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Review

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Superficial Necrolytic Dermatitis: First Case Report in Indonesia and A Literature Review

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ABSTRAK

Superficial necrolytic dermatitis adalah kondisi langka yang diderita oleh anjing berusia lanjut. Ini adalah penyakit fatal dimana gejala kulit yang muncul berasal dari liver dan/atau pankreas. Studi kasus ini dibuat untuk melaporkan sebuah kasus, dari pendekatan dan protokol terapi dari kasus superficial necrolytic dermatitis. Biopsi kulit dilakukan, dan hasilnya ada pola patognomonik khusus yang dikenal sebagai "*red-white-blue*". Ultrasonografi menunjukkan adanya bentukan ireguler hipoekoik berbentuk pola nodular dan parenkim kasar dengan ukuran bervariasi, dari bulat hingga oval. Nodule ini dikelilingi oleh sekumpulan bentukan untaian tipis bersifat hiperekoik. Pola ini dikenal dengan pola "*Honeycomb/Swiss-Cheese*" Dari temuan ini, diagnosis superficial necrolytic dermatitis sudah bisa ditegakkan. Pasien diterapi dengan kombinasi infus asam amino, suplemen liver, dan makanan berprotein tinggi. Sayangnya, pasien meninggal dunia empat bulan setelah diagnosis ditegakkan. Para praktisi harus paham bahwa Gejala kulit bisa merefleksikan abnormalitas pada organ dalam.
Kata kunci: anjing, superficial necrolytic dermatitis, liver, infus asam amino

ABSTRACT

Superficial necrolytic dermatitis is a rare condition that affects older dogs. It is a fatal disease in which dermatologic signs stem from an abnormality of the liver and/or the pancreas. This paper aims to report a case workup and treatment protocol of superficial necrolytic dermatitis in a patient that presented with lameness. A skin biopsy was performed, and revealed a pathognomonic "red-white-blue" pattern. Abdominal ultrasonography revealed a severe irregular hypoechoic shape nodular pattern and coarse parenchyma with variable size from round and oval. The nodules were surrounded by network of thin hyperechoic strands, forming a "honeycomb/ Swiss cheese-like" pattern. From these findings, a diagnosis of superficial necrolytic dermatitis was made. The patient was treated with a combination of amino acid infusion, liver supplement, and a high-protein diet. However, the patient only lived for four months after diagnosis was made. Clinicians need to be aware that dermatologic lesions may be a manifestation of internal or systemic disease.
Keywords: dog, superficial necrolytic dermatitis, liver, amino acid infusion

INTRODUCTION

The skin is the largest organ in the body. It serves a lot of functions, from protection to a marker of internal organ abnormalities (Miller *et al.*, 2013). There are several skin diseases in which dermatologic manifestations are a sign of more serious problems with an internal organ, which could be fatal if left undiagnosed. General practitioners should be able to recognize these particular medical conditions in order to provide timely and life-saving or life-prolonging treatment. One example of such condition is Superficial Necrolytic Dermatitis (SND), also known as Necrolytic Migratory Erythema (NME).

SND is a rare and fatal condition that affect mostly older dogs. This disease is associated with endocrine neoplasia (most commonly pancreatic tumor), especially in humans. In animals, however, it is mostly associated with liver disease, hence this disease is also known as "Hepatocutaneous syndrome (HCS)" (DeMarle *et al.*, 2021). The clinical features most commonly noted by owners prior to presentation are dermatologic signs. Glucagonoma is the most reported as the major inciting problem (Kunovsky *et al.*, 2022; Tolliver *et al.*, 2018).

This article aims to report a typical case of SND, along with the clinical work-up, treatment, and outcome. We also aim to review the current literature of this disease for Indonesian general practitioners.

CASE PRESENTATION

Signalment and history

An 11.5-year-old male intact Samoyed presented for an acute-onset lameness and reluctance to walk. This occurred for the first time about two months prior to presentation, and since that time the dog spent most of his time in sternal recumbency. Heavy crusts over the pawpads appeared at the same time as the lameness began. The patient was still eating normally, and there were no other signs of systemic illness. Prior to the onset of the paw pad crusting the patient was very active, and the onset of lameness was quite acute. Four months before time of presentation, he underwent a surgery for a mass near his anus, which revealed to be a malignant mass (biopsy records and diagnosis unavailable). He was being treated with Albumin capsules, a herbal medicine of unknown name which was supposedly used for anti-neoplastic purposes, and an antibiotic ointment. The ointment seemed at first to dry up the paw lesions, but these recurred shortly thereafter. He had no history of previous skin disease. He was primarily indoor and was on a diet of oatmeal and dry dog food (salmon and chicken and pork combination). He was not on any flea and tick prevention.

Physical examination and clinical findings

There was a very severe and thick crust covering the entire paw pad of all digits of all four feet (Figure 1). A very severe interdigital erythema of all four feet was also noted. Both sides of Quadriceps muscle were mild to moderately atrophic. Oral exam abnormality includes severe dental tartar, with no erosion/ ulceration noted. All mucocutaneous area were normal.

Differential diagnoses

Based on history and clinical signs, differential diagnoses included: Superficial necrolytic dermatitis, pemphigus foliaceus, and cutaneous lymphoma. Skin biopsy was required to differentiate between these diseases.

Diagnostics

Skin cytology (impression method) from the paw pads revealed cocci around 20-50 per high power field. A rapid antibody test for Canine Distemper was negative. Complete blood count (CBC) and blood chemistry results are displayed in Figures 2 and 3.

Histopathology findings (Figure 4) revealed the following changes: the stratum corneum was severely parakeratotic. There was significant edema over the stratum granulosum, along with severe epidermal hyperplasia, forming a "Red-white-blue" pattern from superficial to deep in the epidermis. The basement membrane zone was normal. The dermis had diffuse interstitially distributed neutrophils.

Abdominal ultrasonography revealed a severe irregularly shaped nodular pattern of coarse parenchyma with variably size round and oval hypoechoic nodules. The size of these nodules ranged from 0.2 to 0.8 cm, and they were distributed diffusely in all liver lobes. The nodules were surrounded by network of thin hyperechoic strands, forming a "honeycomb/ Swiss cheese-like" pattern. (Figure 5)

Diagnosis

Based on the pathognomonic histopathology findings, a diagnosis of superficial necrolytic dermatitis was made. Along with the ultrasound result, we concluded the underlying cause of the SND stemmed from the liver issues.

The owner was advised of the grave prognosis of the condition. Intensive supportive care, either in the home or hospital was strongly recommended.

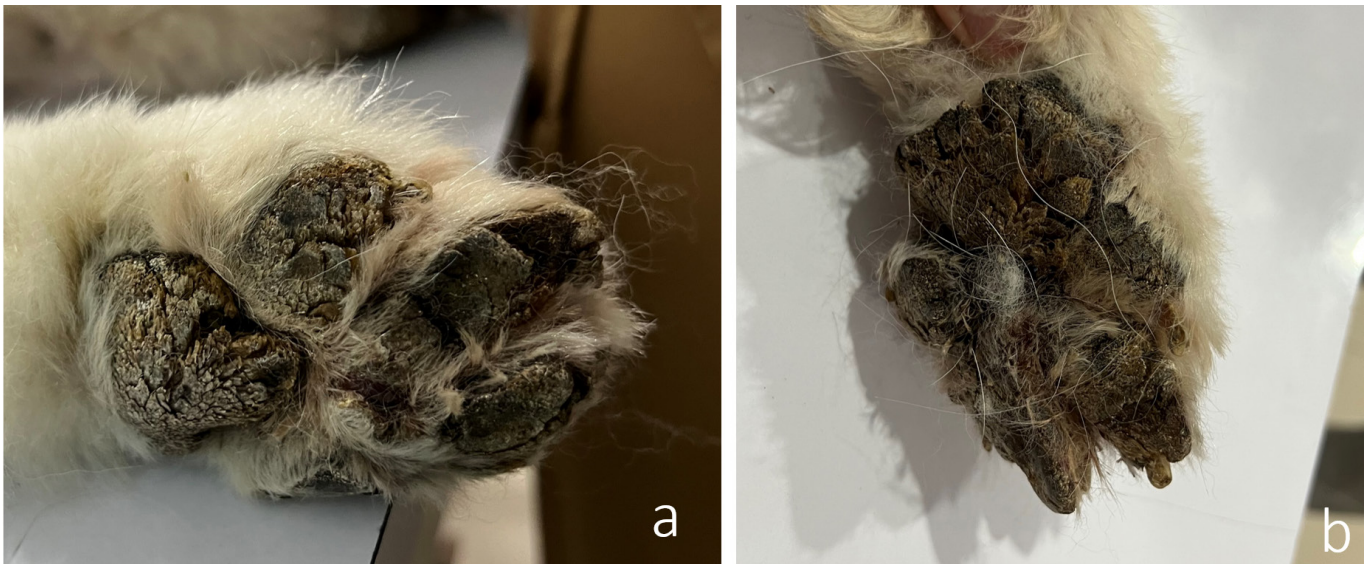

Figure 1 Clinical pictures of the patient on the initial visit. (a) Note the 3rd digit paw pad was partially sloughed off (b) Note the hyperkeratosis, fissures, and ulcerations of the entire paw pads.

	RESULT	LOW	NORMAL	HIGH
WBC White Blood Cells	18.15 10^9/l	HIGH	6.0	17.0
LYM Lymphocyte	2.94 10^9/l		1.0	4.8
MON Monocyte	0.82 10^9/l		0.2	1.5
NEU Neutrophil	14.06 10^9/l	HIGH	3.0	12.0
EOS Eosinophil	0.24 10^9/l		0.0	0.8
BAS Basophil	0.08 10^9/l		0.0	0.4
LYM% Lymphocyte (%)	16.2 %			
MON% Monocyte (%)	4.5 %			
NEU% Neutrophil (%)	77.5 %			
EOS% Eosinophil (%)	1.3 %			
BAS% Basophil (%)	0.5 %			
RBC Red Blood Cells	5.76 10^12/l		5.5	8.5

	RESULT	LOW	NORMAL	HIGH
HGB Hemoglobin	10.2 g/dl	LOW	12.0	18.0
HCT Hematocrit	31.93 %	LOW	37.0	55.0
MCV Mean Corpuscular Volume	55 fl	LOW	60.0	77.0
MCH Mean Corpuscular Hemoglobin	17.7 pg	LOW	19.5	24.5
MCHC Mean Corpuscular Hemoglobin Concentration	31.9 g/dl		31.0	39.0
RDWc Red Blood Cell Distribution Width, Coefficient of Variation	19.8 %		14.0	20.0
RDWs Red Blood Cell Distribution Width, Standard Deviation	39.8 fl			
PLT Platelet	276 10^9/l		165.0	500.0
MPV Mean Platelet Volume	9.7 fl		3.9	11.1
PCT Plateletcrit	0.27 %			
PDWc Platelet Distribution Width, Coefficient of Variation	41.4 %			
PDWs Platelet Distribution Width, Standard Deviation	19.4 fl			

Figure 2 Complete blood count (CBC) results

Treatment and outcome

Treatment plan consisted of SAMe supplementation (Samylin® for large breed) one capsule once daily, Zinc sulfate 220 mg once daily. Dietary plan per day consisted of 175 grams of chicken breast twice daily, two pieces of boiled egg white, and 150 grams of sweet potato. The owner was also advised to bring the patient in for an IV amino acid infusion once a week. Chlorhexidine 4% was prescribed to clean the paw pads.

Two months after the diagnosis, on recheck exam, the owner reported the dog was doing well at home. Due to the owner's perception, previous recommendations including the amino acid infusion, supplements, and dietary plan were not followed. Upon examination, the thick crust over the paw pads had worsened, as had the muscle atrophy of both quadriceps. There were diffusely distributed epidermal

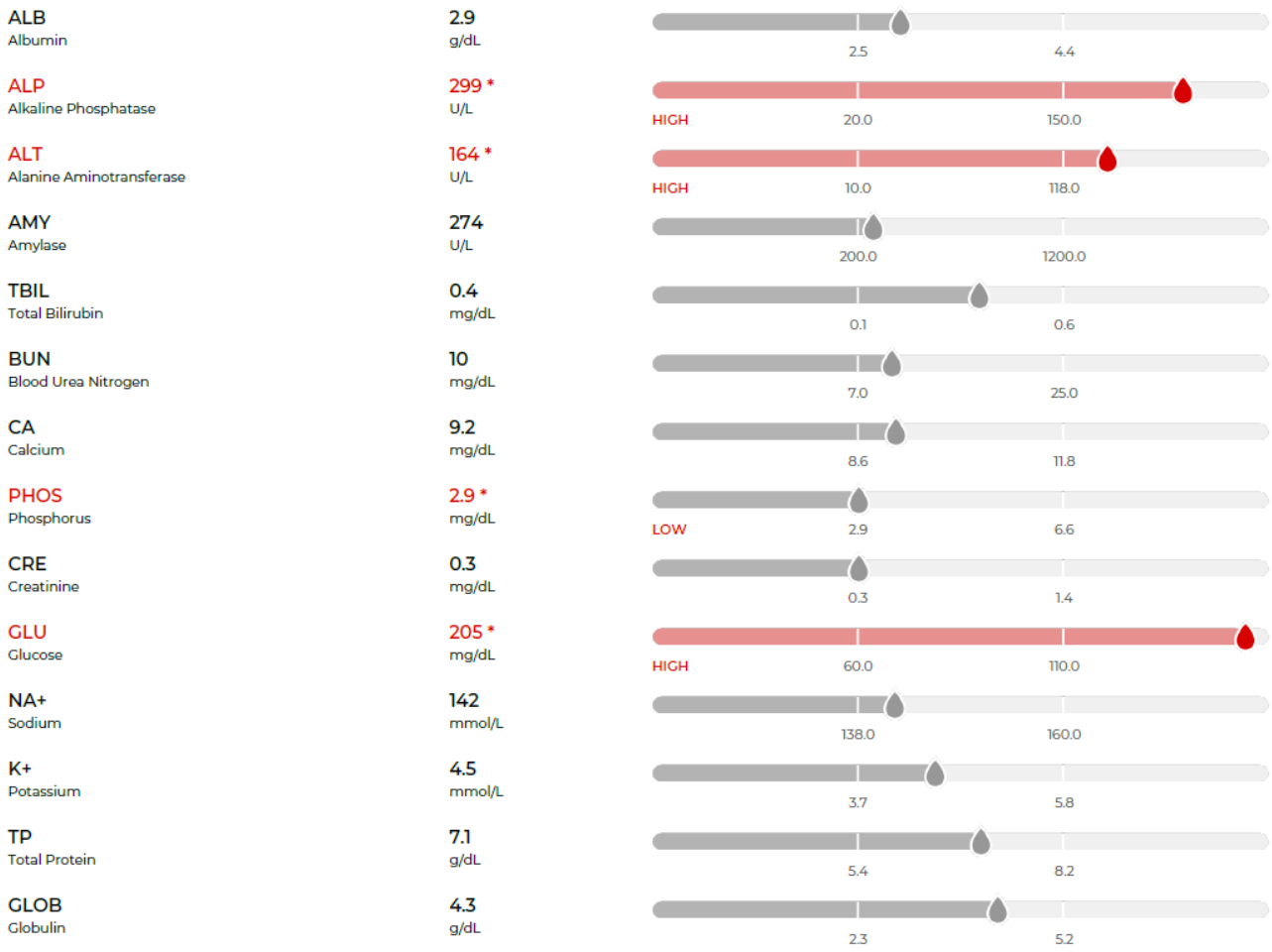

Figure 3 Blood chemistry results

collarettes over the back legs as well as severe erythema over the scrotum and ventral abdomen with a pungent smell suggestive of urine scald. Overall, the dog appeared much worse compared to the first visit.

The owner agreed to try an amino acid infusion on the following day. The dog was given 500 mL of Amino acid fluid (Viamin®) intravenously over eight hours. Contents of the infusion are displayed in table 1. The infusion was performed once weekly for three weeks. By the third week after the infusion, the dog was in lateral recumbency and was refusing to eat. The patient was referred to the other clinic for an intensive care. Unfortunately, the patient died a day after the hospitalization presumably from the liver failure.

Table 1 Amino acid infusion bag content details for each 100 mL

Composition	Amount
L-arginine HCl	85 mg
Sodium Glutamate	136 mg
L-Histidine HCl	34 mg
L-Leucine	136 mg
DL-Isoleucine	68 mg
L-Lysine HCl	102 mg
L-Methionine	34 mg
DL-Phenylalanine	102 mg
L-Threonine	68 mg
DL-Trypthopan	34 mg
DL-Valine	170 mg
L-Cysteine	34 mg
Thiamine HCl	10 mg
Riboflavin Sodium Phosphate	4 mg
Pyrridoxine HCl	0.1 mg
Cyanocobalamin	5 microgram

DISCUSSION AND LITERATURE REVIEW

Case discussion

In our case, the diagnosis of superficial necrolytic dermatitis was made based on a combination of bloodwork, histopathology, and ultrasound. Despite

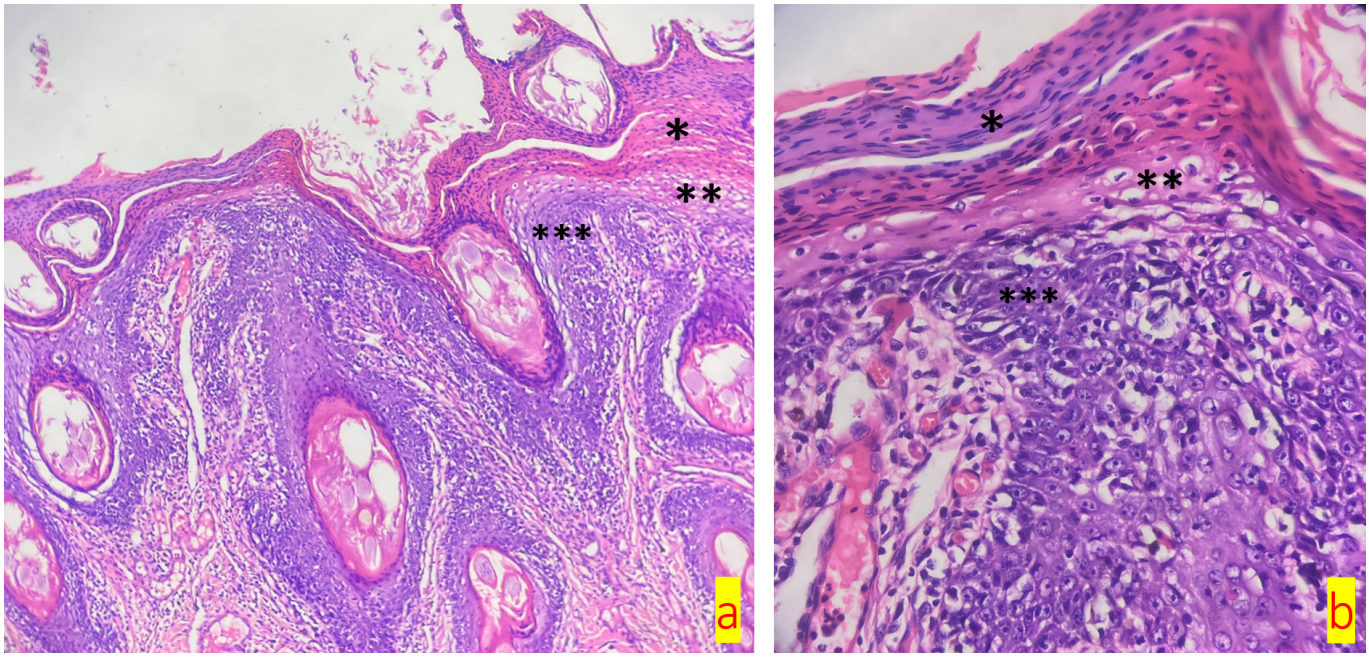

Figure 4 Histopathology findings: (a) On 10x magnification. Note the epidermis is severely parakeratotic, along with the epidermal edema and hyperplasia. (b) On 40x magnification.

This pattern represents the "French flag" pattern, i.e., Red-White-Blue pattern
* Severe parakeratosis symbolizes the "red"
** Epidermal edema symbolizes the "white"
*** Hyperplastic epidermis symbolizes the "blue"

its rarity, this disease has been well-described in the literature, and all of our diagnostic findings in this case are considered classic or textbook for this disease.

It was very unfortunate that the owner did not start any treatment until two months after the diagnosis. While the prognosis for this disease is poor/grave, a proper treatment plan could have extended the lifespan of the patient, and improved his quality of life. In this case, the patient died about four to five months after the diagnosis was made. The reported lifespan for this condition was around four months (DeMarle *et al.*, 2021). In our patient, the lifespan is longer. It was unclear why the owner did not pursue treatment as soon as possible after the diagnosis was made, but it was assumed due to financial constraints, labor-intensity of the treatment, the owner's disbelief of the diagnosis, or a combination of the above.

Literature review Etiopathogenesis

As described in the introduction, SND is a condition with cutaneous clinical signs associated with either pancreas or the liver, with liver being the most commonly affected organ in dogs (DeMarle *et al.*, 2021). In our case, there was an elevation of ALT and ALP, which indicated liver may be the major organ affected, although in rare cases, gallbladder coud show an elevated ALT as well. However, there is also an increase in blood glucose. While this may indicate diabetes mellitus, repeated blood glucose on the following day was within normal limits, leading to the interpretation that the initial hyperglycemia was artifactual, secondary to a post-prandial blood draw.

There are several inciting causes of SND. Chronic phenobarbital use has been associated with development of liver abnormalities (March *et al.*, 2004). Another liver pathology that has also been implicated in this disease is Cooper-associated hepatitis (Talbot *et al.*, 2023). Idiopathic causes have been also reported.

Regardless of the pathology of the underlying internal organ(s), almost all dogs display dermatologic signs, which may be due to amino acid deficiencies. As shown in a retrospective study, it was reported that dogs affected with SND often have persistent hypoaminoacidemia and aminoaciduria (Loftus *et al.*, 2022). Another study noted low plasma amino acid concentrations, including for alanine, arginine, asparagine, citrulline, glutamine, lysine, methionine, ornithine, proline, serine, and threonine (Hall-Fonte *et al.*, 2016).

This condition commonly affects older dogs. A

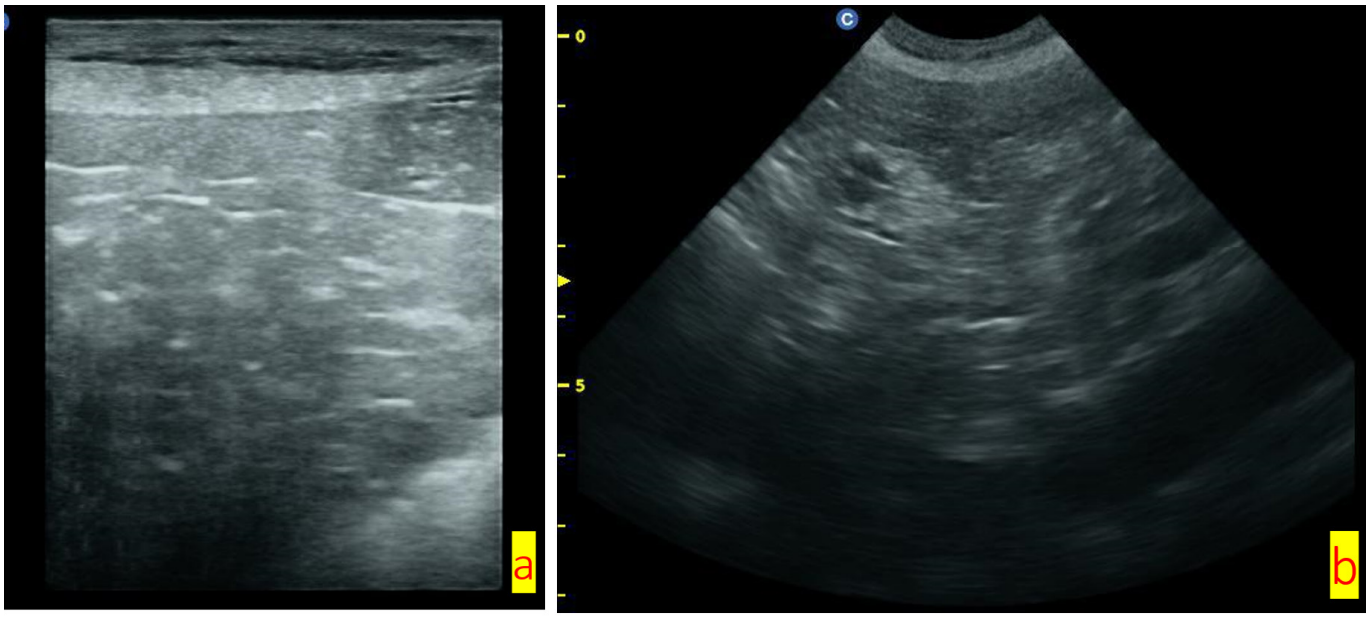

Figure 5 Ultrasound of the liver: Abdominal ultrasonography revealed a severe irregularly shaped nodular pattern of coarse parenchyma with round and oval hypoechoic nodules. These ranged in size from 0.2 to 0.8 cm and were distributed diffusely in all liver lobes. The nodules were surrounded by network of thin hyperechoic strands, forming a "honeycomb/ Swiss cheese-like" pattern. (a) Sagittal plane view of the liver from the ventral midline showing characteristic "Honeycomb" characteristic n the left liver. (b) Sagittal plane view of the liver from the ventral midline showing characteristic oval masses (hypoechoic nodules) of varying size found in the right liver.

retrospective study reported that the median age of affected dogs is eight years old (Hall-Fonte *et al.*, 2016). No sex predilection is noted (Hall-Fonte *et al.*, 2016). There are some breed predilections reported in several studies, including Labrador Retrievers, Shih Tzus, Beagles, Cocker Spaniels, and German Shepherds (DeMarle *et al.*, 2021; Hall-Fonte *et al.*, 2016)

In humans, the terminology NME is more commonly used, and glucagonoma is the most common underlying cause (Kunovsky *et al.*, 2022). While uncommon, there have been reports of SND in dogs associated with glucagonoma or diabetes mellitus (Isidoro-Ayza *et al.*, 2014). In some cases, the inciting cause is idiopathic, where both of the liver and the pancreas are normal (Isidoro-Ayza *et al.*, 2014).

Clinical signs

Paw pad hyperkeratosis and/or fissures are the area most common lesions seen. Indeed, in an older study, 21 out of 22 dogs were affected on the paw pads (Gross *et al.*, 1993). A newer literature review revealed similar result, in which 23 out of 24 dogs (96%) had lesions on the paw pads (DeMarle *et al.*, 2021). Other than the paw pads, mucocutaneous junctions (i.e., vulvar, anal, oral, prepuce) are also commonly affected. In the same study, almost half (46%) of dogs had lesions over the mucocutaneous zones. In our case, the mucocutaneous junctions were not affected.

With the paw pads being fissured/ulcerated, lameness and reluctance to walk is commonly seen, which may be the first sign that the owner notices at home. Lateral recumbency can be seen in severe cases. In our case, the first sign that the owner noted was dorsal recumbency and inability to walk with four feet. The owner never noticed the paw pads were abnormal until the dog was brought to the clinic. Other clinical signs are nonspecific, including lethargy, inappetence, weight loss (Hall-Fonte *et al.*, 2016).

Diagnostics

Several historic and diagnostic findings can raise the index of suspicion for SND, including gross appearance of the paw pads, plasma hypo aminoacidemia, and the honeycomb-like pattern to on abdominal ultrasound (DeMarle *et al.*, 2021). However, not every SND case woill have all features mentioned above.

In a study, the most common hematologic abnormalities for dogs with SND are microcytosis and low PCV (Hall-Fonte *et al.*, 2016). A report found out there is no significant difference of bloodwork result of SND dogs with and without skin lesion (Hall-Fonte *et al.*, 2016), although SND without skin lesion is

extremely rare.

Blood chemistry changes are also noted in SND. The most common changes include increases in serum ALP, alanine aminotransferase (ALT), aspartate amino transferase (AST), and -gamma-glutamyltranspeptidase (GGT) (Hall-Fonte *et al.*, 2016).

Histopathology is required for final diagnosis. Histopathologic features of SND are highly pathognomonic, and are dubbed the "French Flag", or "Red-White-Blue" pattern. Red represents parakeratosis on the stratum corneum of the epidermis. White represents intracellular and extracellular edema on the epidermis, while blue represents hyperplastic epidermis. In some cases, keratinocyte apoptosis has been also reported as a finding (DeMarle *et al.*, 2021; Gross *et al.*, 2005; Gross *et al.*, 1993; Outerbridge *et al.*, 2002).

Hepatic ultrasound may reveal the characteristic honeycomb-like pattern to the liver parenchyma (DeMarle *et al.*, 2021; Jacobson *et al.*, 1995). A liver biopsy may be needed further to investigate the liver's condition. Several hepatic abnormalities noted in this disease include degenerative glycogen or microvesicular lipid vacuolation (Hall-Fonte *et al.*, 2016).

Treatment options

Several treatments have been attempted for this condition, including Protein powder, eggs, S-adenosyl methionine (SAMe), vitamin E, Zinc, Fatty acids, and oral Glutamine (DeMarle *et al.*, 2021). However, most reports used a combination of therapy instead of a single medication. Therefore, it may be difficult to discern which medication or supplement works best.

Intravenous amino acid and lipid infusion has been long used for SND. In multiple reports, this treatment resulted in clinical remission for six to 24 months (Bach & Glasser, 2013; Jaffey *et al.*, 2020; Outerbridge et al., 2002).

As previously mentioned, glucagonoma can also be associated with SND despite its rarity. In a report, Octreotide, a somatostatin analogue, has been used to treat one dog successfully for a month before the dog was euthanized (Oberkirchner *et al.*, 2010). In a case of copper-associated hepatitis, copper-chelation has been successfully used to treat SND in one dog (Talbot *et al.*, 2023).

Prognosis

Prognosis for SND is grave, in which based on several reports, the median survival time is around 82 days, ranging from 3 to 1267 days post diagnosis (DeMarle *et al.*, 2021). This prognosis may be due to the liver and metabolic failures. In our case, the dog died four months after the diagnosis, with the first two months was untreated. To have a better outcome, it is strongly advised to initiate treatment as soon as possible when the diagnosis is made.

In conclusion, general practitioners should be aware that dermatologic lesions may indicate much more than simple allergies or pruritus. Instead, they may reflect underlying pathologies of internal organs in urgent need of proper treatment. In the case of superficial necrolytic dermatitis, it is important to know that secondary infection may make the lesions worse, therefore it should be controlled, when present.

Indonesian general practitioners are advised to perform complete bloodwork especially in older animals suffering from a skin condition. Referral or an online consultation should be made when the patient is not responding to the empirical medications. This will ensure an even greater veterinary care for our patients in Indonesia.

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