal ultrasound, blood count, and serum biochemistry (creatinine, urea, albumin, potassium, phosphorus, Ionic calcium, GGT, total bilirubin, and fractions) were requested, whose biological materials were collected the next day, after the patient was hydrated.

Abdominal ultrasound (8 Hz, B mode, linear probe) showed changes in the right kidney (loss of internal architecture due to discrete cortical thickening) and liver (discrete hepatomegaly). Cytology of the nasal lesion indicated suppurative inflammation. The hemogram showed mild mature neutrophilia changes (14,784 cells/µL - Ref.: 2,500 to 12,500 cells/µL), mild lymphopenia (1,344 cells/µL - Ref.: 1,500 to 7,000 cells/µL), and monocytosis (2,112 cells/µL - Ref.: 0 to 1,500 cells/µL), characterizing chronic stress. Serum Biochemistry showed values above the reference for serum phosphorus (8.4 mg/dL - Ref.: 2.6 to 5.5 mg/dL) and ionic calcium (6.45 mg/dL - Ref.: 3.1 to 5.1 mg/dL), in addition to azotemia (urea 180.7 mg/dL - Ref: 10.0 to 60.0 mg/dL, and creatinine 3.48 mg/dL - Ref.: 0.8 to 1.8 mg/dL). Urinalysis indicated low urinary density (1.018 - Ref.: 1.035 to 1.060) and discretely increased UPC (0.44 - Ref.: below 0.4). There were no changes in serum GGT activity (3.28 IU/dL - Ref.: 1.0 to 10 IU/dL), total bilirubin (0.4 mg/dL - Ref.: 0.1 to 0.6 mg/dL), and direct (0.13 mg/dL - Ref.: 0.0 to 0.3 mg/dL), and indirect bilirubin (0.27 mg/dL-Ref.: 0.1 to 0.6 mg / dL). SBP was re-evaluated, being hypertensive (174 mmHg), having been prescribed amlodipine besylate BID PO (1.25 mg/animal) to control arterial hypertension until further evaluation in two weeks.

The patient returned only after two months, and the tutor reported recurrent epistaxis and hyporexia, without improvement. On physical examination, the nasal lesion was crusted and hemorrhagic (Figure 1), with the presence of a clot in the right nostril, which, when manipulated, started bleeding, soon stopping with ice. In addition, there was cushion hyperkeratosis (Figure 2A) in all four limbs. Blood count and prothrombin activity time (PAT) and Activated Partial Thromboplastin



Source: Images provided by LACIPA/CVE/UFSC.

Figure 1. Macroscopic image obtained in the necropsy of a female feline with no defined breed. Face with bilateral epistaxis and crustose nasal lesion (arrow).

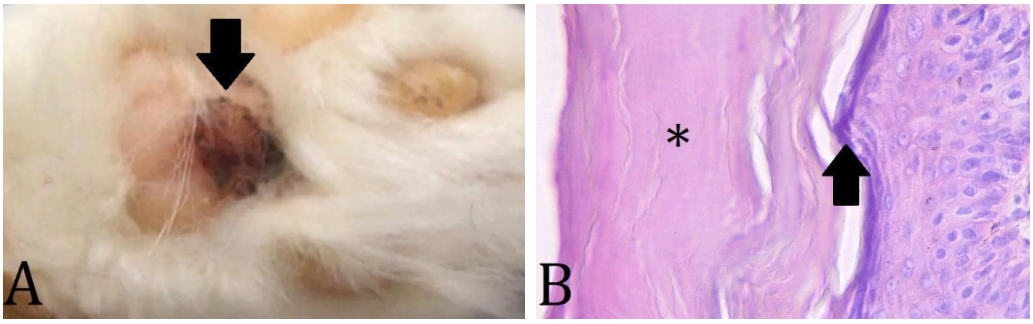
Time (APTT) tests were requested, with prolonged results for PAT (13.3 seconds - Ref.: 7 to 10 seconds) and APTT (30.5 seconds - Ref.: 9 to 11 seconds).

A biopsy of the lesions was then indicated. On the day of the procedure, at anamnesis, the tutor reported a capricious appetite, and, on physical examination, the patient was dehydrated (9%) but normotensive (mean SBP of 117 mmHg). Rehydration was performed with 250 mL Ringer-lactate via IV in an infusion pump at a speed of 80 mL/h to perform the incisional biopsy of the plantar pad and nasal lesion under sedation. After anesthetic recovery, the patient was released with the recommendation of a high-calorie diet. The tutor reported the death of the animal three days after the procedure.

The corpse was sent to LABOPAVE/CVE for necropsy. The histopathological analysis was performed using the fragments collected in biopsy and those collected in necropsy. The report indicated cirrhotic hepatomegaly, with whitish round spots in the right medial lobe (Figures 3A and 3B), kidneys with irregular capsular surfaces, hyperkeratosis of the pads, and crusted nasal lesions. Microscopically, the liver showed loss of trabecular organization, absence of sinusoids, necrotic areas in the centrilobular region, and hepatocytes with fatty degeneration (Figure 3C). The kidneys presented tubular necrosis, amorphous eosinophilic material in the tubular lumen, and interstitial lymphoplasmocyte infiltrate. The pads showed an increase in the keratin layer without the presence of nuclei due to orthokeratotic hyperkeratosis (Figure 2B). The nose presented necro-suppurative dermatitis with a large number of neutrophils and cellular debris. The definitive pathological diagnosis was hepatocellular carcinoma and superficial necrolytic dermatitis in the nostril and pads.

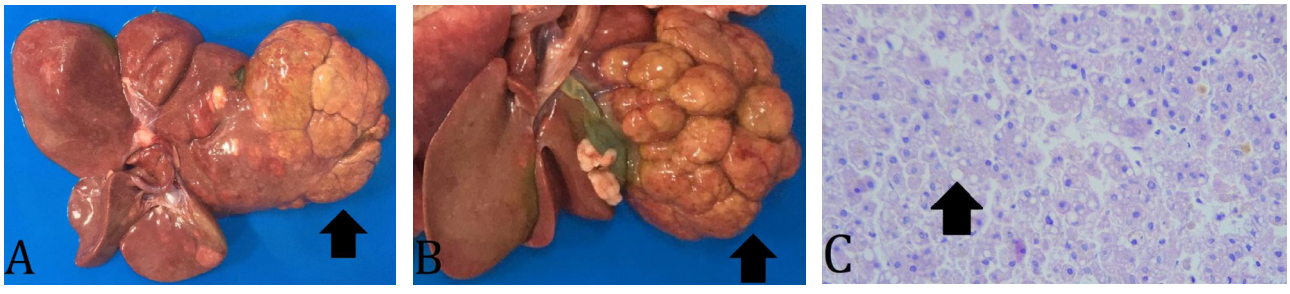
DISCUSSION AND CONCLUSIONS

The clinical manifestation of the patient reported is consistent with what is described in the literature for HCC, showing signs of lethargy, weight loss, coagulopathy, and possible liver disease on ultrasound examination (Balkman, 2009; Barros, 2016). The presence of crustose nasal lesion and pad hyperkeratosis in the four limbs, along with histological characteristics of orthokeratotic hyperkeratosis, keratinocyte degeneration, and basal cell hyperplasia of the epidermis in the plantar pad biopsy, and parakeratotic hyperkeratosis, keratinocyte degeneration, and basal cell hyperplasia of the epidermis in the nose biopsy, led to the diagnosis of superficial necrotic dermatitis (SND), consistent with Gross *et al.* (2006), who report macro and microscopic changes such as crusts and ulcers in mucocutaneous junctions or adjacent to lesions, ventrolateral trunk alopecia, and hyperkeratosis of plantar pads, along with



Source: Images provided by LABOPAVE/CVE/UFSC.

Figure 2. (A) Macroscopic image obtained in the necropsy of a female feline with no defined breed. Plantar pads with hyperkeratosis (arrow). (B) Microscopic image of pads obtained in a biopsy, histological section (H.E.; 40X magn.) showing increased keratin bed without the presence of nuclei (asterisk) and areas with degenerated keratin fibers (arrow).



Source: Images provided by LABOPAVE/CVE/UFSC.

Figure 3. mages obtained in the necropsy of the female feline with no defined breed. (A) Diaphragmatic face of the liver, lobe affected by massive morphology neoplasia (arrow). (B) Visceral face of the liver, neoplastic masses of the affected lobe (arrow). (C) Microscopic image of liver obtained in necropsy, histological section (H.E.; 40X magn.) presenting loss of trabecular organization and hepatocytes with fatty degeneration (arrow).

parakeratotic hyperkeratosis, keratinocyte degeneration, and basal cell hyperplasia of the epidermis at histopathological evaluation through biopsy.

SND disorders are very rare in felines, with few reported cases (Asakawa; Cullen; Linder, 2013; Sahinduran; Ozmen, 2017) and no description of pathological mechanisms and species-specific treatments. SND is more frequently reported in dogs, having its probable origin in liver diseases causing hepatocutaneous syndrome, increasing the hepatic catabolism of amino acids, generating skin lesions, and presenting iatrogenic origin to the use of phenobarbital (Jaffey *et al.*, 2020). According to Loftus *et al.* (2021), HCC may predispose hepatocutaneous syndrome in dogs. According to Gross *et al.* (2006), there is usually an association between SND and severe hepatocyte vacuolation.

Biochemical laboratory tests revealed the presence of azotemia, which is considered a possible abnormality in cats with PHN (Johnson, 2008). In addition, according to Grant and Forrester (2001), neoplasms can cause chronic secondary glomerulonephritis. However, this was not the picture developed by this patient, also with hyperphosphatemia and renal senility on ultrasound examination, as the histopathological examination was indicative of interstitial nephritis. Thus, chronic kidney disease (CKD), with concomitant systemic arterial hypertension (SAH) (Greene *et al.*, 2014), is defined here as a comorbidity. The patient had low body and muscle mass scores, conditions closely related to CKD in cats (Greene *et al.*, 2014). On the other hand, sarcopenia in feline patients can lead to overestimated systolic blood pressure results when measured from the radial artery (Whittemore; Nystrom; Mawby, 2017). Nasal bleeding can be partially justified by SAH and the coagulopathy detected since prolonged results in PAT and APTT tests, one of the clinical signs associated with HCC (Balkman, 2009; Barros, 2016; Goussev *et al.*, 2016), were identified. Due to the prolongation in both parameters, disseminated intravascular coagulation (DIC) may have occurred, although there are no clear parameters for this diagnosis (Baker, 2015).

Hepatic neoplasms can increase organ size (Kealy; McAllister; Graham, 2012), presenting hyperechoic or hypoechoic and focal or diffuse masses (Watson; Bunch, 2010). A common alteration in HCC is the evidenced alteration of vascular architecture since they are hypervascularized tumors (Teshima *et al.*, 2013). As for the patient, on the abdominal US, a normoechogenic liver was observed, with homogeneous parenchyma and preserved vascular architecture, with the only alteration being discrete hepatomegaly with irregular contours and rounded edges. The fact that the neoplastic masses were not identified during abdominal palpation or US is attributed to their subsequent growth since the examinations were performed two months before the worsening of the hepatocutaneous syndrome and subsequent death of the animal. Although Banzato *et al.* (2020) do not consider contrast-enhanced ultrasonography (CEUS) a sensitive enough technique to differentiate PHNs in felines, Ercolin *et al.* (2024) consider sonoelastography and CEUS more sensitive in identifying and differentiating PHNs than B-mode US. In addition, computed tomography and magnetic resonance imaging are considered more sensitive in detecting minor changes at an early stage (JOHNSON, 2008). However, none of these examinations were performed for this patient. After necropsy, it was confirmed that the patient's neoplasm involved only one hepatic lobe, presenting a massive form, according to Liptak (2019).

Histologically, HCC may present a trabecular, adenoid, or solid pattern (Barros, 2016). Vacuolation in neoplastic hepatocytes is the most common characteristic, regardless of the pattern, and can be associated with the deposition of glycogen or lipids. Solid pattern carcinoma is poorly differentiated and characterized by pleomorphic cells and hepatocyte vacuolation (Cullen, 2017), consistent with the histopathological results.

The rarity of cases involving HCC and SND in cats makes diagnosis difficult, and the available literature is scarce. The SND framework is the most emblematic since clinical signs are difficult to associate with liver diseases, and it is essential to verify the concomitant presence of high serum concentrations of liver enzymes in suspected cases. Exfoliative dermatitis, mainly associated with thymoma and cutaneous lymphoma, is rarer and should be considered a clinical differential diagnosis (Gross *et al.*, 2006).

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