initial visits but at subsequent presentations or any time there is a change in the signs of the disease. In some cases, a dog or cat may be presenting for a dermatologic disease, and during treatment for that disease a drug eruption may occur. The relationship between the new eruption and the drug that was given for the dermatologic disease is what should be considered. The history is critical for tentatively diagnosing a drug reaction. Features that are considered helpful to make a diagnosis include:

1. A drug not taken before is given more than 7 days prior to onset of the eruption, but repeat drug exposure can occur sooner.
2. The eruption is occurring while the patient is on the drug or the drug has only recently been discontinued.
3. Stopping the drug results in resolution of the lesions, generally rapidly or within 7 to 14 days.
4. If repeat exposure occurs generally a similar reaction occurs. (This is generally only done when reactions are mild, because serious reactions should be avoided and rechallenge is contraindicated. This also occurs when the role of a drug was unknown, and repeat exposure induces the same reaction.)
5. Other causes for the eruption are ruled out as a cause of the eruption.

One other criterion often used in human medicine for the tentative diagnosis of a drug reaction is:

6. Features of the eruption are considered consistent with a drug reaction and correlate to eruptions the suspect drug is known to cause.

Unfortunately, their is not enough experience with the number and type of drugs causing reactions in veterinary medicine as they have in humans. Therefore, our list that fits this last criterion is relatively smaller. Comparing suspect cases to what has been described in humans may be helpful.

In general, no specific or characteristic laboratory findings indicate drug eruption. Results of in vivo and in vitro immunologic tests depend on the mechanism of action and have been shown to have some use in humans.[392,397] Tests used include intradermal testing, patch testing, lymphocyte transformation (blastogenesis), toxicity testing, and dermatopathologic analysis. Sensitivity and specificity of such testing is generally unknown, although there is evidence they have value in diagnosing some CADR.[438,439] How helpful they may be in veterinary medicine has not been evaluated. One report of a dog with Sweet syndrome did use lymphocyte transformation (blastogenesis) assays to suggest that two antibiotics being given with carprofen were less likely to be the cause of the drug reaction.[413] Since these tests are rarely used and of unknown specificity and sensitivity in dogs and cats, the diagnosis of CADR is based on clinical findings and the association with the drug history and eruption as described earlier.

Since the diagnosis is often based on the history, a variety of diagnostic algorithms and drug scoring systems were described for CADR in humans[440-443] and have been modified and applied to dogs.[416,444] The following section lists the most recent drug score criteria described in a study of 29 dogs that assessed the possibility for drugs causing severe eosinophilic dermatitis.[416]

DRUG SCORE

This system assigns a numerical score (+3 to –3) based on the following criteria:

1. A score of +1 (suggestive) was given if the lesions appeared more than 7 days after first administration of the drug or less than 1 day after readministration.
2. A score of +1 was given if the lesions resolved after removal of the drug, with no other therapeutics. A score of 0 (inconclusive) was assigned if other drugs were given simultaneously. A score of –1 (incompatible) was given if the lesions persisted despite drug withdrawal or if the patient improved without drug withdrawal.
3. A score of +1 was assigned if the drug was readministered and the patient relapsed, a score of 0 if no rechallenge occurred, and a score of –1 if no recurrence was seen after challenge.
4. A positive drug score was deemed suggestive of a casual drug association. A zero score was inconclusive. A negative score indicated that a drug association was unlikely.

The value of these drug scoring systems in humans is questioned, and their accuracy has been shown to vary, with studies showing the sensitivity and specificity ranging from 0% to 50% and 53% to 100%, respectively.[439,445] Since even less is known about the use of drug score values in dogs, they may be interesting to use but certainly can not be relied upon to determine when the diagnosis is appropriate.

Just as the clinical morphology of drug reactions varies greatly, so do the histologic findings. Histopathology is most helpful to diagnose specific syndromes that are known to have an association with drug eruptions and have a specific set of histopathologic changes required for a tentative diagnosis. Such syndromes include erythema multiforme, toxic epidermal necrolysis, sterile neutrophilic dermatosis, eosinophilic cellulitis, superficial suppurative necrolytic dermatitis, and vasculitis. The most important aspect of getting histopathologic support for a diagnosis of cutaneous drug reaction is that the pathologist is given the drug history when biopsies are submitted, and they should be alerted whenever a drug reaction is suspected.

CLINICAL MANAGEMENT

The prognosis for drug reaction is usually good unless other organ systems are involved or there is extensive epidermal necrosis. Therapy of drug reaction consists of (1) discontinuing the offending drug, (2) treating symptoms with topical and systemic medications as indicated, and (3) avoiding chemically related drugs. Drug reactions may be poorly responsive to glucocorticoids, although some immunologically mediated reactions respond to glucocorticoids, cyclosporine, pentoxifylline, or immunosuppressive regimens. Another option for severe or poorly responsive cases is IVIG, which was reported effective in two severe cases.[446]

ERYTHEMA MULTIFORME

Erythema multiforme is described as an uncommon disease in dogs and a rare disease in cats, characterized by acute onset of a cutaneous inflammatory reaction featuring epidermal apoptosis and lymphocytic satellitosis.[447] In humans, it is a disease clinically characterized by acute onset of typical lesions (target lesion) and a usually mild and self-limited but commonly recurrent mucocutaneous rash that is associated with infections, the most frequent being herpesvirus infections.[448-450] These clinical features are not usually seen in the dog or cat, where the number one association described is drug reaction and not infectious disease.[444,447] The question is what relationship there is between erythema multiforme and Stevens-Johnson syndrome. Toxic epidermal necrolysis has been described for years in human and veterinary medicine and at times considered similar to erythema multiforme. In human medicine, these diseases are now considered separate entities.[449-452] It is still controversial in veterinary medicine, with

the diseases being separated by some[447] and not others.[444,453] The discrepancy in veterinary medicine most likely reflects that the diagnosis is often based on histopathologic findings, and the strict clinical criteria applied to human lesions has not been applied in dogs or cats. If these clinical criteria were to be applied, it is very likely erythema multiforme is an exceedingly rare disease, and most cases would have been diagnosed as Stevens-Johnson syndrome or toxic epidermal necrolysis, which is why they and erythema multiforme would seem related in veterinary medicine.

CAUSE AND PATHOGENESIS

In humans, erythema multiforme that fits the strict criteria of having typical target lesions is most commonly associated with herpesvirus infections, but also several other viral infections including parvovirus, and some bacterial infections including *Mycoplasma*.[452] Drug reactions are an uncommon cause when strict clinical criteria of target lesions are met.[450,452,454,455] In dogs, reported triggering factors are drugs, idiopathy, bacterial infections, *Pneumocystis* pneumonia, parvovirus, food, neoplasia, and possibly herpesvirus.[47,133,407,444,447,453,456-459] A review of erythema multiforme in 44 dogs reported drugs to be responsible in 26 (59%).[47] Another report of 34 dogs showed only 7 (19%) had a probable drug reaction when possible causal drug exposure was based on drug implication criteria used in humans.[444] The most common drugs have been trimethoprim-potentiated sulfonamides, penicillins, and cephalosporins. In the cat, the majority of cases have been related to drug reactions, though herpes has also been associated; one cat with herpes was treated with drugs and then developed erythema multiforme.[47,133,460-462]

The exact pathogenesis is not known, but in human erythema multiforme associated with herpesvirus, nonreplicating viral particles have been found in epidermal keratinocytes, and these attract herpes-specific $CD4^+$ T_H1 lymphocytes, resulting in upregulation of IFN-γ-mediated immune response and eventually keratinocyte apoptosis.[463] The reaction in herpes patients is not associated with TNF-α, but drug-induced erythema multiforme is associated with upregulated TNF-α and not IFN-γ, showing that two different pathologic mechanisms exist in the development of erythema multiforme.[463,464]

The role of viral particles in epidermal cells has not been well evaluated in dogs and cats. Parvovirus has been seen in canine erythema multiforme and herpes in cats and has also been suggested as a cause in dogs.[447,458,462] In dogs, erythema multiforme is thought to represent a host-specific cell-mediated hypersensitivity reaction directed toward some antigenic stimulus.[47,360] Studies indicated that the immunohistochemical findings in skin lesions from dogs with erythema multiforme and acute GVHD were similar.[360] Epidermal and follicular keratinocytes markedly expressed ICAM-1, MHC II, and to a lesser extent, CD1a. Expression of these molecules is likely to tether leukocytes and keep them in the epithelium. The simultaneous expression of MHC II and CD1a provides altered keratinocytes with the capability of antigen presentation. Keratinocytes in adjacent noninflamed epidermis also expressed ICAM-1 and MHC II, suggesting that upregulation of both adhesion molecules may represent an early phase in the development of erythema multiforme. CD44 was markedly upregulated in keratinocytes and infiltrating cells, and it is involved in T-lymphocyte activation and site-specific extravasation of lymphocytes into tissues. Intraepithelial infiltrating cells were mainly $CD3^+$, CD8-$\alpha\beta^+$, TCR-$\alpha\beta^+$ T lymphocytes, with smaller numbers of $CD4^+$ T lymphocytes. $CD1^+$, $CD11c^+$ Langerhans cells were increased in number. The majority of dermal infiltrating cells were also $CD3^+$, CD8-$\alpha\beta^+$, TCR-$\alpha\beta^+$ T lymphocytes. $CD1^+$, $CD11c^+$ dermal dendrocytes were also increased in number.

The phenotypic changes in keratinocytes in canine erythema multiforme indicate that alteration of the keratinocyte (e.g., by drugs, infectious agents) might be a primary factor in disease pathogenesis.[360] Upregulation of ICAM-1 and MHC II, perhaps through production of IFN-γ and TNF-α by $CD8^+$ (cytotoxic) and $CD4^+$ (helper) T lymphocytes, also occurs. Keratinocyte apoptosis results, but the exact mechanism has not been determined in dogs.[292,360]

CLASSIFICATION SCHEMES

Over the years, there has been much confusion regarding classifying cases, especially severe cases, as erythema multiforme. In fact, it led to subclassification of erythema multiforme into erythema multiforme minor and major. Erythema multiforme minor is relatively mild, has an acute onset of lesions that includes classic target lesions usually involving the extremities, has no fever or prodromal symptoms, and if there is mucosal involvement, it is usually mild and limited to the oral cavity.[450,452] These cases are self-limited, and lesions clear within weeks. Cases classified as major were more severe, had more mucosal involvement, and often other signs such as malaise or pyrexia. The terms *target-like lesion* or *atypical target lesion* also became more popular, and cases started being mixed between Stevens-Johnson syndrome and erythema multiforme major. A study in human patients requiring hospitalization for severe disease with lesions compatible with erythema multiforme major or Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) proposed a clinical classification.[454] Four types of lesions were defined for these cases:

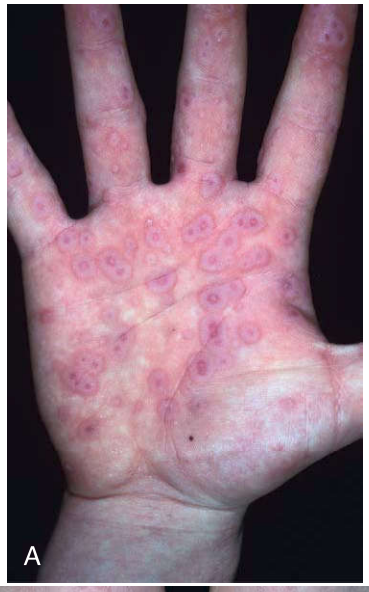
1. Typical target lesions are round and have well-defined borders and three zones of color. The center is erythematous or purpuric and may have a bullae, the next zone is lighter erythema and raised due to edema, the third zone is another erythematous ring.
2. Raised atypical target lesions are poorly defined and only have two zones of color with erythema, and one is raised and edematous.
3. Flat atypical target lesions are also poorly defined and have two zones of color; they may have a central bulla; they lack the raised edematous zone.
4. Macules with or without blisters that could be purpuric or erythematous.

It is still emphasized how important it is to have strict definitions of the typical target lesion and those lesions in humans are shown in Figure 9-39.[452] Two main features were used to separate these cases: presence of the type of lesion and extent or body surface area of epidermal detachment. In the original study and two more follow-up studies with many more patients, this clinical classification has been shown to be valid, accurately applied by different dermatologists, and correlates with diagnosis and etiology.[455,465] The typical target lesions and raised atypical target lesions are most often associated with the diagnosis of erythema multiforme and herpesvirus, whereas both flat lesions are more often associated with SJS/TEN due to drug eruptions. More recently it was suggested that a fifth lesion be added, the flat typical target lesion. The major differentiating feature that separates erythema multiforme from SJS/TEN is that erythema multiforme cases have raised lesions and in SJS/TEN, even when they have three zone lesions, the lesions are flat in zone 2 and only raised centrally if there is a bulla or vesicle.[466] It is very apparent that a key feature in classifying these cases is the type of cutaneous lesion present. The current recommendation in human medicine is that the presence of typical target lesions or raised atypical target lesions

Table 9-7 Proposed Criteria for Clinical Classification of Erythema Multiforme and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

Clinical Lesions	EM min	EM maj	SJS	Overlap	TEN
Flat or raised, focal or multifocal, target or polycyclic lesions	Yes	Yes	No	No	No
Number of mucosal surfaces involved	None or 1	>1	>1	>1	>1
Erythematous or purpuric, macular or patchy eruption (percent of body surface)	<50	<50	>50	>50	>50
Epidermal detachment (percent of body surface)	<10	<10	<10	10-30	>30

EM maj, erythema multiforme major; EM min, erythema multiforme minor; Overlap, SJS/TEN overlap syndrome; SJS, Stevens Johnson syndrome; TEN, toxic epidermal necrolysis.
Table from Hinn A, Olivry T, Luther P: Erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis in the dog: Clinical classification, drug exposure, and histopathologic correlations. *J Vet Allergy Clin Immunol* 6:13–20, 1998.



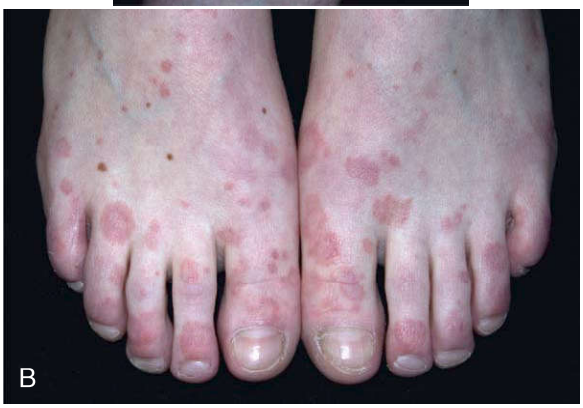


FIGURE 9-39 Target lesions on the palms and soles are highly characteristic of erythema multiforme. Lesions begin as dull red macules that develop a vesicle in the center. The periphery becomes cyanotic. *(From Habif TP.* Clinical Dermatology, *ed 5, St. Louis, 2010, Elsevier.)*

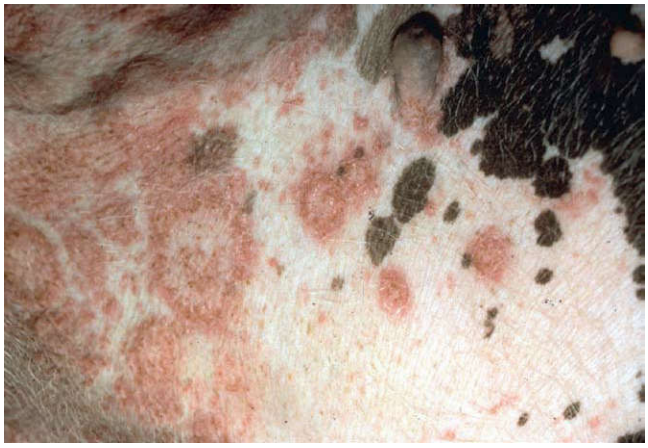


FIGURE 9-40 Erythema multiforme minor due to Tribrissen in a dog. Note annular erythematous target lesions on flank.

supports the diagnosis of erythema multiforme and describes all forms of that entity, eliminating the terms *major* and *minor*, and that the Stevens-Johnson syndrome and toxic epidermal necrolysis be called *Stevens-Johnson syndrome/toxic epidermal necrolysis*.[450,452,467]

In veterinary medicine, the confusion was compounded by common acceptance of a diagnosis based primarily on histopathologic findings and the fact that no strict definition of a target lesion has been applied.[444,447,468] Even when a clinical classification was adapted for use in dogs (Table 9-7), there was no strict definition of a target lesion.[444] The inclusion criteria for the study defined lesions of erythema multiforme as "cutaneous isolated macular or polycyclic target lesions," and there is no further description of what a target lesion is. The majority of papers in veterinary medicine do not show target lesions that would pass as typical three-zone target lesions in human texts. It is felt that lack of a defined clinical target lesion and the use of histopathology to justify a diagnosis of erythema multiforme in veterinary medicine has led to many cases that likely represent Stevens-Johnson syndrome being published as cases of erythema multiforme. This opinion is supported by the predominance of drug-induced erythema multiforme in veterinary medicine. One article[47] evaluated target lesions in a series of 16 cases and defined the typical target lesion thusly:

"Early lesions were annular, erythematosus macules, papules, and plaques. These lesions enlarged centrifugally and often coalesced to form bizarre polycyclic patterns. At this stage, the lesions showed little or no surface pathology (scale, crust, erosion, oozing, alopecia, etc). The periphery of the lesions remained indurated and erythematous, while the centre cleared, becoming progressively less indurated and erythematous. The centre often became cyanotic or purpuric. These were classic 'target' or 'iris' or 'doughnut' lesions" (Fig. 9-40).

This "classic target lesion" was detected in 6 of 16 (37.5%) of dogs with erythema multiforme and of those, two were idiopathic, one food induced, and three drug induced.[47]

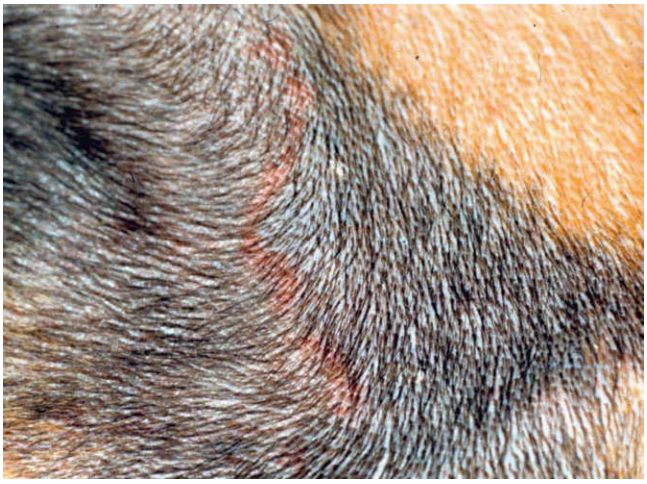


FIGURE 9-41 Canine erythema multiforme due to cephalexin. Serpiginous erythema.

Another study classified erythema multiforme based on proposed canine criteria of flat or raised focal or multifocal target or polycyclic lesions, less than 50% of the body surface affected with an erythematous or purpuric macular or patchy eruption, and less than 10% of the body surface showing epidermal detachment.[444] Based on current criteria in humans, this range of lesions should not be included, but it may still be helpful to use the other two criteria as an aid to diagnosis. This classification scheme should be reevaluated, with strict definitions of target or raised atypical target lesions being required for a diagnosis of erythema multiforme.

CLINICAL FEATURES

The following description is based on what has been published in veterinary medicine as erythema multiforme, though as mentioned, at most only 38% of the cases had classic target lesions. Erythema multiforme is uncommon in dogs and cats, accounting for only 0.4% and 0.11%, respectively, of all the canine and feline dermatology cases examined at a university practice.[47] Prodromal or concurrent clinical signs may reflect the underlying cause but should also make one consider the diagnosis of Stevens-Johnson syndrome, because other signs are usually lacking in humans with erythema multiforme.

The skin lesions described in dogs and cats are variable, but they are usually characterized by an acute symmetrical onset. Most commonly, erythematous macules (Fig. 9-41) or slightly elevated papules that spread peripherally and clear centrally, producing annular or arciform patterns, are seen. Other lesions described include urticarial plaques and vesicles and bullae resulting in ulcers. The term *target lesion* should be applied only when the accepted human definition is present as previously described. Mucosal lesions are similar in onset and symmetry but are usually erythematous and may progress to vesicular, bullous, and ulcerative lesions (Fig. 9- 42, *A* and *B*). The oral ulcers are often hemorrhagic and coated by grayish-white pseudomembranes of necrotic epithelium and fibrin. The maculopapular form of erythema multiforme initially is characterized by lack of surface pathology (lack of scale, crust, oozing, hair loss). The urticarial form of erythema multiforme is characterized by a normal overlying skin and haircoat and the persistence of urticarial lesions, as opposed to the evanescent nature of the wheals in true urticaria. Erythematous lesions with adherent keratinous crusts may also occur (Fig. 9-42, *B* and *C*).

FIGURE 9-42 **A**, Oral mucosal erythema in a dog with erythema multiforme. **B**, Oral erythematous macules were also present, and crusts are also seen in a perioral pattern. **C**, Hyperkeratotic crusty lesions over erythematous macules to erosions in a dog with erythema multiforme.

Patients with maculopapular eruptions are usually asymptomatic and represented only 13.6% of cases described in the largest review.[47] Other animals with what would typically be erythema multiforme major may become systemically ill (fever, depression, anorexia) and have extensive vesiculobullous and ulcerative lesions. The most commonly affected body sites in

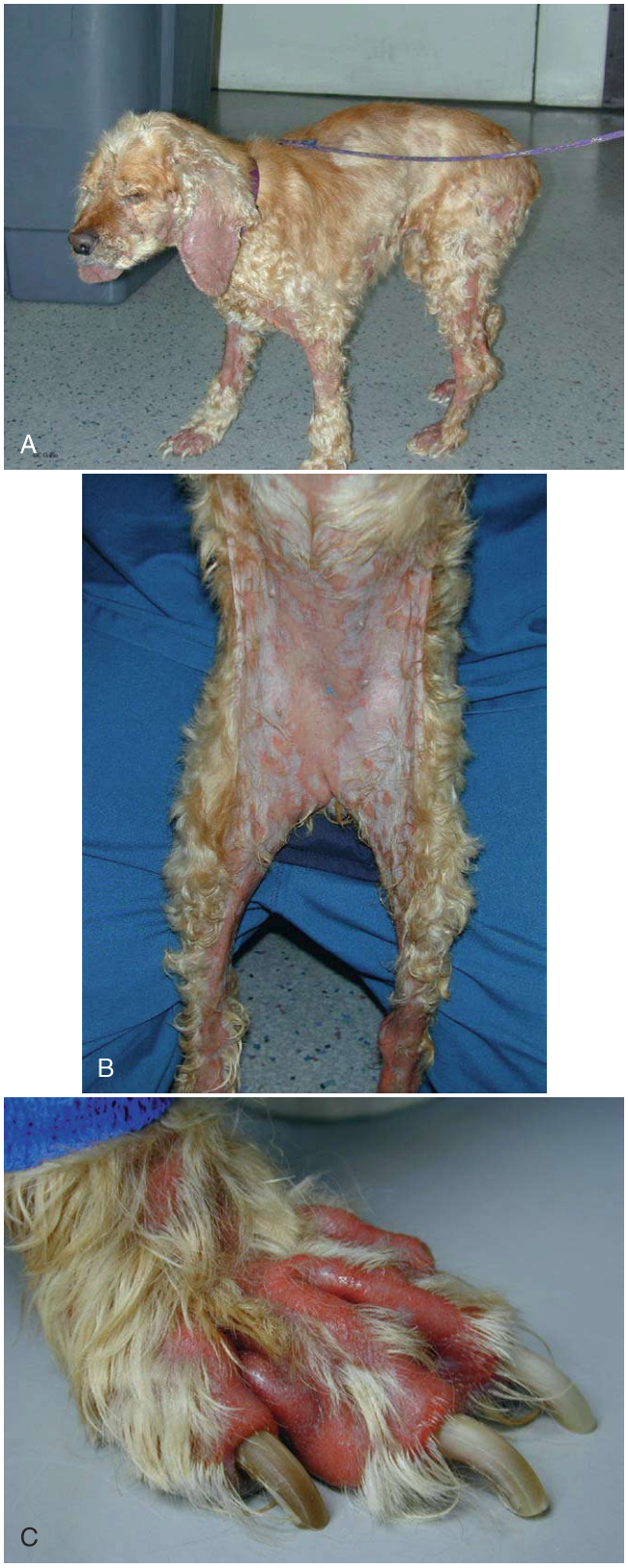


FIGURE 9-43 Typical case of severe erythema multiforme with facial, pinnal, ventral, and extremity lesions of erythematous macules, erosions, and ulceration. Note atypical target lesions present.

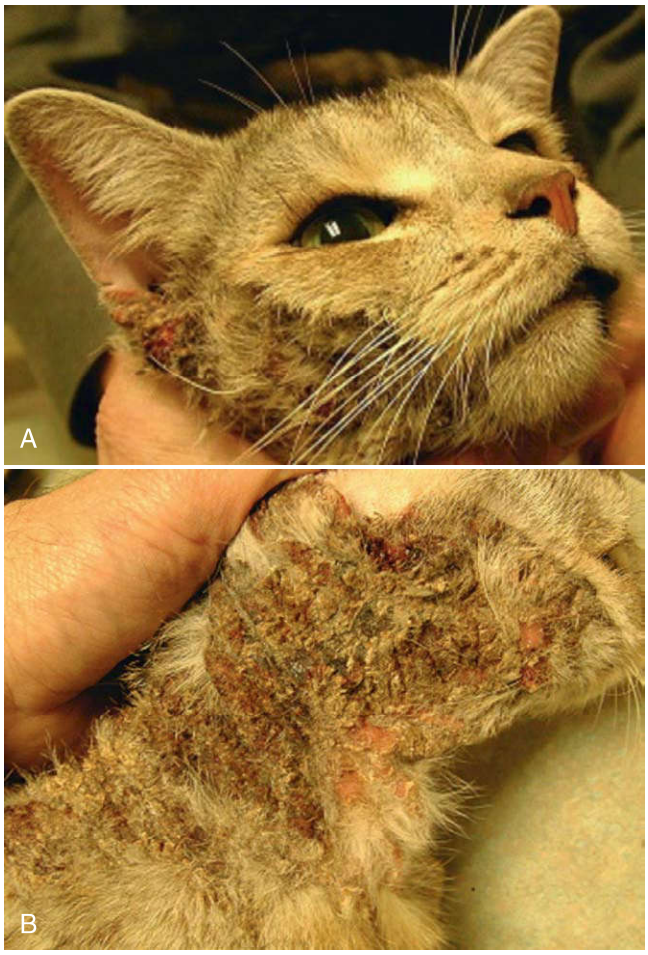


FIGURE 9-44 **A,** Erythema multiforme in a cat with crusted erythematous and ulcerative lesions of the lateral face. **B,** Lesions extended to neck and dorsal trunk.

dogs include the ventrum (Fig. 9-43) (especially axillae and groin; 65.9% of cases), mucocutaneous junctions (47.7%), oral cavity (31.8%), pinnae (25%), and footpads (20.5%).[47] Skin lesions are occasionally painful (22.7%) but rarely pruritic (4.5%). Target lesions (15.9%), Nikolsky sign (11.4%), and pitting edema of the distal limbs (11.4%) occur occasionally.[47] Old dog idiopathic erythema multiforme tends to involve the face and ears.[447]

In cats, lesions are predominantly ulcerative and crusted; vesiculobullous has been described (Fig. 9-44). Trunk and mucocutaneous junctions are most commonly affected.[47]

DIAGNOSIS

Insofar as the classic target lesion is apparently very rare in veterinary medicine, its presence would likely have a very limited differential, but because no studies have really looked at this, a biopsy is essential to support the diagnosis of an apoptotic disorder. The differential diagnosis for flat polycyclic erythematosus lesions or an "atypical" target lesion would include bacterial folliculitis, dermatophytosis, demodicosis, urticaria, and other vesicular and pustular disorders. Raised atypical target lesions would add urticaria to the previous differential diagnoses. Definitive diagnosis should require the classic target lesion or at least a raised atypical target lesion and a supportive skin biopsy, which also helps by ruling out other diseases such as folliculitis. Skin biopsy findings alone are insufficient for a diagnosis of erythema multiforme because they do not accurately distinguish between diseases characterized by apoptosis.[444,450] Neither are there any apparent histopathologic differences between cases with suspected triggers and those without (i.e., idiopathic).[47] The most typical finding in cases with erythema multiforme is keratinocyte apoptosis with

lymphocytic satellitosis, and this may be individual cells or progress to confluent areas of the epidermis, leading to ulceration.[469,470] There is usually an interface dermatitis. Rare cases have been reported with predominantly hair follicle involvement.[469]

A trigger for the disease should be pursued with a thorough history of a possible drug exposure, infections, or neoplasia. Polymerase chain reaction (PCR) testing for the presence of virus in the skin, particularly herpes and parvovirus, is indicated; recognition of such a triggering disease may lead to additional treatment options. Idiopathic cases occur and may be more common in old dog erythema multiforme. Diet trials should also be attempted prior to making such a diagnosis, since food has been a reported trigger.[47]

Direct immunofluorescence testing usually yields negative results but may demonstrate IgG, IgM, or C3 between epidermal keratinocytes, around globoid bodies in the superficial dermis, or in association with dermal blood vessel walls.[47,411]

CLINICAL MANAGEMENT

Erythema multiforme may run a mild course, spontaneously regressing within a few weeks. An underlying cause should be sought and corrected whenever possible, an intervention that may result in spontaneous resolution.[47] Severe vesiculobullous cases of erythema multiforme require supportive care and an exhaustive search for underlying causes. When trigger factors can be identified and eliminated, the erythema multiforme usually resolves within 3 weeks.[47] Immunosuppressive drugs such as glucocorticoids, azathioprine, and cyclosporine have been used for treating some cases. IVIG, an expensive treatment useful for a variety of immune-mediated diseases, has been effective in some life-threatening cases.[460,471] Pentoxifylline has anecdotal reports of benefit.

TOXIC EPIDERMAL NECROLYSIS

TEN is a rare, life-threatening, extensive vesiculobullous and ulcerative disorder of skin and oral mucosa in dogs, cats, and human beings. As noted earlier, TEN and Stevens-Johnson syndrome in humans are now believed to be the same disease, with the latter less extensive and severe. These are separate from erythema multiforme.[472,473]

CAUSE AND PATHOGENESIS

In humans, TEN is usually considered an adverse drug reaction, but a small number of cases have been associated with other causes, including vaccine reactions, neoplasia, infections, and pregnancy.[472-475] This appears to be true in dogs and cats as well. Genetics also plays a role in humans, where it has been shown the reaction to the drug carbamazepine is associated with HLA-B1502.[476] Over 200 drugs have been associated with TEN in humans, though most cases are related to a group of 14 high-risk drugs.[472,474] A variety of drugs and causes have been associated with TEN in dogs, most notable are the antibiotics trimethoprin sulfa, cephalosporins and penicillins (Box 9-2).[25,133,430,477-480] Flea dips were implicated in both a dog and cat that experienced TEN.[481] Some cases have been associated with other disease such as pseudomonas otitis and anal sacculitis. The definitive association with the disease has not been made. Some of these had been treated with drugs and since even topicals may induce the disease the exact cause is uncertain. Some cases are idiopathic.

The pathomechanism of TEN is not exactly known but is believed to be a cellular immunologic reaction involving primarily keratinocytes; however, T cells and macrophages may play some part. In humans, massive keratinocyte apoptosis is the key event.[472] *Apoptosis* is a form of programmed cell death that results in cell shrinkage, nuclear pyknosis, then karyorrhexis and formation of plasma membrane–bound apoptotic bodies.[482] The massive apoptosis appears to be triggered by two pathways. The perforin-granzyme pathway involves formation of perforin channels in the cell membrane that allow granzyme to enter the cell and activate the intracellular caspase enzyme system. Activation of cell surface death receptors also occurs by binding of cytokines from the TNF family, most notably TNF-α and Fas-ligand.[474,483,484] Activation of the death receptors results in activation of the intracellular caspase system that triggers apoptosis.[473,482]

There are elevations in multiple other cytokines; in TEN, IL-13 is elevated but is not elevated in erythema multiforme.[483,485] Increased levels of glutathione-S-transferase in keratinocytes early in lesion development has led to the hypothesis that drug interactions lead to production of intracellular reactive oxygen species and subsequent keratinocyte damage.[473] In dogs, a study evaluating a histopathologic marker for apoptosis did not find it in any of seven cases diagnosed as TEN, though apoptotic cells were found in other diseases including erythema multiforme.[292] This discrepancy has yet to be explained and raises the question of whether the mechanism in dogs is similar to humans. Certainly it is still unknown in dogs.

Box 9-2 Causes of TEN/EM Reactions in the Dog

Antibiotics
Amoxicillin
Amoxicillin clavulanate
Cephalexin
Chloramphenicol
Enrofloxacin
Erythromycin
Gentamicin
Lincomycin metonidazole
Ormetoprim-sulfadimethoxine
Penicillin
Tetracycline
Trimethoprim-sulfadiazine
Trimethoprim-sulfamethoxazole
Infections
Pseudomonal otitis externa
Staphylococcal dermatitis
Anal sacculitis
Miscellaneous
Anesthetic agents
Aurothioglucose
Chlorpyrifos
Beef and/or soy (in diet and chewable heartworm preventive)
Diethylcarbamazine
D-limonene
Dinotefuran/permethrin
Idiopathic
Ivermectin
Levamisole
L-Thyroxine
Moxidectin
Otic drops
Phenobarbital

CLINICAL FEATURES

There are no apparent age, breed, or sex predilections. Clinically, TEN is usually characterized by an acute onset of constitutional signs (pyrexia, anorexia, lethargy, depression) and multifocal to generalized erythematous macules or patches usually involving the body and multiple mucosal surfaces.[430,444,469,480] It has been proposed that the percentage of body affected with ulcerations or epidermal detachment be used to separate Stevens-Johnson syndrome (<10%), overlap