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TITLE OF CASE
Hepatocutaneous syndrome in a Maltese, diagnosis, treatment and the value of CT in the diagnosis

SUMMARY
A 10-year-old Maltese neutered female was presented for lip dermatitis and mild generalised pruritus. On examination, there were multiple lesions affecting the peri-oral and peri-nasal mucocutaneous junctions as well as distal limbs. Serum chemistry and a bile acids test were indicative of hepatocellular injury and hepatic dysfunction. Plasma amino acids were markedly depleted. Ultrasonography of the liver revealed a honeycombed appearance. A CT scan was performed to rule out a porto-vascular abnormality, hepatic or pancreatic neoplasia. CT hepatic findings are described in this confirmed case of hepatocutaneous syndrome for the first time. This is the first reported case of HCS in Hong Kong. The dog was treated with a high-quality protein diet and amino acids transfusions. Eight months later the dog was still alive with good control of clinical signs.

BACKGROUND
Hepatocutaneous syndrome (HCS) is an uncommon disease reported in dogs, cats and rhinoceros that affect the liver with secondary skin involvement and is associated with a poor prognosis.[1-5] Skin disease associated with internal organ pathology was first described in humans in 1942, due to internal malignant neoplasia and was termed necrolytic migratory erythema (NME).[6] In veterinary medicine, a comparable syndrome was first described in 1986 in 4 diabetic dogs with clinical and histopathological features similar to those of NME and was referred to as canine diabetic dermatosis.[7] Other terms interchangeably used for this syndrome are superficial necrolytic dermatitis (SND) and metabolic epidermal necrosis (MEN). HCS is used when concurrent hepatic disease is present, whereas SND and MEN describe the cutaneous disease. This syndrome has been associated in dogs with diabetes mellitus, hepatic vacuolar disease and cirrhosis, and rarely with pancreatic or hepatic glucagonoma.[7-9] Pancreatitis, mycotoxicosis, copper storage disease and prolonged

phenobarbitone use have also been reported as potential causes in dogs.[10-12] Amino acids depletion and diabetes mellitus are often associated with HCS but not with any other primary hepatopathies, suggesting that a primary hepatopathy or toxicity are unlikely causes of secondary HCS.[13]

Affected dogs are middle-aged and older. Although there is no clear gender predisposition, males have been reported in higher numbers by several authors.[3 4 13 14] There is no known breed predisposition either, with reports including cross breeds and pure breeds such as terrier, collie, Maltese, German shepherd, Shetland sheepdog and Shih Tzu, where a heritable component has been speculated.[3-5 13] Dogs present with distinctive skin lesions such as hyperkeratosis of the footpads, erythema, crusting, alopecia and erosions.[3 4 10 14] The skin areas affected include the footpads, oral mucocutaneous junctions, muzzle, eyes, nose, pressure points on distal limbs and trunk, perineum and ventral abdominal wall.[3 4 10 14] Lameness, lethargy, anorexia and weight loss are common clinical signs due to pain from footpads and other skin lesions.[3 4 10]

Although the exact pathogenesis is unknown, depletion of plasma amino acids, with or without glucagon elevation, is believed to be a predominant feature.[3 5 10 13 15-17] The stratum granulosum requires amino acids for its continuous growth and regeneration, and amino acid depletion may cause epidermal protein deficiency and subsequent necrosis[17]. Hypotheses for amino acid depletion include excessive uptake and catabolism when utilized by hepatocytes for gluconeogenesis and for the urea cycle.[10 14] Excess glucagon may lead to gluconeogenesis and hepatic catabolism of amino acids to produce glucose.[3 9 15 16 18 19] Other theories include deficient amino acids transportation due to hypoalbuminemia,[3 20] lack of hepatic glucagon degradation and glucagon secretion by a tumour.[3 9 15 16 18 19]

Hepatic insufficiency has been associated with diabetes mellitus in human medicine, however, with the exception of HCS, has not been demonstrated in veterinary medicine.[4] Hyperglycemia and insulin-dependent diabetes mellitus in association with HCS have been reported in numerous studies with incidences of 16-27%, and 41% for the latter.[4] The cause of the hyperglycemia and insulin-dependent diabetes mellitus remains unexplained and develops in the majority of cases, often late in the course of the disease after hepatopathy and dermatopathy are evident.[3 4 13]

Dermatohistopathological examination of cutaneous lesions in HCS reveals distinctive "red, white and blue" appearance that is due to eosinophilic parakeratotic hyperkeratosis, epidermal oedema, and hyperplasia of basal epidermis.[3 13 21] Necrosis, clefting and separation of the parakeratotic layer occasionally occurs.[3 13]

As opposed to lesions seen in chronic hepatitis and cirrhosis, hepatic lesions in HCS are diffuse, non-inflammatory with degenerative vacuolar changes, causing parenchymal collapse and the typical appearance of proliferative nodular hepatopathy.[13] Hepatic encephalopathy may develop in the later stages of liver disease and euthanasia is often elected when either hepatic or dermatological disease is severe and refractory to treatment.

Median survival time has been reported to be as low as 1.6 months from the time of diagnosis or up to 3 months from the time of development of skin lesions.[9 10 14] An exceptionally prolonged 24 months survival was reported for a dog after amino acids and lipid intravenous infusion.[22]

A recent report categorized the severity of the disease as minimal or subclinical when only typical hepatic lesions with subtle to absent cutaneous lesions were present. In moderate and severe categories worse skin lesions carried a poorer prognosis that led to shorter survival times.[5] Early diagnosis is therefore paramount for the appropriate management and for increasing quality of life and life expectancy. Diagnostic sensitivity increases with a multimodal approach in which blood analysis, amino acids assessment,[5 14] characteristic hepatic ultrasonography changes,[21 23] and histopathology,[4 10 21-23] collectively support a final diagnosis.

The use of CT to diagnose abdominal pathology is rapidly increasing due to ever increasing numbers of CT machines in academic institutions and large private veterinary hospitals. Older dogs often undergo a CT scan for a variety of reasons and liver pathology due to HCS could be an incidental or comorbid finding or the diagnosis has been made by other means but a CT scan is still performed to look for comorbid pathology prior to instigating expensive palliative treatment. To the authors' knowledge, there is only one HCS report where CT is briefly described in a dog with advanced hepatic cirrhosis as the underlying cause of the skin pathology.[15]

We present the first report of HCS in Hong Kong and elaborate on the value of CT in confirming the diagnosis.

CASE PRESENTATION

A 10-year-old female neutered Maltese dog was presented at the primary care section of our Small Animal Teaching Hospital with suspected lip pyoderma and pruritus noticed one month before presentation, with waxing and waning episodes of lethargy but no other reported clinical dermatological or systemic signs. On physical examination, the dog had mild nasal, perioral, periocular and pedal erythema but no footpad hyperkeratosis. Superficial pyoderma was diagnosed with a cytological exam for skin assessment. A complete blood count and a serum chemistry profile revealed mild changes of microcytosis (MCV 60.3 fL, ref. 61-73), hypochromasia (MCH 20.0 pg, ref. 21.2-25.9), reticulocytosis (128.8 K/µL, ref. 10.0-110.0), elevated globulins (48 g/L, ref. 25-45), alkaline phosphatase (ALKP) (708 U/L, ref. 23-212) and moderately increased alanine aminotransferase (ALT) (745 U/L, ref. 10-125). Bile acids, by a SNAP in-house test, were elevated beyond the upper reference limit both pre- and postprandially (>30 µmol/L, ref. <25) and blood was sent to a laboratory to confirm these findings. A urine analysis showed bilirubinuria (2+, ref. negative to 1+) and urobilinogenuria (3+, ref. negative to 1+) with a USG of 1.030. A preliminary abdominal ultrasound revealed a normal sized liver with a very irregular reticular architecture showing a reticular appearance, which seemed normal in size. Symptomatic treatment for the skin lesions and the hepatic pathology was started, and a revisit appointment was scheduled.

INVESTIGATIONS

A week after the initial presentation the dog was admitted for further investigation. Results from the bile acids stimulation test collected at the initial visit were confirmatory of hepatic dysfunction (postprandial 137.5 µmol/L, ref. 0.0-73.4 µmol/L). Follow up liver function tests revealed normal plasma ammonia (NH3 -11 µmol/L, ref. 0-98) and decreased enzyme values (ALKP 239 U/L, ALT 235 U/L. Clotting times were assessed prior to the liver fine needle aspirate (FNA) and were within normal limits (APTT 89 sec, ref.72-102, PT 17 sec, ref. 11-17). A complete plasma amino acid analysis showed decreased values in 19 out of 26 amino acids (Table 1).

TABLE 1. Complete amino acids analysis.

Tests	Results*	Reference Range*
L-Alanine	185	389+/-9
L-Arginine	45	102+/-3
L-Amino-n Butyric Acid	9	6+/-2
L-Asparagine	23	41+/-1
L-Aspartic Acid	6	7+/-0.2
L-Citrulline	18	41+/-2
L-Cystine	4	46+/-1
L-Glutamic Acid	59	24+/-1
L-Glutamine	93	495+/-9
Glycine	105	266+/-8
L-Histidine	92	71+-2
3-Methyl-L-histidine	8	6+/-1
L-Isoleucine	64	51+/-1
L-Leucine	95	120+/-3
L-Lysine	104	131+/-5
L-Methionine	32	57+/-2
L-Ornithine	20	35+/-2
L-Phenylalanine	97	45+/-1
L-Proline	60	249+/-8
Hydroxy-L-Proline	10	67+/-4
L-Serine	93	107+/-3
Taurine	58	77+/-2
L-Threonine	77	178+/-5
Tryptophan	88	60+/-2
L-Tyrosine	29	39+/-1
L-Valine	140	158+/-4

*All values in nmol/mL

Left and right lateral and dorsoventral thoraco-abdominal radiographs were unremarkable with the liver of normal size.

Abdominal ultrasonography revealed pathology limited to a normal sized liver with irregular borders. A diffuse nodular pattern was evident caused by variably sized round to oval relatively hypoechoic regions, 5 – 13 mm in diameter, of apparently normal liver tissue. The nodules were surrounded by a network of thin relatively hyperechoic strands, the echogenicity of which was less than the portal vessel walls. This pattern was typical of the honeycomb or Swiss cheese-like pattern, previously reported as pathognomonic for HCS (Fig 1).[21] [23]

Fine needle aspirates were taken of the liver and cytology revealed evidence of hyperplasia with bilayered hepatic plates, and a small proportion of hepatocytes exhibited a minimal vacuolar change in the periphery of the cell.

A helical whole-body CT (General Electric 16 slice Brivo CT385, GE Healthcare, Waukusha, USA) was performed under general anaesthesia. Mediastinal window images were acquired (window width 400; window level 40) with a slice thickness of 1.25 mm. Survey and 3 post contrast administration series were acquired. Iopamidol 300 mg I/ml (Omnipaque, GE Health Care) was given intravenously by manual injection at 2 ml/kg followed by scans at 17 seconds (hepatic arterial phase), 43 seconds (hepatic portal phase) and at 3 minutes (perfusion phase) after completion of the injection. Survey CT showed normo-attenuating hepatic tissues (mean Hounsfield units (HU) 70) with nodules, up to 8 mm in diameter, obviously bulging from the margins (Figs 2a and 3a). The arterial phase showed somewhat indistinct and distorted arborized hepatic arteries and pulmonary veins (Figs 2b and 3b). The portal venous phase had multiple hyperattenuating hepatic nodules, with a mean HU of 170, separated from each other by hypoattenuating internodular stroma (Figs 2c and 3c). During the perfusion phase, the internodular stroma became hyperattenuating with relatively hypoattenuating nodules but still with a mean HU of 150 (Figs 2d and 3d). Mild gall bladder oedema was seen on the post-contrast images. Changes were believed to be compatible with HCS by the consultant radiologist (RMK).

Histopathology of the liver and representative skin lesions were suggested but the client declined. The dog was scheduled for an amino acids transfusion 2 weeks later and the client agreed to central catheterisation and skin biopsy sampling at this time. Skin biopsies were collected from lesions on the nasal planum and footpads for confirmation of suspected HCS. Haired skin revealed classic 'red-white-blue" changes of hepatocutaneous syndrome/superficial necrolytic dermatitis (Figs 4 and 5). The red corresponded to marked surface parakeratosis. The white matched the minimal to marked spongiosis/intracytoplasmic oedema of the stratum spinosum layer, with occasional clefts at this level, filled with serum or blood, with separation of overlying epidermis producing erosions in some areas. Occasional to rare individually necrotic keratinocytes within basal and suprabasilar levels were seen, rarely accompanied by small lymphocytes. The blue was due to marked basal epidermal hyperplasia. The superficial dermis exhibited patchy, mild, perivascular lymphocyte-rich inflammation.

A second hepatic function test was performed 3 months after the initial diagnosis, which generated normal results (postprandial 55.1 µmol/L, ref. 0.0-73.4). An initial insulin test was not performed as glucose was normal and the dermatopathy was not attributed to pancreatic disease. Four months after initial diagnosis the patient converted to diabetes mellitus with markedly elevated blood glucose (>25 mmol/L, ref. 3.89-7.95) and glucosuria (+3, ref. –ve) without clinical signs of secondary disease. A fructosamine test confirmed prolonged hyperglycemia over the previous 2 weeks (842 µmol/L, ref. 222-348). Insulin was tested a month later after treatment with exogenous porcine insulin (Caninsulin, MSD Animal Health) had been started. Exogenous insulin was withheld for 36 hours before testing not to interfere with the results (0.55mIU/L, ref. 20-25). The result generated was confirmatory for diabetes mellitus.

DIFFERENTIAL DIAGNOSIS

Initially presenting mild skin and pedal lesions could have been easily interpreted as allergic dermatitis and pyoderma, both very common in the canine population of Hong Kong where a warm and humid climate prevails much of the year. More severe dermatopathies such as a mild form of zinc dermatosis or autoimmune disease such as pemphigoid complex remained less likely differentials. The partial clinical response to anti-pruritic therapy, oral

and topical antibacterials suggested an additional aetiology was present. Treatment with corticosteroids was considered contraindicated due to underlying hepatic disease.

The mild to moderate hepatic enzymes elevation suggested differentials including hepatitis, hyperadrenocorticism, corticosteroid administration and hepatic neoplasia. Hyperadrenocorticism predominantly causes an increase in ALKP and is a common potential cause of elevated liver enzymes in geriatric patients. Hyperadrenocorticism was improbable however, as adrenal glands were normal on imaging, urine was concentrated and no proteinuria or hypertension had been reported. There was no recent history of drug administration such as anticonvulsants or corticosteroids and no knowledge of exposure to mycotoxins, making iatrogenic hepatopathy or toxicity unlikely. Cholestasis is frequently associated with elevated ALKP and can be caused by intrahepatic or extrahepatic biliary obstructive conditions such as cholecystitis, cholangiohepatitis, gallbladder mucocele, cholelithiasis and hepatobiliary, pancreatic or gastrointestinal neoplasia, however, elevated bilirubin was not present in this case, therefore obstructive cholestasis was unlikely.

Differential diagnoses for the elevated bile acids stimulation test results included an acquired portosystemic shunt, chronic advanced hepatitis, hepatic fibrosis and cirrhosis. A second bile acids stimulation test result was normal 3 months after initial diagnosis and made the previous suspicion of liver dysfunction a probable secondary condition (suggesting liver dysfunction had recovered). Furthermore, other markers for liver dysfunction such as blood ammonia, albumin, total plasma protein, blood urea nitrogen and blood glucose did not support hepatic insufficiency/liver failure.

Liver imaging findings reported a normal liver size and no evidence of a portovascular anomaly. Hepatic or pancreatic neoplasia, including a glucagonoma, were important differentials as the latter has been closely associated with SND and could have been responsible for all the clinical signs and laboratory findings, however, no masses were found and the liver FNA failed to reveal neoplastic cells. The typical honeycomb ultrasonographic appearance of the liver was unique and consistent with HCS and has not been reported in any other types of liver disease or pancreatic neoplasia.

The late findings of hyperglycemia and glucosuria could have been of secondary origin, caused by pancreatitis but no gastrointestinal signs were reported and hyperfructosaminemia and hypoinsulinemia confirmed the conversion of the HCS patient to diabetes mellitus.

TREATMENT

A topical diluted iodine solution 1:10 (Betadine, Mundipharma) was initially prescribed for the treatment of the skin lesions. Antibiotic oral therapy, amoxicillin/clavulanic acid (12.5 mg/kg PO q12h, Clavulox, Pfizer), was prescribed for 2 weeks to treat a suspected secondary bacterial infection pending definitive diagnosis. A JAK enzyme inhibitor, oclacitinib (0.4 mg/kg PO q 12h, Apoquel, Zoetis) was also prescribed at initial presentation for 2 weeks to control pruritus and was continued as a long-term therapy at a maintenance dose (0.4 mg/kg PO q24h) due to the good response reported by the client.

The treatment approach for the suspected hepatopathy and possible hepatic dysfunction included a controlled high-quality protein diet with increased antioxidants and reduced copper content (Hepatic diet, Royal Canin). Additional treatment included S-adenosylmethionine (20mg/kg PO q24h, Denosyl, Nutramax) and ursodeoxycholic acid (10 mg/kg PO q24h, Ursosan, PRO.MED.CS), both prescribed at the first visit and continued to date for glutathione supplementation and antioxidant protection and for cytoprotective and immunomodulatory effects respectively.

Amino acids transfusion at a concentration of 8% (Aminoplasmal B 8% solution, Braun), was given at 25 ml/kg over an 8-hour infusion via central catheterization every 10-14 days for 5 consecutive treatments. Following histological diagnosis of HCS continuation of amino acids transfusion was justified, with maintenance hepatic diet and the addition of egg yolks (1 egg yolk/5 kg q24h), omega-3 fatty acids (80 mg/kg PO q24h, Omega 3,6,9, VetriScience) and Vitamin E supplementation (5 mg/kg q24h, Evion, Merck) all of which have been continued to date as part of the dermatological and hepatic management.

Porcine insulin lente (0.5-1 IU/kg SC q12h, Caninsulin, MSD Animal Health) was added 4 months after initial diagnosis when the patient converted to diabetes mellitus and has been adjusted accordingly for control of glycaemia.

OUTCOME AND FOLLOW-UP

After the initial treatment with oral antibiotics, antiallergics and topical antibacterial the skin showed moderate partial improvement. Oclacitinib has been continued long term and successfully controlled pruritus. Further improvement of skin lesions followed the first amino acids infusion one month after initial presentation, with less erythema and decreased pruritus. The owner reported the dog's demeanour had improved after the infusion of the amino acids so the infusion therapy was given every 2 weeks for an additional 4 treatments. As expected the liver lesions did not show any ultrasonographic improvement but the patient remained stable during recheck visits for the two-weekly intravenous infusions. Serum chemistry parameters showed mild improvement after sequential assessment post-treatment. Twelve weeks after the initial diagnosis of HCS, the patient was still clinically stable with well-controlled skin lesions and not reported signs of systemic disease such as hepatic encephalopathy. At that time, amino acids infusions were discontinued at the client's request, as the client wanted to monitor the dog's progress at home. The client expressed money and welfare concerns regarding further treatment since it involved sedation and central catheterisation for the administration of therapy.

A month after the last infusion the skin lesions had not progressed and the patient's demeanour remained bright and active but then the patient converted to diabetes mellitus. Insulin therapy was started and better control of blood glucose was achieved.

DISCUSSION

This case report describes the diagnosis and the management of HCS syndrome in a 10-year-old Maltese dog, highlighting the usefulness of triple phase abdominal CT

angiography. HCS has been already reported in Maltese dogs in previous studies.[5] [14] Typical skin lesions in HCS include hyperkeratosis of the pads, erythema and crusting of mucocutaneous junctions in nasal, perineum, perivulvar and perianal regions, as well as skin lesions on muzzle, scrotum, distal limbs, hocks and elbows.[3] [5] [8] [15] [21] Footpad hyperkeratosis was reported in up to 91% of dogs in one study,[3] but in our report, the pads were macroscopically unremarkable with interdigital erythema and focal dermatitis as the only clinical feature. The skin lesions observed at presentation in the current case were milder than those typically described by other authors, conceivably associated with a more advanced stage of disease. Milder clinical signs were also observed in our case report, with waxing and waning hyporexia, intermittent lethargy and pruritus. In contrast, more severe signs such as anorexia, weight loss, lethargy, lameness and ambulatory pain are commonly reported in dogs suffering from advanced stages of this syndrome.[3] With the milder signs observed in this case study the diagnosis of HCS could easily have been missed if further diagnostics had not been carried out.

Microcytosis without anaemia or hypohemoglobinaemia were present. Microcytosis is commonly associated with iron deficiency, portosystemic shunting or vitamin B6 (pyridoxine) deficiency, but not with anaemia of chronic disease.[4] In the present report, portosystemic shunting was ruled out based on CT angiography and on a second bile acids stimulation test, but iron or pyridoxine deficiencies were not investigated. Serum chemistry abnormalities were also consistent with previous HCS studies where ALKP has been reported to be consistently elevated and there is seldom elevation of total bilirubin.[3] [4] [13] It is speculated that the cause of elevated ALKP is from induction due to skin lesions with acute phase inflammatory response or due to chronic illness related glucocorticoid isoforms.[4]

Necrolytic migratory erythema is commonly associated with pancreatic or hepatic glucagon-secreting tumours in humans.[6] [24] In dogs, hepatopathy has been reported as the most frequent cause of HCS and its association with a functional glucagonoma has rarely been proven.[8] [16] [21] The pathophysiology involves amino acid depletion necessary for collagen synthesis required for tissue trauma repair. The reason for this amino acid deficiency is unclear and hyperglucagonemia has been inconsistent in cases of HCS. A reason for this has been the difficulty in quantifying the concentration of glucagon, lack of standard methods and the potential presence of different unmeasured isoforms.[4] [5] Glucagon was not tested in our dog due to the lack of agreement in current literature and the unlikely presence of a glucagonoma as per our ultrasound and CT imaging. It is possible in this case that glucagon was elevated without a glucagonoma since increased glucagon could be associated with hepatopathy and altered hepatic catabolism. A complete plasma amino acids analysis confirmed a decrease in 73% of all the assessed amino acids in this study. Our results were in agreement with previous studies that reported depletion of amino acids specifically involved in the urea cycle (arginine, ornithine), glutathione synthesis (glutamine, glycine, cysteine) and collagen synthesis (proline, hydroxyproline).[5] A number of plasma amino acids (L-a-Amino- butyric acid, phenylalanine and 3-methylhistidine) have been reported to be increased in other studies,[5] as was the case in our patient. The increases are considered to be biologically relevant as they might be due to malnutrition, hepatic injury and decrease of other amino acids.

Radiography is not an essential diagnostic tool for HCS but is important to rule out concomitant pathology that could affect how to proceed with case management.

Abdominal ultrasonography as a useful diagnostic aid was first described in 1994,[25] followed up with comprehensive reports in 1995 and 1996.[21] [23] The ultrasonographic findings correlated with histopathology findings from confirmed cases, which proved hypoechoic nodules to be normal or slightly regenerated liver remnants and the echogenic strands to be remnant fat laden degenerate hepatocytes and condensation of pre-existing reticulin stroma.[21] [23] Operator expertise plays a role in observing the slightly nodular appearance of the liver contour. The latter is much easier to see if ascites is present in which case the nodular appearance would be highlighted by the surrounding anechoic fluid. Liver pathology implicated in HCS includes hepatic cirrhosis and phenobarbitone toxicity.[10] Ascites has never been described in the classic HCS cases. If a small hyperechoic liver is seen in the presence of ascites, then liver cirrhosis must be a consideration. HCS secondary to phenobarbitone hepatotoxicity did not have classical honeycomb or Swiss cheese-like appearance but rather diffusely increased echogenicity, often with ascites. These dogs had changes compatible with cirrhosis and fibrosis on histopathology.[10]

 Liver cytology in the current case indicated hepatocellular hyperplasia was present, as large pieces of hepatic parenchyma were aspirated so that bilayered hepatic plates were seen. The vacuolar change was minimal, which is consistent with the mild hepatopathy present.

Histology would have been more useful in this case, as cytology is limited in terms of being able to accurately assess hepatic architecture.

Triple-phase CT angiography has become a mainstay imaging procedure in the diagnosis of many abdominal disorders to distinguish a variety of neoplastic conditions and vascular anomalies, particularly within the liver.[26-32] The liver has a dual blood supply, the hepatic artery and the portal vein with the latter supplying the bulk of the blood flow and oxygenation of the liver parenchyma. In the unanaesthetised dog, the portal vein contributes about 80% of the hepatic blood flow whereas in man during abdominal surgery portal vein contribution was about 74%.[33] [34] The hepatic artery primarily nourishes the liver framework, vessel walls and biliary system,[35] whereas the portal vein predominantly nourishes the hepatocytes. This is put to good effect by imaging the varying blood flow phases. In HCS non-contrast enhanced CT images, no internal liver structures can be distinguished except for hypoattenuating hepatic veins and the gall bladder is seen as a relatively hypoattenuating structure. However, on careful scrutiny, the peripheral nodular appearance can be seen. The hepatic arterial phase, imaged before any contrast reaches the portal system, allows visibility of some intrahepatic arteries and veins with no further distinction of other tissues due to the small volume the artery contributes to hepatic flow. The portal venous phase allows contrast enhancement of normal liver tissue and thus allowing the hepatic nodular pattern to be seen relative to the under-perfused collapsed hepatic stroma. In the perfusion phase, the stroma is relatively hyperperfused to the normal hepatic tissues, which now only receives a low concentration of contrast via the portal vein, thus allowing greater visibility of the stroma.

Distinguishing CT findings in dogs with cirrhosis and HCS may not be easy and no detailed literature could be found on cirrhosis CT studies. Cirrhosis usually has a smaller liver with extensive fibrosis and when presented clinically, often has ascites present. One CT study in a dog with HCS as a result of hepatic cirrhosis is described but unfortunately lacks descriptions of the CT procedures and no triple phase angiography was performed.[15]

Skin histopathology greatly aided the final diagnosis of HCS in this patient, as the 'red, white, blue' pattern of epidermal changes is virtually pathognomonic for this condition. Histopathology also effectively ruled out pyoderma or allergic skin disease as the cause of the non-specific skin lesions observed clinically. Appropriate therapy could then be implemented, with the cessation of antibiotics and control of pruritus introduced.

Early diagnosis and appropriate treatment are paramount to prevent further deterioration of skin lesions and avoid hepatic failure, which eventually leads to euthanasia. Approximately 87% of dogs suffering from this syndrome are reported to die or be euthanized.[3] Supportive treatments such as antibiotic therapy, analgesia, liver supplements and diet correction, have all been part of therapeutic protocols for HCS. Amino acid infusions 2 weeks apart were included as part of the treatment with a positive response, improving demeanour and skin lesions. Administration of hyperosmolar amino acids containing fluids as was used in this case is preferably administered via central catheters to avoid the likelihood of thrombophlebitis, oedema and cellulitis.[3] Other potential adverse effects to amino acids infusions include the occurrence of thromboembolism, catheter dislodgement, haemorrhage and hepatic encephalopathy. Additionally, there is a significant financial cost intrinsic to the treatment with hospitalisation for at least 8-10 hours and the need for repeat sedation. These were factors that influenced the decision of the client to discontinue treatment after 5 courses of amino acids infusions over a 10-week period. A potential way to circumvent some of the risks is administering a lower concentration infusion readily available (Procalamine 3%, B. Braun), which could be used safely in peripheral vessels, but the volume needed and the administration time to give a similar dosage would be affected by its lower concentration, casting doubts on the benefits of its use. Another alternative would have included the addition of intravenous lipids together with amino acids infusion, which allowed an increase between treatment intervals, from 2 to 6 weeks, and was a successful combination to manage HCS for 24 months in one case study.[22] Excess of dietary protein intake or amino acids infusions could lead to hepatic encephalopathy when the liver function is compromised. Liver function was adequate in our dog and she tolerated the administered treatment well. High-quality moderate content protein was elected as a suitable diet, with the addition of egg yolks after discontinuation of amino acids infusions.

The severity of skin lesions appears to be a negative prognostic indicator in reported cases. Longest survival times have been recorded for dogs without cutaneous lesions or with less aggressive clinical signs.[4] The skin lesions were milder at the time of presentation in this case study, which supports the slow or non-progressive nature of the disease. A positive response to our therapeutic protocol resulted in improved skin lesions, which improves

overall patient quality of life which remained good at the time of article submission, 34 weeks after admission.

HCS remains a perplexing disease with challenging diagnostics and therapeutics that carries a poor prognosis. However, the early diagnosis, when clinical signs are still mild, will facilitate management and an improvement in the quality of life and survival time. The addition of advanced diagnostic imaging such as CT can be both supportive for the diagnosis of HCS as well as valuable for ruling out other concurrent pathologies such as neoplasia or a portovascular anomaly. Nonetheless, the authors acknowledge the need for further studies to corroborate the CT features described in this paper.

LEARNING POINTS/TAKE HOME MESSAGES

- Hepatocutaneous syndrome generally affects smaller dogs of middle age, and although typical severe skin lesions often reported, the skin may not always be severely affected.
- The ultrasonographic liver honeycomb or Swiss cheese appearance with the appropriate clinical signs can be pathognomonic for the disease.
- Early diagnosis may positively impact the prognosis if treatment is started promptly.
- Treatment with amino acids infusion and higher quantity and quality protein has been beneficial and has improved lesions and quality of life.
- CT can both help ruling out other potential diseases such as neoplastic or portovascular disease and support the diagnosis of HCS.

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FIGURE/VIDEO CAPTIONS

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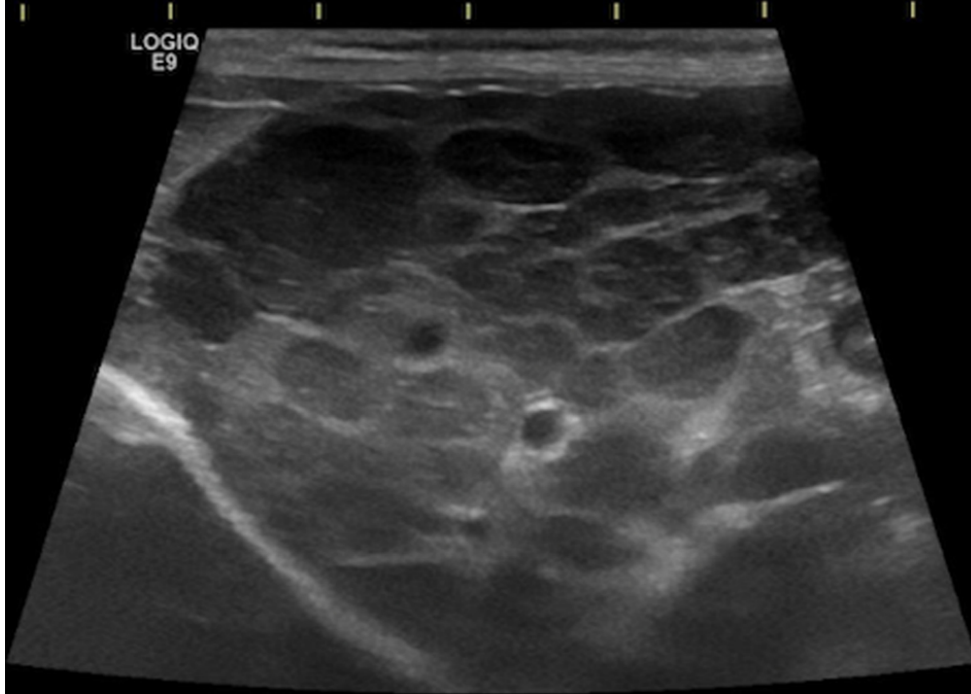
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FIG 1: Transverse ultrasound image of the cranial abdomen illustrating hypoechoic liver nodules surrounded by more echogenic hepatic stroma giving a Swiss cheese-like appearance. The oblique hyperechoic line at the bottom left of the image is the diaphragm-lung interface and the central anechoic circle with echogenic wall is the portal vein.
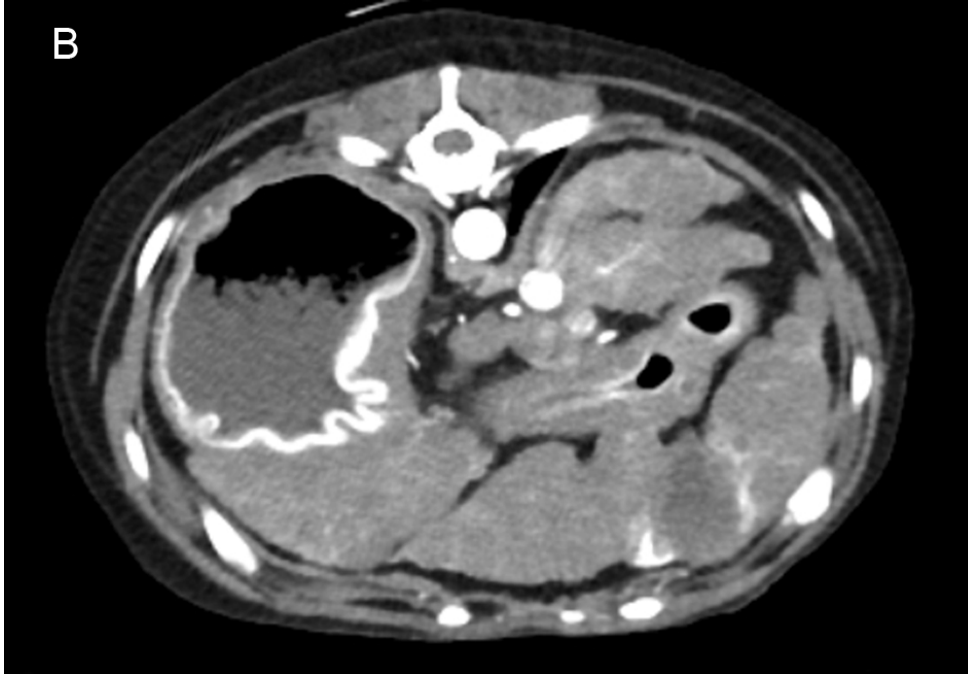
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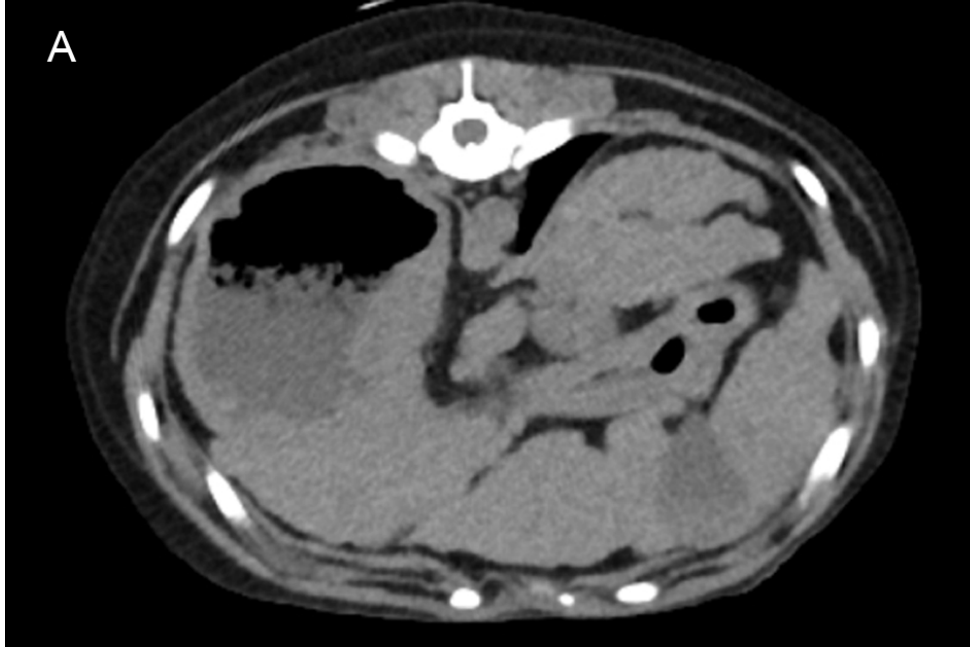
FIG 2: Transverse hepatic CT images of the mid liver in a mediastinal window (WW400; WL 40). The gastric fundus is on the left and the hypoattenuating structure on the bottom right is the gallbladder, (a) Survey (b) Arterial phase (c) Portal-venous phase and (d) Perfusion phase. See text for detailed description.
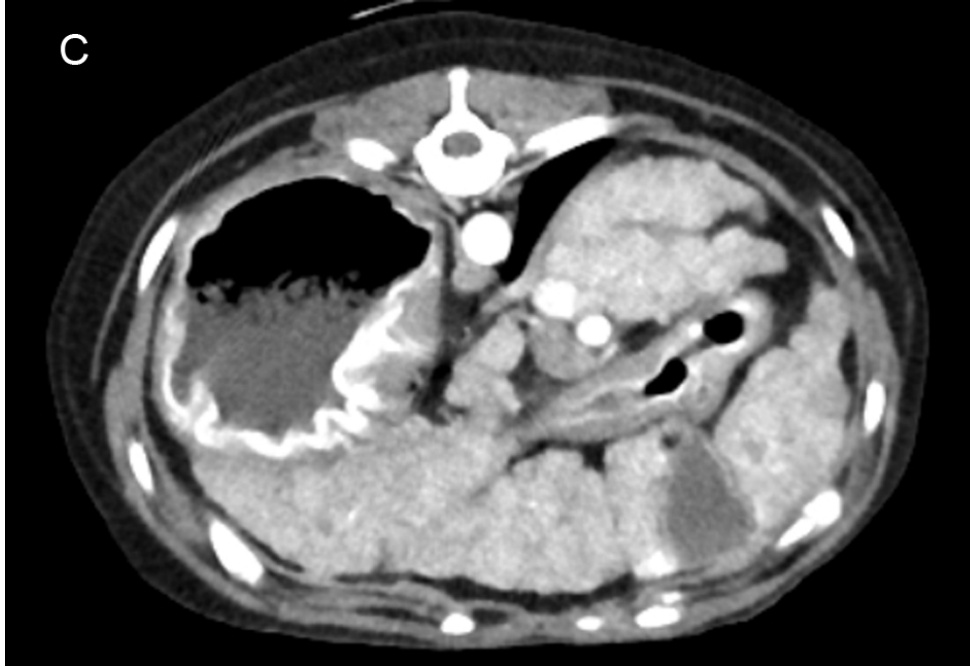
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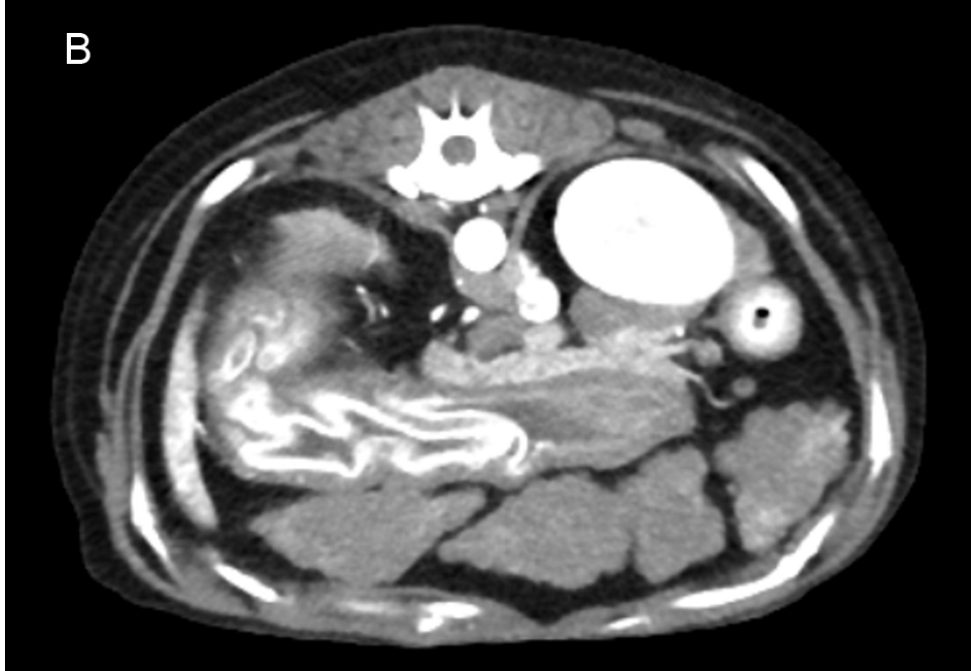
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FIG 3: Transverse hepatic CT images of the caudal liver showing the lobes ventrally in a mediastinal window (WW400; WL 40). The gastric fundus is on the left and right kidney at the top right of the images, (a) Survey (b) Arterial phase (c) Portal-venous phase and (d) Perfusion phase. See text for detailed description.

80x57mm (300 x 300 DPI)

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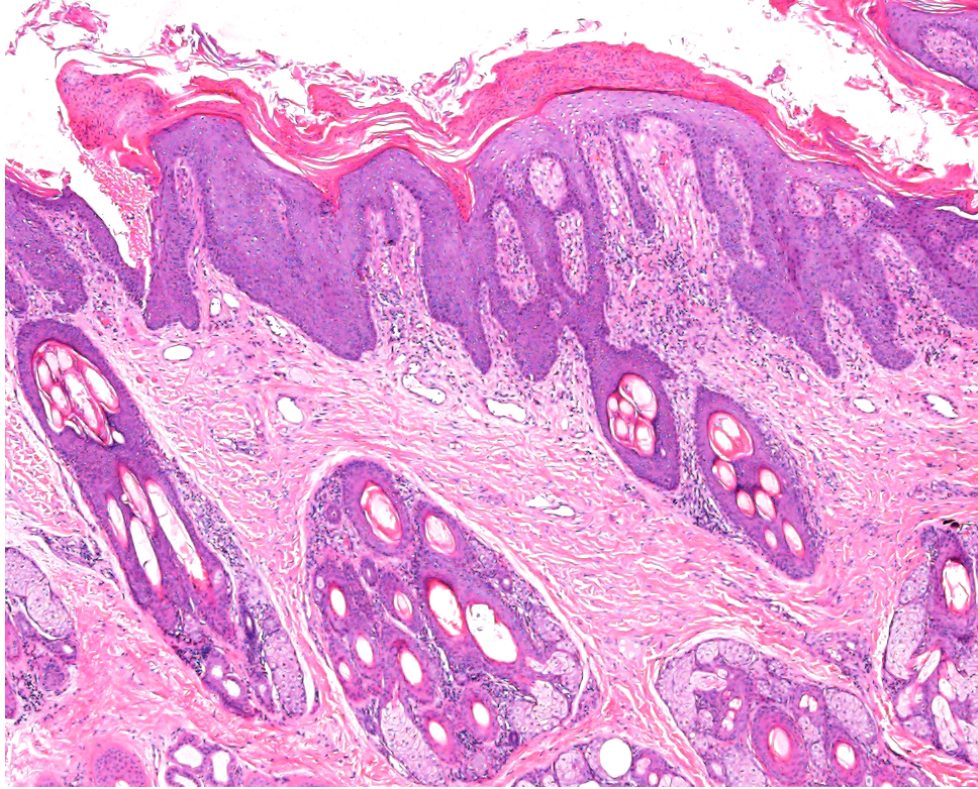
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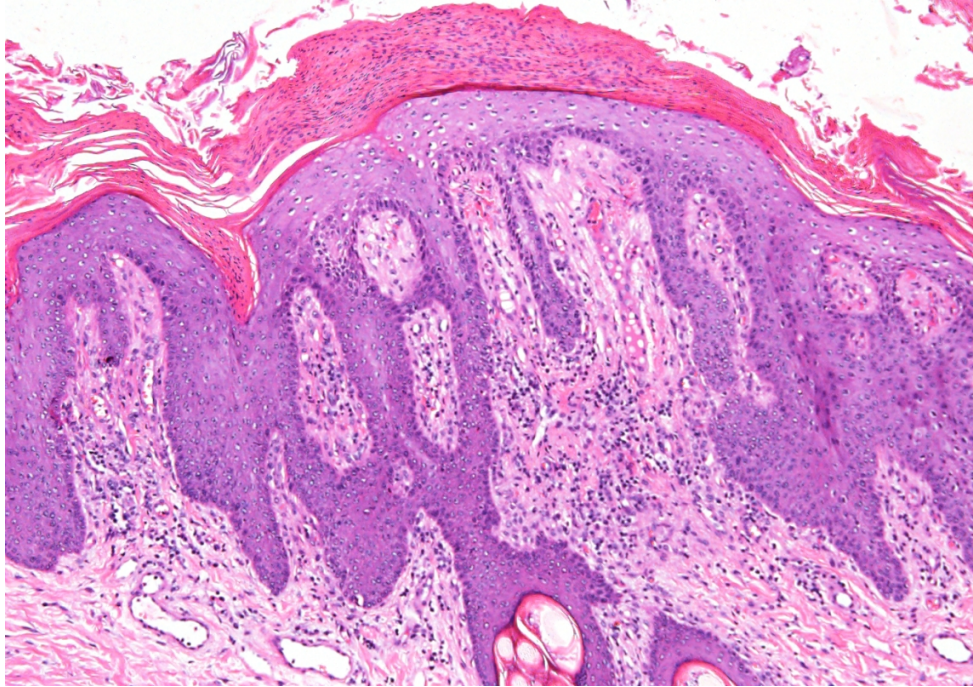FIG 4: Skin from foot pads at margin of haired skin and pad. H and E. x 4 objective.

FIG 5: "Red, white and blue" tissue change; parakeratotic hyperkeratosis (red), spongiosis of stratum spinosum (white) and basal epidermial hyperplasia (blue). Superficial dermis has mild, perivascular, lymphocyte rich inflammation. H and E. x 10 objective.