Inflammatory and Immune-Mediated Dermatologic Emergencies in Dogs

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Dermatologic disease commonly prompts dog owners to present their pets to an emergency clinician. Although uncommon, true life-threatening dermatologic emergencies exist, and early recognition is important for long-term survival.

Erythema multiforme (EM) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) are diseases in which keratinocyte cell death causes erosion and/or ulceration. Patients with SJS/TEN have especially extensive lesions where necrosis is a common feature, and the loss of large areas of skin can be life threatening.

Cutaneous vasculitis may alert the clinician to the development of systemic vasculitis and can cause severe lesions, including necrotic lesions at the extremities, ears, and tail tips. Some dogs with vasculitis may be systemically ill, depending on the size and site of the vessels attacked.

Sterile neutrophilic dermatosis (Sweet-like syndrome or SLS) may cause acute development of erythematous skin lesions in association with significant systemic infiltrate. Canine acute eosinophilic dermatitis with edema (CAEDE or Wells-like syndrome) typically presents as the development of acute gastrointestinal signs, followed later by development of erythematous lesions on the skin. Angioedema and urticaria are more common but less likely to be life threatening.

This article outlines the major features of each disease, along with best practices for diagnosis and management in an emergency setting.

Abstract

Emergency clinicians are commonly presented with dermatologic complaints. This article discusses the approach to emergency diagnosis and treatment of uncommon but life-threatening inflammatory and immune-mediated dermatologic diseases, including erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis, and cutaneous vasculitis. Sterile neutrophilic dermatosis (Sweet-like syndrome) and canine acute eosinophilic dermatitis with edema (Wells-like syndrome) are described due to their acute nature and concurrent systemic signs. The more common but less serious conditions of urticaria and angioedema are also described.
Take-Home Points

- Erythema multiforme (EM) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) all involve keratinocyte cell death resulting in loss of the epidermis.
- Drug reactions should be strongly considered in EM, SJS/TEN, and cutaneous vasculitis. Early withdrawal of the drug trigger is needed in conjunction with supportive care to improve clinical signs.
- Compared with EM associated with an identified trigger, idiopathic EM is more likely to become chronic and require immunomodulatory therapies.
- Accurate history and biopsy of nonulcerated lesions are critical to obtain a diagnosis in all of these diseases.
- Canine acute eosinophilic dermatitis with edema should be considered in dogs with acute development of gastrointestinal signs followed by development of erythematous cutaneous lesions.
- Urticaria typically resolves within 1 to 2 days if the trigger is identified and removed; therefore, other differentials should be considered if plaques or papules persist past this time frame.
- Cetirizine may be more effective than diphenhydramine at preventing histamine release in dogs.

ERYTHEMA MULTIFORME AND STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

EM and SJS/TEN are characterized by cytotoxic T-lymphocyte targeting of keratinocytes at all layers of the epidermis. These are considered by some to be diseases along a continuous spectrum in veterinary patients, with EM the mildest, followed by SJS, then TEN; however, others consider canine EM to be a separate disease from SJS/TEN. Clear clinical criteria for diagnosis and distinction of EM and SJS/TEN in veterinary medicine are not yet completely established and are largely adopted from human medicine.

Clinical lesions of EM are highly variable and may consist of ulcers, crusts, and erythematous macules or papules. Central pallor or purpura may be seen, but classic “target” lesions are uncommon. Lesions are often well demarcated and may be polycyclic, arciform, or serpiginous (FIGURES 1 AND 2). Distribution is...
most often truncal, particularly in the axillary and inguinal regions (FIGURE 3). In some cases, lesions may involve mucocutaneous junctions, paw pads, and pinnae (FIGURE 4). Patients with EM may show systemic signs, including fever, anorexia, lethargy, and depression, or their signs may be limited to the skin.

The main clinical feature that defines SJS/TEN is epidermal detachment and necrosis; therefore, affected patients typically have a positive pseudo-Nikolsky sign, in which pressure on the affected erythematous skin causes separation at the dermoepidermal junction. Lesions may initially consist of erythematous or purpuric macules and patches, which become erosions and ulcers after the epidermis detaches. Lesions are often distributed on the trunk, mucocutaneous junctions, and paw pads. Systemic signs are common in SJS/TEN, including anorexia and lethargy or depression. Pain may be associated with the lesions. SJS/TEN is often fatal and is a true dermatologic emergency.

Hinn et al differentiated SJS by epidermal detachment affecting less than 10% of the body surface area, while more than 30% of the body surface area is affected in TEN; however, this allows for some patients to be excluded on the SJS/TEN spectrum (i.e., those that fall between 10% and 30% involvement).

Many cases of EM and SJS/TEN are drug-induced, with drug association more common in SJS/TEN than EM. Careful consideration should be given to any recent medications in cases where EM or SJS/TEN is suspected. Antibiotics have been most commonly implicated, especially sulfonamides, cephalosporins, and penicillins. Diet, vaccination, bacterial infection, and viruses have also been reported as underlying causes of EM.
Early assessment and withdrawal of suspected drug triggers are important for case management, and is especially critical in cases of SJS/TEN. Immunomodulatory therapy is often administered, with rapid glucocorticoid tapers being commonly recommended. Efficacy of immunomodulatory therapy is not yet well established in acute drug-induced disease. Supportive care and pain management should be provided, and hospitalization is recommended in SJS/TEN. Preventing secondary bacterial infection and sepsis is necessary when there are significant areas of ulceration. When EM arises spontaneously without drug involvement, it is more likely to be chronic and may require lifelong management with immunosuppressive medications. Chronic EM may respond to glucocorticoids, azathioprine, modified cyclosporine, mycophenolate mofetil, or oclacitinib.

Biopsy for histopathology should be performed for definitive diagnosis, and samples with intact epithelium should be included. EM and SJS/TEN cannot be distinguished based on histology alone. Histopathologic findings include keratinocyte apoptosis with lymphocyte satellitosis and variable epidermal necrolysis.

Hyperkeratotic EM has also been described and is sometimes referred to as “old dog EM.” This is a chronic EM characterized by plaques and thick adherent crusts and scale (FIGURE 5). Histopathologically, hyperkeratosis and parakeratosis are seen in addition to the apoptotic keratinocytes. Hyperkeratotic EM is more often idiopathic.

Commonly affected locations for acute vasculitis are those with minimal collateral circulation, including the central aspects of paw pads, the distal tail, and pinnal margins.

CUTANEOUS VASCULITIS

Vasculitis refers to an inflammatory or immune-mediated process that targets blood vessels. Hypersensitivity reactions, particularly type II and type III hypersensitivity, are thought to be important to the pathogenesis of vasculitis, with type II hypersensitivity playing the most important role in animals.

Initially, lesions may appear markedly erythematous or purpuric, and diascopy should demonstrate failure to blanch. Edema may also be noted. Diascopy involves pressing a glass slide to an area of reddened skin and evaluating to see whether pressure creates pallor. It should be noted that other causes of bleeding into the skin (e.g., coagulopathy, trauma, EM) can also cause purpura that fails to blanch on diascopy, and these differentials should also be considered.

With time, necrosis may develop and cause ulcers, which can be deep or crateriform (FIGURES 6 AND 7).
Commonly affected locations for acute vasculitis are those with minimal collateral circulation, including the central aspects of paw pads, the distal tail, and pinnal margins (Figure 8). There is a wide spectrum of disease severity. Systemic signs are common in acute vasculitis and may include fever, anorexia, lethargy, and depression. Patients may also be painful, particularly if there is significant ulceration.

These clinical lesions can have several causes, including drug reactions, vaccination, neoplasia, food hypersensitivity, and a wide range of infectious diseases. Many cases are idiopathic and presumed to be immune-mediated. Evaluating for and eliminating any potential triggers are an important part of therapy, and a thorough history should be obtained for the owner, with any recent changes in medication, diet, and environment considered.

Ideally, infectious causes of vasculitis, including vector-borne disease, should be evaluated for, particularly when immunosuppressive therapy is planned. In addition to the minimum database (i.e., complete blood count, serum biochemistry, urinalysis), acute and convalescent titers can be considered for vector-borne diseases. Blood cultures can be considered if sepsis is a differential. Biopsy for histopathology is recommended to confirm clinical suspicion, with a sample submitted for tissue culture if infectious causes are suspected. Samples should be collected from 3 to 5 sites, including early-, mid-, and late-stage disease if available. The panniculus should be included, particularly if there is any nodular or deep character to the lesions on palpation. Ideally, with acute vasculitis, changes to the cutaneous vessels will be noted, and inflammatory cells may be seen infiltrating the vessel wall, with endothelial cell swelling. Local hemorrhage and edema are typically seen due to the vessel wall compromise. Ischemic changes are commonly seen secondary to hypoxia, causing pale or smudgy collagen and faded or atrophic follicles and adnexal units. This description does not apply to cell-poor vasculitis, such as is seen in rabies vaccine reactions; this is a more chronic form of vasculitis resulting in ischemic dermatopathy and is not emergent.

If no trigger or infectious cause is identified, glucocorticoids are often implemented. Initially, anti-inflammatory doses of glucocorticoids can be considered to address the vascular inflammation without significantly increasing the risk of immunosuppression in case of infectious vasculitis. Depending on the level of suspicion for infectious causes, some clinicians start with antimicrobial therapy for 24 to 48 hours, only implementing glucocorticoids if there is no response. Pentoxifylline, vitamin E, and omega-3 fatty acids can be helpful in cases of vasculitis, though effects are not typically rapid. It is common to start glucocorticoids and pentoxifylline at the same time and, once the disease is in remission (2 to 3 weeks), taper glucocorticoids while the patient remains on pentoxifylline.

In immune-mediated vasculitis, additional immunomodulatory therapies may be used, such as modified cyclosporine or azathioprine. Doxycycline or tetracycline with niacinamide is sometimes used for vasculitis, but this practice is controversial due to increasing concern for antimicrobial stewardship. In neutrophilic cutaneous vasculitis, sulfasalazine may be effective, but patients should be monitored closely for hepatopathy.

STERILE NEUTROPHILIC DERMATOSIS (SWEET-LIKE SYNDROME)

SLS is a rare skin condition in which acute neutrophilic inflammation develops in the skin. The most typical dermatologic presentation is the acute development of erythema and edema that may be localized or...
generalized and that commonly affects the ventrum. Although the ventrum is the most classic lesion location, cases have been described affecting all cutaneous body sites. Lesions also commonly include erythematous papules, macules, and plaques, which may coalesce. Pustules, crusts, erosions, and erythematous nodules have also been described.

Joint effusion or immune‐mediated polyarthropathy has been reported in several cases. Less specific systemic signs associated with SLS include fever, gastrointestinal signs, lymphadenopathy, lethargy, and anorexia. In severe cases, systemic inflammatory response syndrome and respiratory distress may occur, which can be fatal. Extracutaneous neutrophilic infiltrate has also been described. The most common clinicopathological abnormalities include hypoalbuminemia, anemia, and neutrophilia with a left shift. In individual cases, hyperbilirubinemia, elevated alanine transaminase and alkaline phosphatase, azotemia, thrombocytopenia, positive antinuclear antibody, and increased C-reactive protein have also been reported.

Cytology should be performed to differentiate SLS from pyoderma. SLS should be considered in patients with systemic signs of illness, acute erythematous skin lesions, and no microorganisms seen on cytology. Biopsy for histopathology is recommended to confirm clinical suspicion. Histopathologic features include interstitial or periadnexal neutrophilic infiltrate with edema in the absence of vasculitis, and epidermal hyperplasia in the absence of any infectious etiologic agents.

Patients with suspected or confirmed SLS should be evaluated for underlying disease that may be acting as a trigger, as the disease is thought to be a form of hypersensitivity reaction. The human analog, Sweet syndrome, commonly occurs secondary to neoplasia, pregnancy, or other inflammatory disease, and it may develop after an infection or vaccination. In dogs, some cases have been associated with recent administration of carprofen or robenacoxib. Given that arthropathy is now understood to be a relatively common extracutaneous clinical sign in this syndrome, the author must allow that it is possible these medications are being prescribed in response to the disease, rather than precipitating its development. SLS has been associated with acute myeloid leukemia in a 1-year-old Chihuahua.

SLS can be treated in the acute phase with glucocorticoids and supportive care. Drug withdrawal should be considered if there is concern for a drug reaction based on recent medical history. Long-term therapy with another immunosuppressive medication, such as modified cyclosporine or mycophenolate mofetil, may be needed if recurrence develops as glucocorticoids are tapered.

**CANINE ACUTE EOSINOPHILIC DERMATITIS WITH EDEMA (WELLS-LIKE SYNDROME)**

CAEDE is characterized by an eosinophil-heavy granulocytic inflammatory infiltrate into the skin, which is thought to be the result of a hypersensitivity reaction. Cutaneous signs of CAEDE are similar to those of SLS: acute development of raised or flat erythema and edema that is most often distributed over the ventrum. Pruritus occurs in more than one-third of CAEDE cases but has been reported in only a single case of SLS. The extracutaneous signs differ somewhat; CAEDE is typically associated with gastrointestinal signs, especially acute-onset vomiting, and joint effusion has not been reported. Fever is seen less often in CAEDE than in SLS. Rarely, dogs with CAEDE develop systemic inflammation or respiratory distress. Miniature schnauzers and English bulldogs may be overrepresented.

**CAEDE is typically associated with gastrointestinal signs, especially acute-onset vomiting, and joint effusion has not been reported.**
CAEDE have been reported to have a history of atopic dermatitis (due to food or environmental allergens).\textsuperscript{10} CAEDE has been reported to occur as a result of a food allergy in the literature,\textsuperscript{18} and the author has seen a case of food hypersensitivity–induced CAEDE. One dog with CAEDE was reported to have a history of immune-mediated thrombocytopenia, and another went on to develop immune-mediated hemolytic anemia.\textsuperscript{10} CAEDE has also been reported in association with T-cell lymphoma.\textsuperscript{19}

Treatment of CAEDE involves drug withdrawal, glucocorticoids, and supportive care. An elimination diet trial should also be considered, with follow-up scheduled with the primary care veterinarian to assess response to treatment. Provocation is necessary to confirm the diet as a trigger in the individual patient.

**URTICARIA AND ANGIOEDEMA**

Urticaria refers to the wheal-and-flare reaction that occurs when mast cells degranulate, releasing histamine into the skin. The wheal refers to the raised, indurated skin caused by local edema, and the flare refers to the erythema caused by local vasodilation.\textsuperscript{20} Though typically round, wheals may be linear or may coalesce to form extensive irregular shapes. When histamine release is more extensive, generalized or diffuse edema may develop over the entire affected area, called angioedema. Angioedema may feel firm or may pit with palpation. Angioedema can also be associated with anaphylaxis, a life-threatening allergic reaction.

Urticaria occurs acutely after exposure to the trigger and often resolves spontaneously within 1 to 2 days, although some cases may develop chronic urticaria if the trigger is not identified and eliminated. Many different types of allergens can cause urticaria in sensitized individuals. Insect bites and stings are associated with urticaria, and multiple bites or stings may be reported in cases of angioedema (e.g., involving the entire face after exposure to a nest or hive).\textsuperscript{21} Urticaria and angioedema can also occur as part of a vaccine reaction.\textsuperscript{21} Causes of mast cell degranulation are numerous and may not always represent hypersensitivity, as mast cell degranulation can occur due to physical and thermal stimulation. Cases of urticaria due to stress and infectious disease can also occur.\textsuperscript{21}

Antihistamines and glucocorticoids are commonly used to treat urticaria. Glucocorticoids may be administered as an injection on an emergency basis or orally in milder cases. Although diphenhydramine is one of the most widely used antihistamines in canine patients, there is minimal evidence to support its efficacy in preventing mast cell degranulation and histamine release in dogs.\textsuperscript{22} One study evaluating the effect of diphenhydramine and cetirizine on intradermal histamine reactions showed good effect for cetirizine but no effect for diphenhydramine.\textsuperscript{22} When injectable glucocorticoids are needed in the emergency setting, it remains reasonable to administer diphenhydramine rather than withhold antihistamines. However, the author now recommends cetirizine when oral antihistamines are needed. Hydroxyzine, which is metabolized to cetirizine in the body, is also appropriate but may cause excessive sedation.

If a trigger can be identified, avoidance should be attempted. Allergen-specific immunotherapy (ASIT) can be attempted to desensitize patients to *Hymenoptera* allergens that cause urticaria, angioedema, and anaphylaxis; however, some clinicians may have greater concern for adverse reactions during allergy testing and immunotherapy in patients that have a history of significant allergic reaction, and this risk should be discussed with the owner prior to proceeding. Ongoing preventive treatment with antihistamines is recommended, and the author usually recommends premedicating with an antihistamine prior to ASIT in these patients if elected. For dogs with a history of anaphylaxis, epinephrine injection pens can be considered, but these are cost-prohibitive for many owners, and data regarding dosing, safety, and efficacy are lacking in dogs. ASIT is effective only for urticaria that is a hypersensitivity reaction to an identified trigger allergen.
Urticaria should not be confused with papules or short-coated pyoderma, which are also associated with allergy. Papules in short-coated dogs may cause the hairs to raise in a way that can be visually confused with urticaria, particularly by owners. Unlike typical urticaria, these lesions may be present for several days and arise gradually over time, and expected cytology findings include neutrophils, nuclear streaming, and cocci. Rarely, urticaria can persist and become chronic. If chronic urticaria is suspected, histopathology is recommended to confirm that lesions are histologically consistent with urticaria, rather than recurrent pyoderma or nodular or plaque-like cutaneous diseases.

**SUMMARY**

To maximize the chances of a positive outcome in dermatologic emergencies, clinicians must be familiar with these diseases and be able to quickly diagnose them and treat them appropriately. An accurate history is critical to identify possible triggers. It is also important to biopsy lesions with an intact epidermis to make a diagnosis, as ulcerated lesions are typically of minimal benefit.

**References**


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Dr. Brame is a clinical assistant professor in the dermatology service at the College of Veterinary Medicine at Michigan State University. She earned a DVM degree at North Carolina State University in 2017 and stayed for her small animal rotating internship. She completed a residency in dermatology and allergy at the University of Pennsylvania. Dr. Brame particularly enjoys immune-mediated disease and allergies.