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CASE REPORT

Peripheral Eosinophilia in a Confirmed Case of Canine Acute Eosinophilic Dermatitis with Edema (Wells-Like Syndrome)

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Abstract: This case report describes a peripheral eosinophilia in a dog diagnosed with canine acute eosinophilic dermatitis with edema (CAEDE). A 1-year-old female spayed Terrier Mix canine presented as a referral from their primary care veterinarian for gastrointestinal signs that were recently treated, but ongoing, and a new dermatopathy. Her leukogram revealed an eosinophilia, not previously present at the onset of her gastrointestinal signs, and skin biopsies were consistent with diagnosis of CAEDE. Although the definitive cause of the development of CAEDE in this patient is ultimately unknown, the patient made a full recovery following treatment with corticosteroids over a three-week treatment course. To the authors' knowledge, this is the first report of a confirmed diagnosis of CAEDE to present with peripheral eosinophilia on complete blood count (IDEXX Procyte Dx).

Keywords: CAEDE, WLS, gastroenteritis, dermatopathy, metronidazole, eosinophil

Introduction

Canine acute eosinophilic dermatitis with edema (CAEDE) is an uncommonly reported dermatopathy in dogs.[1–4] This condition manifests most commonly in patients with a reported recent history of moderate to severe gastrointestinal disease that subsequently develop dermatologic lesions.[1] Generally, patients most often have gastrointestinal signs initially with progression to dermatologic lesions; however, it does not always have to be in this order, or the signs can occur concurrently.[2] In these patients, gastrointestinal disease includes acute vomiting, diarrhea and hematochezia with most patients having a history of being treated in some capacity for their clinical signs.[1,2] This condition can be challenging to diagnose as the cutaneous manifestations vary, the co-occurrence of gastrointestinal and dermatologic clinical signs is not commonly encountered and the reported cases of this condition appear to be rare.[1]

Traditionally, diagnosis of this disease process is based on clinical suspicion and is confirmed or supported via skin biopsy results.[1] Histologically, this disease process is characterized by an eosinophil-heavy granulocytic infiltrate of the skin.[3] The presence of a greater proportion of eosinophils on histopathology samples is the key factor in differentiating CAEDE from other types of dermatopathies, mainly sterile neutrophilic dermatosis (Sweet-like syndrome).[3] No other clinicopathologic findings have been established in veterinary medicine to help guide the clinician to a diagnosis.

In canine reports of this condition, these patients have not had an eosinophilia on leukogram and the focus has been on the eosinophilic infiltration on histopathology.[4] This case report details peripheral eosinophilia attributed to the biopsy-confirmed diagnosis of canine acute eosinophilic dermatitis with edema in a canine patient with recent gastrointestinal signs treated with metronidazole.

Case Summary

A 1-year-old female spayed Terrier Mix weighing 3.38 kg was referred to a tertiary referral hospital for evaluation of gastrointestinal signs and secondary skin lesions. The patient originally presented to the referring veterinarian eight days

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prior for a two-day history of vomiting, diarrhea and anorexia. Owner started to feed a bland diet at onset of clinical signs with no success in improvement of signs. Physical exam during this visit revealed moderate dehydration and tense abdomen on palpation. During this visit, bloodwork (IDEXX Procyte Dx, IDEXX Catalyst One) was performed revealing mild hemoconcentration, Hct 61% (reference interval: 37.3–61.7%) and slight eosinopenia, 0.05K/uL (reference interval: 0.06–1.23 K/uL). An in-house CPL (IDEXX Snap CPL) was performed and revealed to be abnormal. Outpatient medical management was performed with the patient receiving 100mL subcutaneous fluids (LRS) and 1mg/kg maropitant citrate (Cerenia, Zoetis) administered subcutaneously. For treatment of her underlying clinical signs, she was discharged from hospital with maropitant citrate (Cerenia, Zoetis) 12mg per os every 24 hours, metronidazole (Ayradia, Vibrac) 35mg per os every 12 hours, sucralfate (Carafate, Nostrum Lab Inc). 0.5g per os every 8 hours for 5 days, and Proviable-Forte paste/capsule kit (Nutramaxx) 1–2mL per os every 12 hours for 3 days, then give 1 capsule per os or sprinkled on food every 24 hours until gone.

The patient re-presented to the referring veterinarian five days later for hematochezia, regurgitation and continued anorexia. Physical exam revealed mild dehydration and a tense but non-painful abdomen on palpation. A Chem8 (Abbott iSTAT) was performed and was unremarkable. A 4Dx (IDEXX Reference Lab, 4DX Plus) was performed and was negative for all. A fecal ova and parasite with giardia panel (IDEXX Reference Lab, Fecal Ova and Parasites with Giardia) was sent out and returned as negative. The patient was hospitalized at this time with the referring veterinarian. Treatments included LRS at 1.5 times maintenance, maropitant citrate (Cerenia, Zoetis) 1mg/kg intravenous every 24 hours, metronidazole (B Braun Medical) 10 mg/kg intravenous every 12 hours, Proviable-Forte (Nutramaxx) 1 capsule per os every 24 hours, carpromorelin (Entyce, Elanco) 3mg/kg per os every 24 hours, and sucralfate (Carafate, Nostrum Lab Inc). 0.5gm tablet per os every 8 hours. During hospitalization, the patient developed circular skin lesions on her ventral abdomen and a crusted, raised pustular lesion on her dorsal cervical region. Clotting times were performed (Idexx Coag Dx Analyzer) and revealed to be normal – PT 11s (reference interval: 11–17s) and PTT 89s (reference interval: 72–102s). The patient's referring veterinarian was concerned for a drug reaction, so all medications were discontinued, and she was started on diphenhydramine (Armas Pharmaceuticals) 2.2mg given once intramuscularly prior to referral. The patient developed a soft heart murmur during her hospitalization, suspected to be secondary to intravenous fluid administration. CBC and Chemistry (IDEXX Procyte Dx, IDEXX Catalyst One) were performed revealing a new moderate eosinophilia, 2.11 K/uL (reference interval: 0.06–1.23 K/uL) and an improved hematocrit, 42.3% (reference interval: 37.3–61.7%). Her gastrointestinal signs subsided, and she was subsequently discharged on diphenhydramine HCl (Vetadryl, PRN Pharmacal), mupirocin ointment 2% (Muricin, Dechra), Douxo Calm Serum Spray (Ceva) and Douxo Pyo Shampoo (Ceva). The night of discharge it was noted that her stool quality improved with no hematochezia and she ate a bland diet well. The morning after discharge, clinical signs reoccurred – vomiting, regurgitation and anorexia. At this time the primary care veterinarian referred the patient to a tertiary referral hospital for continued workup and hospitalization for her gastrointestinal and dermatologic signs.

On presentation to the referral Emergency Service, the patient was mildly dehydrated, had raised ulcerated papules along her dorsal cervical and thoracic region and had light pink macules on her ventral abdomen (see Figures 1–3). Complete blood count (IDEXX Procyte Dx), chemistry (IDEXX Catalyst One), venous blood gas (Siemens Healthineers) and clotting times (IDEXX Coag Dx Analyzer) were performed revealing mild eosinophilia, 1.58K/uL (reference interval: 0.06–1.23K/uL), but otherwise unremarkable. A complete blood count was sent out to the laboratory (IDEXX Reference Laboratory), which confirmed her present eosinophilia at 1.61 K/uL (reference interval: 0.07–1.49K/uL). An abdominal ultrasound was performed with a boarded veterinary radiologist due to persistent gastrointestinal signs revealing small intestinal altered wall layering with normal thickness, hypoechoic normal size jejunal lymph nodes and bilateral hyperechoic renal medulla. For further investigation of her dermatologic changes, she has a culture and sensitivity of the affected regions (IDEXX Aerobic and Anaerobic Culture and Sensitivity) and two punch biopsies of the skin were performed on presentation and sent out for pathologist review (VDx Veterinary Diagnostics). The patient was hospitalized on NormR at maintenance, maropitant citrate (Cerenia, Zoetis) at 1mg/kg intravenous every 24 hours for nausea, ampicillin sodium/sulbactam sodium (Unasyn, Eugia US LLC) at 30mg/kg intravenous every 8 hours for treatment of skin lesions while biopsies and culture results were pending, and gabapentin (Neurontin, Avet Pharmaceuticals) at 10 mg/kg per os every 8 hours for pain control. The patient did well in hospital with

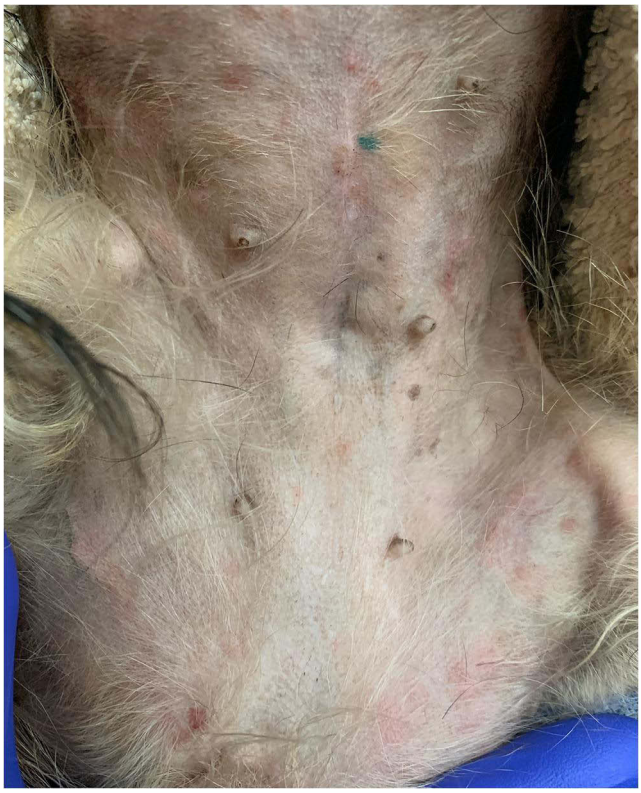

Figure 1 Lesions on presentation to the referral hospital. This image is of the patient's ventral abdomen where there are lesions that appear as macules and are target-like in appearance.

no vomiting or diarrhea noted overnight and eating well each time food was offered to her. Her dermatologic lesions were subjectively static, so she was discharged the following day. She was sent home with maropitant citrate (Cerenia, Zoetis) 8mg per os every 24 hours as needed for nausea, gabapentin (Neurontin, Avet Pharmaceuticals) 50mg per os every 8–12 hours as needed for patient discomfort, amoxicillin trihydrate/clavulanate potassium (Clavamox, Zoetis) 62.5mg per os every 12 hours while pending diagnostics results, and diphenhydramine HCl (Vetadryl, PRN Pharmacal) as previously prescribed by the referring veterinarian. The owners were instructed to discontinue the ointment, medicated spray and medicated shampoo until the biopsy results return.

Three days after discharge the pathologist report returned noting perivascular to diffuse interstitial eosinophilic dermatitis with marked amounts of edema and abundant numbers of eosinophils and few histiocytes extending down into the subcuticular fat. The pathologist conclusion was as follows: severe, acute diffuse interstitial to perivascular eosinophilic dermatitis and panniculitis with marked edema, and rare eosinophilic vasculitis (suspect CAEDE). Based off these results and her recent history of gastrointestinal signs, a diagnosis of CAEDE was concluded. Due to this she was prescribed prednisolone (PAI Pharma) at 1mg/kg per os every 24 hours until recheck. Her culture and sensitivity results returned with no growth the following day.

The patient was rechecked twelve-days post-discharge for suture removal. The owners noted that the patient had no further gastrointestinal signs and skin lesions were resolving. On physical exam the lesions appeared to be healing with crusts forming across the previously impacted regions and no further pustules were appreciated. At this point the patient was currently receiving prednisolone (PAI Pharma) at 1mg/kg per os every 24 hours. Given patient response but residual dermatologic lesions, the treatment course was extended, and it was recommended owner to continue same dose until otherwise directed. The patient was rechecked again twenty days post-discharge for evaluation of dermatologic lesions (see Figures 4–5). Physical exam revealed healed skin lesions with minimal desquamation. At this time her prednisolone (PAI Pharma) was weaned to 0.5mg/kg per os every 24 hours for seven days, then 0.5mg/kg per os every 48 hours for seven days, then stopped. Patient

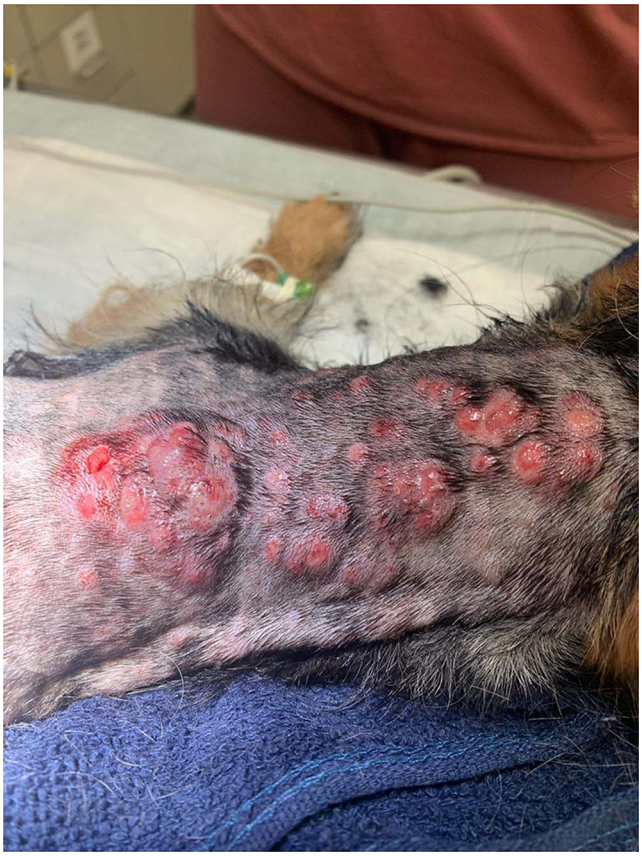

Figure 2 Lesions on presentation to the referral hospital. This image is of the patient's dorsal thorax and cervical region where there are raised and moist papules present. The patient's hair was shaved to evaluate the extent of the lesions and to allow for punch biopsies to be obtained.

tolerated wean and no further concerns were noted. The patient made a complete recovery and there has been no recurrence of gastrointestinal or dermatologic signs at time of writing this paper.

Discussion

This is the first report describing a case of peripheral eosinophilia secondary to canine acute eosinophilic dermatitis with edema (CAEDE or Wells-like syndrome). CAEDE is an uncommonly diagnosed dermatologic syndrome encountered in veterinary medicine.[1,2,4] It was first described in canine patients in 1999, when Holm et al published a case series of nine dogs that presented with acute onset of erythematous arciform to serpiginous plaques with edema on the pinnae and ventral surfaces of the abdomen and thorax.[4] Skin biopsies revealed profound eosinophilic dermal infiltrates, focal areas of collagen fiber degeneration surrounded by eosinophils, dilated vessels and dermal edema.[4] This disease process is referred to as Wells-like syndrome because it shares similar clinical features with the human syndrome, Wells syndrome, or eosinophilic cellulitis.[2–4] Wells syndrome is a rare human dermatosis of both eosinophilic and granulomatous cellulitis that was first described in the 1970s.[3,5] In a 2012 case series by Sinno et al it was found that 67% of human patient's diagnosed with Wells Syndrome had peripheral eosinophilia on bloodwork.[5] An eosinophilia on leukogram has not been previously reported in canine patients.[4] Our patient did not present with a peripheral eosinophilia, but this emerged with the onset of dermatologic lesions (Table 1). This suggests that a peripheral eosinophilia may be a clinical finding in dogs with Wells-like syndrome similarly to human patients with this condition and may help clinicians to recognize this condition earlier in the course of disease to help direct additional diagnostics, such as skin biopsy, and treatment.

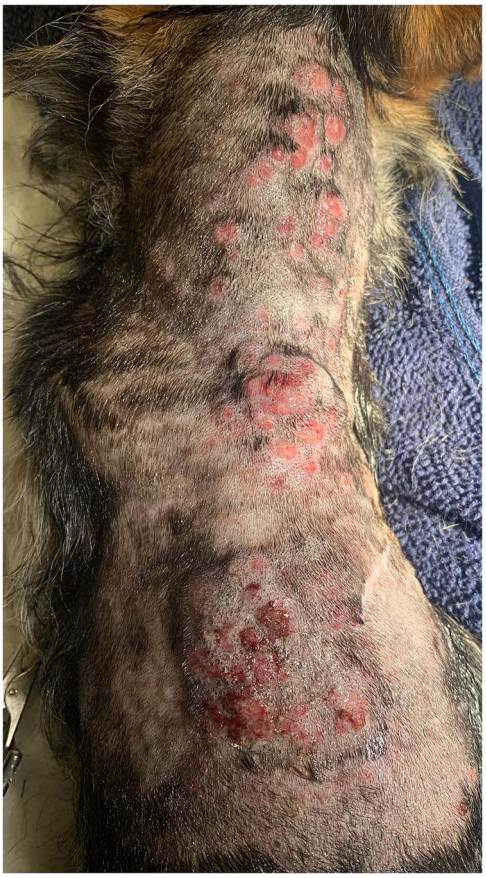

Figure 3 Lesions on presentation to the referral hospital. This is an additional image of the patient's dorsal thorax and cervical region from another angle where you can again see the raised and moist papules present. The patient's hair was shaved to evaluate the extent of the lesions and to allow for punch biopsies to be obtained.

Canine patients who are diagnosed with CAEDE have a history of gastrointestinal signs including vomiting, diarrhea and hematochezia with progression to dermatologic lesions, but this can vary with dermatologic lesions appearing prior to gastrointestinal signs or both occurring concurrently.[2] In a 2006 retrospective study, Mauldin et al, documented an association of CAEDE with gastrointestinal disease.[6] In this study twenty-two of twenty-nine dogs were treated for vomiting and/or diarrhea.[6] Of these patients, seventeen developed skin lesions prior to gastrointestinal upset and five patients developed skin lesions concomitantly.[6] Common factors present in veterinary patients include vomiting, diarrhea, hematochezia, hypoproteinemia, and treatment with multiple medications.[1,2,4] In our case, the patient initially presented to the primary care veterinarian for gastrointestinal signs that were treated with supportive care. There has been some evidence reported that CAEDE may be incited by the use of metronidazole, but there has been no data published to support this claim.[4,6] During the treatment course, this patient was treated with metronidazole for the first seven days of management, which is a commonly used medication in the management of diarrhea and hematochezia. In the previously mentioned 2006 retrospective study, Mauldin et al noted that metronidazole was given to most dogs, but definitive causation could not be proven.[6] The time course of metronidazole use for our patient parallels the findings from the previously mentioned study.

Our patient, after treatment of gastrointestinal disease, developed dermatologic lesions, prompting transfer to a referral hospital for further diagnostics and treatment. There has been a wide range of dermatologic descriptions used for patients diagnosed with CAEDE. These lesions may appear as bright red macules or generalized erythema that is most evident on the glabrous skin of the ventral abdomen.[1,2,4] Additional descriptions of lesions include discrete targetoid (bull's eye) lesions that mimic erythema multiforme and vasculitis, pitting edema or facial edema that resembles urticaria.[1,2,4] In some cases, these lesions may be pruritic.[2,4] Our patient had ulcerated papules on her dorsal thorax and cervical regions with faint macules on ventral abdomen. These

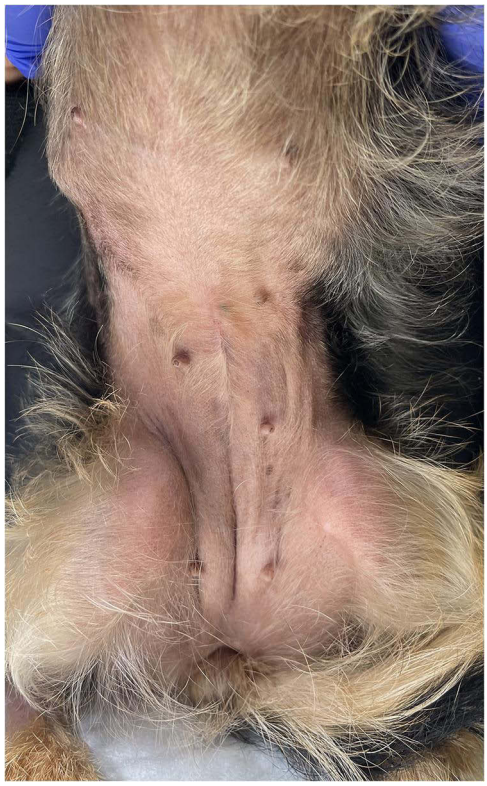

Figure 4 Affected regions at final recheck. This image shows resolution of all ventral lesions that were previously appreciated.

findings are consistent with previous descriptions that CAEDE can present with varying degrees of dermatologic changes, so this disease should be a consideration in the management of acute dermatopathies, especially if a patient is exhibiting gastrointestinal signs.

Diagnosis of CAEDE in these patients has been based on clinical history, physical exam findings and, ultimately, skin biopsy with histopathology of the affected region.[1,2] The aim of this study was to propose that a peripheral eosinophilia in a patient presenting with the clinical signs described previously may serve as a laboratory finding to help guide the clinician to a diagnosis while awaiting the histopathology results. The etiology of this disease process is unknown at this time; however, it is suggested to occur associated with gastrointestinal disease, insect bites, adverse drug or food reactions, and allergic skin disease.[7] It is likely that this syndrome is a manifestation of a systemic type I hypersensitivity reaction.[1] Holm et al proposed that the skin lesions were triggered by hypersensitivity reactions because one of the patients described in their case series developed skin lesions while being treated for giardiasis, but definitive causation could not be established.[4] This is similar to the human, Wells Syndrome, where it is suspected that there are triggers in the development of the syndrome, such as insect bites, viral or bacterial infections, drug eruption, thimerosal-containing vaccines and neoplasia.[5] In this patient, a known trigger was not identified, but given her previous metronidazole exposure, a drug reaction cannot be excluded.

Treatment of this condition usually begins with discontinuation of previously administered medications prior to onset of dermatologic lesions and initiation of supportive care medications for the gastrointestinal signs with gastroprotectants and antiemetics.[1] In this case, the patient's medications were discontinued prior to transport to the referral hospital. Once admitted, the patient was treated with supportive care, pain medications and an antibiotic due to the extent of the present skin lesions. The patient was discharged with an anti-emetic, antibiotic, antihistamine and pain medication. Once diagnosed, the skin lesions should be treated with corticosteroids (prednisone) and antihistamines (diphenhydramine, cetirizine, and hydroxyzine).[1] This patient was prescribed a corticosteroid after histopathology report returned. In patients diagnosed and treated for CAEDE, their

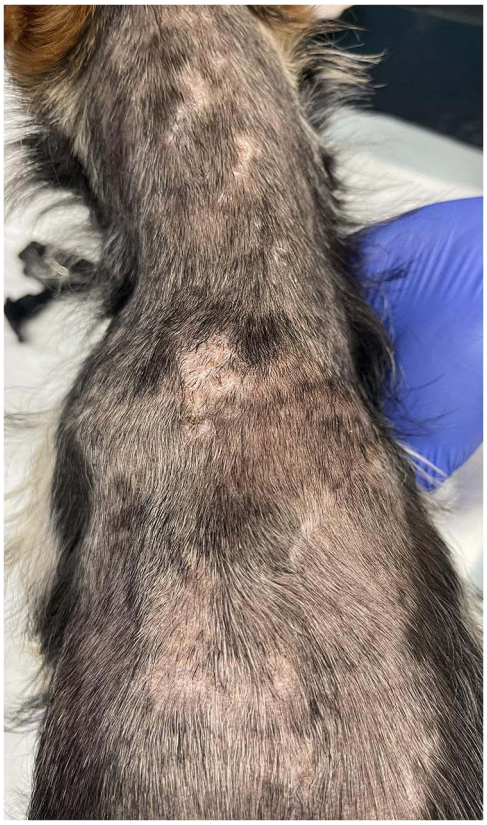

Figure 5 Affected regions at final recheck. This image shows resolution of all raised and moist papules. There are small areas of alopecia present where the larger clusters of papules previously were, dermis is completely healed with minimal scar tissue.

gastrointestinal signs will resolve first in about one week and the skin lesions will resolve second in about three weeks.[1,2] Following discharge, this patient's gastrointestinal signs had resolved, and the skin lesions resolved over a three-week period with corticosteroid treatment. The patient was treated with prednisolone (PAI Pharma) at 1mg/kg/d for twenty days. After the patient's recheck appointment at twenty days, where the lesions where healed, the prednisolone (PAI Pharma) was weaned to 0.5mg/kg/d for seven days, then 0.5mg/kg q48h for seven days, and then discontinued. The patient has had no known recurrence of skin lesion since this occurrence.

In conclusion, we provide a case report documenting peripheral eosinophilia secondary to canine acute eosinophilic dermatitis with edema (Wells-like syndrome). This case illustrates the necessity of including CAEDE as a differential in patients with gastrointestinal signs and secondary skin lesions. If concerned for CAEDE, perform a skin biopsy of affected region(s) for confirmation of diagnosis. While waiting for histopathology results, clinicians can use patient history of gastrointestinal signs, dermatologic lesions and, if present, peripheral eosinophilia to help guide diagnosis until results return.

Table 1 Eosinophilia Levels Performed During Clinical Course of Disease

	Day 1	Day 7	Day 8
Eosinophils (reference range 0.06–1.49 K/μL)	0.05	2.11	1.61

Notes: Day 1 = Initial presentation; Day 7= Recheck with referring veterinarian; Day 8 = Presentation to referral center.

Consent for Publication

The owner of the patient was contacted about the publication of the case study, which includes pictures of the patient. Owner consented to publication and provided completed consent form.

Disclosure

The authors report no conflicts of interest in this work.

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