https://doi.org/10.52973/rcfcv-e34495 Revista Científica, FCV-LUZ / Vol. XXXIV, rcfcv-e34495

Pancreatic panniculitis and glomerulopathy in a Pomeranian dog Clinical case

Paniculitis pancreática y glomerulopatía en un perro Pomerania Caso clínico

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ABSTRACT

A 10-year-old Pomeranian with chronic ulcerative and bullous lesions, that did not respond to previous treatment with amoxicillin, cephalexin, levothyroxine and trilostane, was presented. A primary immune-mediated process was suspected on examination, and multifocal superficial pyoderma was identified. A skin biopsy revealed panniculitis of pancreatic or sterile nodular origin. Further tests confirmed that the dog had ongoing pancreatitis and glomerulopathy. Ultrasonography revealed enlargement of the pancreatic tissue and hyperechogenicity. Treatment with cyclosporine, tetracycline, niacinamide and omega-3 for 8 weeks resulted in a favorable response. However, 4 weeks after clinical improvement of the skin, the dog suddenly became paraplegic and lost deep nociception. Spinal cord compression type Acute Non-compressive Nucleus Pulposus Extrusion (ANNPE) was suspected, but could not be confirmed. This case documents the presentation of pancreatic panniculitis in a Pomeranian and the concomitant occurrence of possibly associated glomerulopathy and spinal cord trauma.

Key words: Steatitis; pancreas; canine; glomerulopathy; ANNPE

RESUMEN

Se presenta el caso de un pomerania de 10 años de edad con lesiones ulcerosas y ampollosas crónicas, que no respondieron al tratamiento previo con amoxicilina, cefalexina, levotiroxina y trilostano. En la exploración clínica se sospechó un proceso inmunomediado primario y se identificó pioderma superficial multifocal. Una biopsia cutánea reveló paniculitis de origen pancreático o nodular estéril. Las pruebas paraclínicas confirmaron que el canino padecía pancreatitis y glomerulopatía. La ecografía reveló agrandamiento del tejido pancreático e hiperecogenicidad heterogénea del parénquima. El tratamiento con ciclosporina, tetraciclina, niacinamida y omega-3 durante 8 semanas dio lugar a una respuesta favorable. Sin embargo, 4 semanas después de la mejoría clínica de la piel, el paciente quedó súbitamente parapléjico y perdió la nocicepción profunda. Se sospechó una compresión medular del tipo "extrusión aguda no compresiva del núcleo pulposo", más no pudo confirmarse. Este caso documenta la presentación de paniculitis pancreática en un Pomerania y la aparición concomitante de glomerulopatía posiblemente asociada y traumatismo medular.

Palabras clave: Esteatitis, páncreas, canino, glomerulopatía, hernia de disco intervertebral

Received: 24/07/2024 Accepted: 14/09/2024 Published: 23/12/2024

INTRODUCTION

Panniculitis is the inflammation of subcutaneous fat, a condition of low prevalence in canines with multiple clinical associations. Clinically, it is characterized by subcutaneous nodules, focal or multiple, distributed classically over the trunk, with draining tracts ("melted cysts"), that cause mild pain, fever, lymphadenopathy or findings of systemic disease at physical examination. Nodules may ulcerate and drain an exudate (oily, yellow, brown or bloody) or scar with crusts and fibrous tissue. Fat inflammation can be triggered by infections (bacteria, fungi, or atypical mycobacteria), immune-mediated conditions (lupus, erythema nodosum, or vasculitis, arthropod bites), trauma (ischemia or chronic pressure), neoplastic conditions (multicentric mastocytoma, cutaneous lymphoma, or pancreatic tumor), nutritional deficiencies (vitamin E deficiency, excess of polyunsaturated fatty acids), drug reactions (vaccines, corticosteroids), or unknown reasons [1, 2, 3, 4, 5, 6, 7, 8].

Pancreatic panniculitis can lead to abnormal test results such as leukocytosis (neutrophilia and left shift or eosinophilia), anemia, and elevated levels of alkaline phosphatase, lipase, amylase, trypsin or hyperlipemia. Blood tests and ultrasound scans can help diagnose pancreatitis. Classic cases of pancreatitis may also include hypoglycemia, hypocalcemia, and hypoalbuminemia [2, 7]. Confirmation of diagnosis involves a biopsy and culture to determine sterile or contaminated panniculitis with a secondary infection [2].

Treatment options for skin lesions include surgical removal or antimicrobial therapy combined with immunosuppressants, tetracyclines, niacinamide, and vitamin E [2]. Recovery usually takes 3–6 weeks although it could take longer. However, the prognosis for pancreatic causes is poor due to high recurrence and progression rates [1, 5, 9].

MATERIALS AND METHODS

Case description

A 10-year-old Pomeranian dog (*Canis lupus familiaris*) with chronic skin disease and hormonal imbalances was presented at the Veterinary Clinic of La Salle University in Bogotá. Six months ago, the patient had a lesion on the ventral tail region, which later spread to the dorsal region. The ulcerous-crusted lesion then extended to the skin of the thorax and neck. The patient also experienced severe itching, blisters, and bullae, which became ulcer and scab lesions. The patient had been treated with oral ampicillin and cephalexin (unknown dose) with chlorhexidine shampoos during the illness period, however, the response was only partial and inconsistent. Also, the dog had been diagnosed previously with hypothyroidism and hyperadrenocorticism (based on reduced total T_4 and free T_4 hormones and cortisol more than 1.4 $\mu g \cdot dL^{-1}$ at 8 hours in a low-dose dexamethasone suppression test performed at another veterinary center) but did not respond accordingly to levothyroxine and trilostane.

On physical inspection, physiological constants were within normal ranges; blood pressure was 152/108 (137) mmHg (SunTech Vet20 Veterinary Blood pressure Monitor, Miami, USA). Dermatologic inspection revealed bilateral hypotrichosis, symmetrical extended to all four limbs, with perineal and tail alopecia, multifocal hyperpigmentation (accentuated in the perineal region) accompanied by erythema, desquamation and epidermal collarettes with pustules and bullae generating severe pruritus (FIG. 1). There were secondary lesions to the pruritus, with multifocal petechiae and ecchymosis as well as scabs and scars. Skin biopsy was performed under local anaesthesia and amoxicillin/clavulanic acid at 12.5 $mg \cdot kg^{-1}$ every 12 hours (h) for 28 continuous days (d), amitriptyline 3 $mg \cdot kg^{-1}$ every 12 h for 28 continuous d and enalapril at 0.25 $mg \cdot kg^{-1}$ every 12 h, plus topical cleaning of lesions with chlorhexidine and cream with neomycin/bacitracin and zinc oxide. Nutraceuticals like omega 3, and vitamins A, and E were also given.

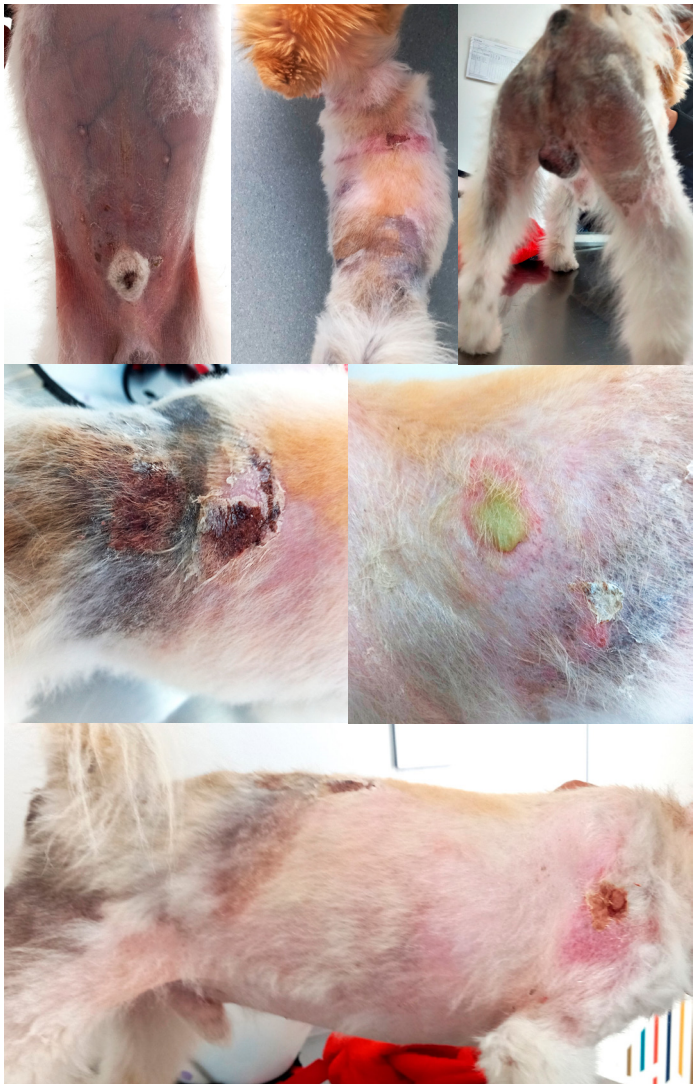

FIGURE 1. Appearance of the skin of a canine with pancreatic panniculitis before treatment

RESULTS AND DISCUSSION

The results of the paraclinical examinations performed on the patient during the diagnostic approach are presented in TABLE I.

The ultrasound findings showed that there were structural changes in the kidneys, liver, and pancreas (Vinno D650, Veterinary model, Suzhou, China). The pancreas had increased echogenicity and a larger size on the right branch. The liver had mild hepatomegaly and reduced differentiation of portal wall visualization. The kidneys showed less

TABLE I
Paraclinical examinations of a 10–year–old, entire male Pomeranian canine with chronic presentation of ulcerative, crusty, blistering, pustular lesions, and symmetrical truncal alopecia

Parameter	Pre–treatment value	Post–treatment value	Unit of Measurements	Reference range
Erythrocytes	7.4	7.07	10^9 cells·µL^{-1}	5.4 – 7.8
Haemoglobin	16	14.3	g·L^{-1}	13 – 19
Haematocrit	52	46	%	37 – 54
Leukocytes	13.6	14.6	10^3 cells·µL^{-1}	6 – 17
Neutrophils	11.2	13.1	10^3 cells·µL^{-1}	3 – 11.5
Lymphocytes	1.4	0.7	10^3 cells·µL^{-1}	1 – 4.8
Monocytes	0.8	0.4	10^3 cells·µL^{-1}	0.1 – 1.4
Eosinophils	0.3	0.3	10^3 cells·µL^{-1}	0 – 0.9
Platelets	237	934	10^3 cells·µL^{-1}	160 – 430
Plasma proteins	5.5	6.4	–	6 – 7.8
Blood biochemistry				
Albumin	–	2.7	g·dL^{-1}	2.3 – 4.0
Globulins	–	5.3	g·dL^{-1}	2.1 – 4.5
ALT	–	158	U·L^{-1}	5 – 125
FA	–	209	U·L^{-1}	17 – 212
Creatinine	–	0.59	mg·dL^{-1}	0.27 – 1.07
BUN	–	16.9	mg·dL^{-1}	7 – 27
Glucose	–	126	mg·dL^{-1}	74 – 143
Cholesterol	385	–	mg·dL^{-1}	110 – 350
HDL	256.6	–	mg·dL^{-1}	> 100
LDL	274	–	mg·dL^{-1}	< 50
Triglycerides	85	–	mg·dL^{-1}	21 – 87
Amylase	593		U·L^{-1}	388 – 1007
Pre–treatment pancreas–specific lipase	547.2	937.7	ng·mL^{-1}	< 200 ng·mL^{-1}
Uroanalysis				
Specific gravity	1022	1019	–	>1030
pH	8	7	–	6.5 – 7.5
Crystals	–	–	mg·dL^{-1}	Negative
Cylinders	Hialines +	Hialines +	cylinder/field	< 1
Erythrocytes	0 – 2	1 – 4	cells/field	< 5
Leukocytes	0 – 2	0 – 2	cells/field	< 5
Bacteria	–	+	–	0
Squamous cells	0 – 1	0 – 2	cells/field	< 5
Transitional cells	0 – 1	0 – 2	–	< 5
UPC (inactive sediment)	1.9	11.7	–	< 0.2

cortico–medullary differentiation, hyperechogenicity of the renal cortex compared to the spleen, and irregular contour. Additionally, the adrenal glands were identified with bilateral hyperplasia but had a normal sonographic appearance (FIG. 2).

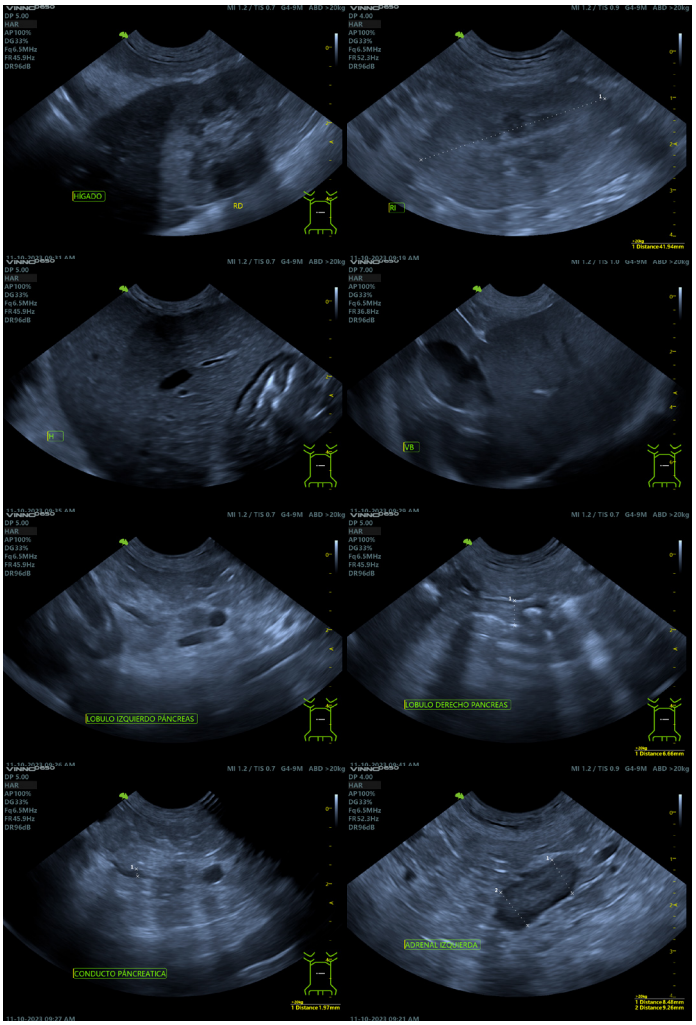

FIGURE 2. Ultrasound images of kidneys, liver, pancreas and adrenal glands of canine with pancreatic panniculitis

The cutaneous tissue was taken with punch biopsy (biopsy punch 8 mm, India). The report indicated severe bleeding in the hypodermis, with multiple eosinophilic areas of amorphous material (lipid saponification) surrounded by PMN, along with adipose tissue necrosis. Intralobular PMN infiltration in the adipose tissue and interstitial infiltration in the superficial and deep dermis were present. The epidermis was normal, with atrophy of appendages, and the presence of hair follicles in the telogen phase. There were areas of bleeding in the superficial and deep dermis. The final diagnosis proposed was an inflammatory pattern suggestive of panniculitis and a possible association with pancreatic panniculitis or idiopathic nodular panniculitis.

After receiving the biopsy results, it was decided to start a treatment plan for the patient. The plan included cyclosporine at a dosage of 5 mg per kg every 8 h, tetracycline at 250 mg every 8 h, and niacinamide at 250 mg every 8 h. This treatment was continued for 8 weeks and some dietary modifications (low–fat maintenance diet). It was also decided to gradually discontinue trilostane.

After eight weeks of treatment, there was a significant improvement in the quality of the coat, with regrowth in the dorsal, thoracic, and

abdominal regions. There were no more ulcerative, crusty, bullous, or complicated lesions with collars and papules, as shown in FIG. 3. However, there were still some areas with uneven coat growth, such as the cervical, perineal region, and the entire tail. Additionally, there was still generalized desquamation in certain regions like the groin and belly. The canine-specific pancreatic lipase continued to be elevated compared to the initial value, as shown in TABLE I.

During the paraclinical examinations, it was found that the patient had persistent proteinuria, suggesting an ongoing glomerulopathy. As a result, the patient has been classified in IRIS stage I, non-hypertensive proteinuric. Amlodipine 0.1 mg·kg^{-1} every 24 h was added to the iECA therapy to treat his condition. However, due to economic reasons, the owner refused the diagnostic approach to identify the probable cause of glomerulopathy.

FIGURE 3. Clinical evolution of the appearance of the skin of a canine with pancreatic panniculitis 8 weeks after treatment

About four weeks later, the patient started showing symptoms of acute spontaneous trauma in the spinal cord, which led to non-ambulatory paraparesis to paraplegia. The patient also experienced progressive loss of deep sensation within 24 h of the onset of these signs, initial spinal hyperesthesia, urinary retention, and fecal incontinence. Neurological examination suggested a high motor neuron lesion for the hind limbs in the thoracolumbar segment. Radiographs [VIVIX. 2024. Flat Panel for Digital Radiography VIVIX-F. VIVIX Corp. Seongnam, Corea del Sur] did not evidence an abnormality consistent with spinal cord compression from Hansen type I disc herniations, fractures or dislocations of the vertebral bodies (FIG. 4). It was not possible to perform an MRI to rule out or confirm other possible differential diagnoses (fibrocartilaginous embolism). Following the clinical scenario, the owner decided to request humane euthanasia of the animal given the compromise of the patient's future quality of life. Due to the owner's dissent, it was also not possible to perform the necropsy of the patient.

Paniculitis associated with pancreatic disease in dogs is a rare and poorly documented condition. The first post-mortem report in a dog with nodular hyperplasia was made in 1982 [10] and the first ante-mortem report was made in 2003 [1]. It is believed to occur due to the saturation of lipase, amylase, trypsin and/or phospholipase-A in the portal or thoracic circulation, which, upon reaching the systemic circulation, results in vascular hyper-permeability, causing the release of lipids into the extracellular space from inflamed adipocytes. The released lipids undergo hydrolysis to become glycerol and fatty acids that trigger inflammatory events, local piogranulomatous reactions in the subcutaneous space and fat necrosis, given their pro-inflammatory effect [4, 5, 11]. The associated pancreatic conditions have been nodular hyperplasia, chronic inflammation, necrosis, adenoma, and adenocarcinoma/carcinoma [1, 3, 4, 9, 12]. In this case, the panniculitis associated with ongoing chronic pancreatitis was documented through the elevation of canine-specific lipase and ultrasound findings.

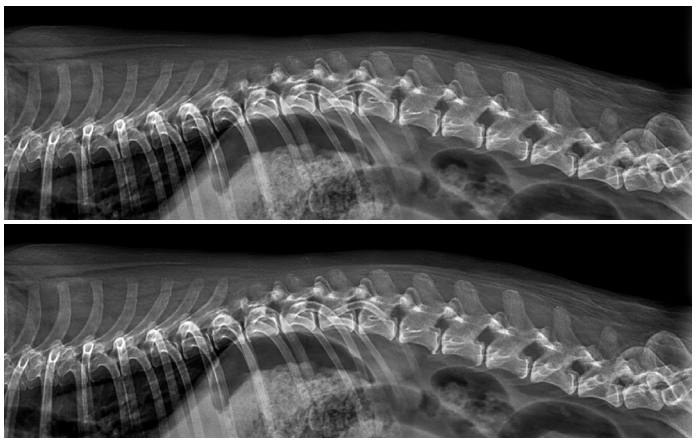

FIGURE 4. Latero-lateral radiographs of the thoracolumbar and lumbar regions in a canine with pancreatic panniculitis and sudden spinal trauma of undetermined origin

In Human Medicine, it has been proposed that the association between pancreatitis and panniculitis may be due to a deficiency of an enzyme inhibitor (alpha–1 antitrypsin) or a reduction in alpha–2–macroglobulin [1, 8, 9]. It has also been documented that the presence of high concentrations of lipase and cytotoxic concentrations of fatty acids in the skin of patients with panniculitis and polyarthritis is one of the triggering factors [9]. However, in canines, the association between alpha–1 antitrypsin has not been confirmed [13], although it is not ruled out as a probable contributing factor [6]. In this patient, the simultaneous occurrence of both diagnoses is suggestive of the disease presentation, and furthermore, the cutaneous therapeutic response to immunosuppression.

Skin biopsy findings were key to the identification of panniculitis. It is recommended to perform a skin culture to diagnose a clinically evident secondary bacterial infection. In addition, a suspicion of mycobacteria causing cutaneous/subcutaneous pyogranulomas and panniculitis (such as *Actinomyces, Nocardia, Blastomyces, Histoplasma, Coccidioides, Cryptococcus, Sporothrix, Aspergillus, Leishmania, Bartonella* and/or mycobacteria) can only be confirmed or ruled out through cultures, differential stains, and respective serologies of each entity. These procedures were not documented in this case [4, 6, 7, 14].

In a study of 14 cases of sterile nodular panniculitis in dogs, it was found that 5 cases (35.7%) had a urinary protein to creatinine (UPC) ratio greater than 0.5 (range 0.9 – 3.61) [7]. This suggests that glomerulopathy may be related to the primary cause of panniculitis. In the same study, 8 of the 14 dogs (57%) had chronic kidney disease caused by protein–losing nephropathy. In human medicine, it is believed that this association is due to the leakage of oxidized lipids, leading to inflammation and fibrosis, or to immune complex–mediated glomerulonephritis.

In the previously mentioned study, 21.4% of dogs were found to have adrenomegaly without any suspected functional adrenal disease [7]. In this patient, despite clinical and paraclinical suspicion, as well as ultrasound findings consistent with hyperadrenocorticism, the comorbidity with panniculitis pancreatic biased the correct diagnosis and increased the probability of a false positive HAC case. The lack of response to trilostane supports this hypothesis. It is worth noting that in this case, the low–dose suppression test with dexamethasone led to a false–positive result, highlighting the need to apply the ACVIM consensus about HAC to minimize the possibility of ambiguous results. The sensitivity and specificity of the test have been estimated to be between 85–100% and 44–73%, respectively [15].

Spinal cord compression caused by idiopathic sterile pyogranulomatous inflammation of the epidural fat has been found in Dachshunds. This condition can lead to paraparesis or paraplegia in these dogs even though there may not be any obvious radiographic abnormalities. Evidence of extradural compression has been found in myelography [16]. The origin of the spinal cord trauma could not be identified in this case. It could be associated with Acute Non–degenerated Nucleus Pulposus Extrusion (ANNPE) or Hydrated Nucleus Pulposus compressive Extrusion (HNPE). Alternatively, it could be due to a fibrocartilaginous embolism [17]. However, a more precise diagnosis cannot be made without MRI data.

Regarding the treatment of panniculitis, previous studies have shown that a single administration of antibiotics does not result in a permanent improvement of cutaneous signs [7, 12, 18]. Therefore, immunosuppression (using glucocorticoids, azathioprine, or cyclosporine) is often used as an additional part of the treatment for pancreatic panniculitis [1, 2, 3, 4, 5, 7, 18]. In this particular case, cyclosporine was chosen as the immunosuppressive treatment after gradually reducing trilostane, having ruled out hyperadrenocorticism. Additionally, the use of corticosteroids is controversial as it may potentially cause chronic pancreatitis, which is why it was not prescribed [19]. According to a report by O'Kell *et al.* (2010), one case achieved the therapeutic success of pancreatic panniculitis once pancreatitis was treated, while seven of eight patients treated with corticosteroids showed improvement [7].

It has been reported that pancreatic panniculitis has responded well to a combination of oral tetracycline and niacinamide. This treatment appears to have an immune–mediated effect, although the exact mechanism is not yet fully understood [2, 4]. Some studies suggest that the combination of tetracycline and niacinamide may suppress leukocyte chemotaxis and leukocyte protease release, which are caused by complement activation from antigen–antibody complexes [20]. Tetracyclines have also been used to treat alpha–1 antitrypsin deficiency related to panniculitis in human medicine [21]. It is believed that this is due to the potential collagenase–inhibitory effect of tetracyclines. In this particular case, doxycycline was chosen due to its efficacy against common Gram–positive skin bacteria (such as *Staphylococcus* spp., including methicillin–resistant S., and *Streptococcus* spp.), and its potential immunomodulatory effects when combined with niacinamide [20].

The selection of ciclosporin as an immunosuppressant for this case was due to its effect on reducing the proliferation of T lymphocytes. This is achieved through blocking the transcription of cytokines, particularly IL–2. Additionally, ciclosporin has anti–inflammatory and cytostatic effects on leukocytes, Langerhans cells, and keratinocytes [20].

CONCLUSIONS

In conclusion, pancreatic panniculitis is a condition that is not well–known in dogs. The case study presented here is of a canine with chronic pancreatic panniculitis who partially responded to immunosuppressive therapy but developed severe glomerulopathy and spinal cord trauma. It is suspected that there may be a link between panniculitis and glomerulopathy and/or spinal cord trauma.

Conflict of interest

The case report was conducted without any potential conflict of interest.

Role of the authors

PB: case analysis, methodology, research, writing, reviewing and editing. IC: case analysis, methodology and reviewing. The authors declare that no ethical or legal standards were omitted in this research.

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