COMPLICATIONS

Cutaneous Adverse Drug Reactions

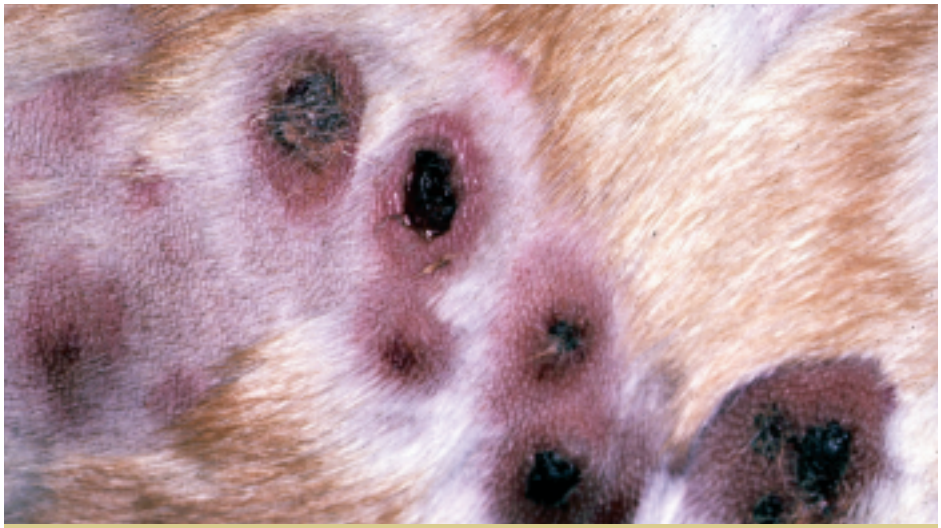
Douglas J. DeBoer, DVM, Diplomate ACVD,
University of Wisconsin-Madison

Drug treatment always carries the risk, albeit a small one, of causing an adverse reaction in a patient. Of all such reactions, cutaneous adverse drug reactions (CADRs, also loosely termed "drug eruptions") are among the most common in humans and animals.[1] These reactions are difficult to diagnose definitively and often go unreported. Therefore, their true prevalence in dogs and cats is not well established, although they have been reported to affect 1% to 2% of all patients examined at specialty dermatology clinics.[2,3]

Any drug may cause a CADR, although antibiotics (particularly potentiated sulfonamide and beta-lactam drugs) seem to be implicated in most cases in small animals.[1–4] Reactions have been seen with topical, oral, and parenteral formulations. In addition, several specific and unique syndromes are associated with particular drugs, such as itraconazole, methimazole, and doxorubicin (see page 9).

Types & Clinical Features

Predictable reactions are related to a known pharmacologic action of a drug and are usually dose-dependent; a familiar example is the alopecia associated with immunosuppressive or antineoplastic drugs. In contrast, *idiosyncratic* reactions are unrelated to the primary pharmacologic effect, are independent of dose, and result from immunologic and/or genetic factors in the host. The dermatologist's rule of thumb is that "idiosyncratic drug eruptions can look like anything." In human medicine, they are believed to be able to mimic nearly any dermatosis; however, small animal patients tend to have more common patterns (**Table**).



Common Patterns of Cutaneous Adverse Drug Reactions in Small Animals

Sudden occurrence of any of these patterns during or shortly after drug treatment should raise the possibility of a cutaneous adverse drug reaction.

- Maculopapular eruptions ("red rashes")
- Urticaria and/or angioedema ("hives")
- Blistering, pustular, and/or ulcerative patterns ("autoimmune-like"); includes erythema multiforme, Stevens-Johnson syndrome, TEN, and pemphigus-like reactions.
- Purpuric or "target-like" lesions (above); can be associated with cutaneous vasculitis or the erythema multiforme/Stevens-Johnson syndrome/TEN "family"
- Exfoliative (scaling) dermatoses
- Pruritus with self-induced excoriations
- Erythroderma (marked to severe, diffuse, cutaneous erythema that may extend over large areas of the body)

Signalment

Drug reactions can occur in any age, breed, or sex of animal, but particular breeds tend to be predisposed to certain syndromes—for example, sulfonamide reactions in Doberman pinschers.[4] Interestingly, although humans with HIV infection are at increased risk for CADRs,[5] this association has not been recognized for FeLV- or FIV-positive cats. In general, drug eruptions usually occur within 1 to 3 weeks after starting drug therapy, often appear suddenly, and persist for 1 to 3 weeks after discontinuation of the offending medication. Because CADRs can "look like anything," *it is important to obtain a thorough drug history from a patient with any type of recent-onset, sudden, unexplained skin disease*. Unfortunately, many patients experiencing a CADR often have serious diseases that are being treated with a variety of drugs concurrently or in sequence, which makes determination of the offending drug difficult.

continues

Diagnostic Testing

No specific diagnostic test is uniformly helpful for establishing the diagnosis of a CADR. Histopathologic findings from skin biopsies vary widely and could include perivascular dermatitis, interface dermatitis, vesicopustular dermatitis, panniculitis, granulomatous dermatitis, epidermal necrosis, or vasculitis. Although no specific histologic pattern uniformly suggests the presence of a CADR, biopsy of skin lesions is recommended, as it helps to eliminate differential diagnoses that may appear similar to a drug reaction.

Etiology

The clinical and histologic pleomorphism seen in CADRs reflects that they occur through a variety of mechanisms, most of which are incompletely understood. Some CADRs may partially involve "classic" type I, II, III, or IV hypersensitivity reactions—for example, allergic contact dermatitis, which is occasionally induced by a neomycin-containing topical skin or ear preparation and is considered a type IV delayed-type hypersensitivity reaction (**Figure 1**).

In other cases, increasing evidence points to the importance of drug-specific, T-lymphocyte clones in the pathogenesis of these diseases. Cytotoxic T-cells may directly destroy keratinocytes, and other types of T-cells may induce pathologic conditions through release and induction of a variety of cytokines and other molecules that promote cutaneous inflammation or even apoptosis.[6] Unfortunately, the number of underlying mechanisms that can be involved in a CADR also manifests as variable responses to different treatments.

The Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis "Family"

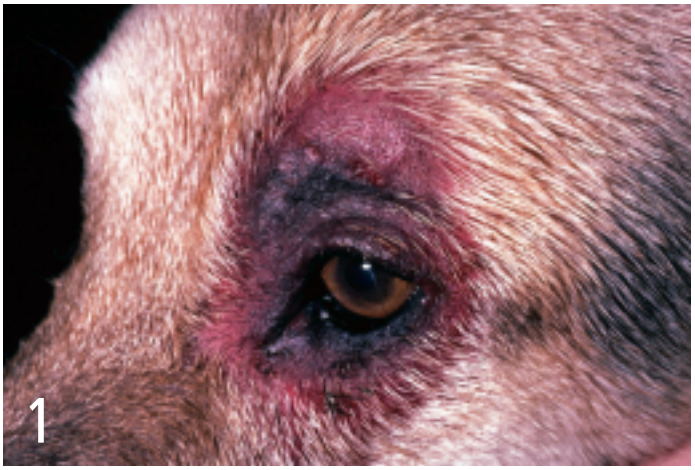
Much confusion and debate has centered on how to clinically differentiate between the members of this "family" of diseases. From a practical standpoint, it is sufficient to recognize a few key points.

- Lesions may be difficult to appreciate in long-haired animals without careful clipping of the hair coat. They consist of some combination of the following, which may appear on the skin and/or mucous membranes:
  - Flat to raised "target" lesions (central healing, peripherally spreading [**Figure 2**])
  - Erythematous or purpuric macular to patchy eruptions
  - Ulcerations
  - Epidermal detachment—in severe cases of toxic epidermal necrolysis (TEN), one third or more of the epidermal surface can become detached, resulting in sudden "sloughing" (**Figure 3**).
- Systemic signs may be present and can vary from mild to severe, usually relating to the severity of the skin disease.
- In *some* cases these diseases are clearly related to a drug reaction, but it must be emphasized that they may also be secondary to infection or neoplastic disease or be idiopathic in origin.

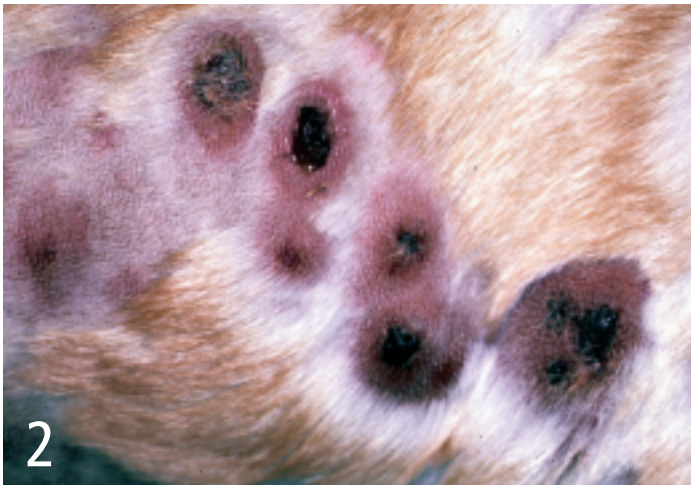
Although they are uncommon, these diseases are among the most serious CADRs; they are characterized by possible progression and potentially fatal outcomes. The clinical course varies—although patients with erythema multiforme have a rather dramatic appearance, it is considered a relatively mild disease because if the underlying precipitating cause can be found and eliminated, most cases recover with supportive care within 1 to 3 weeks. On the other hand, patients with TEN constitute the rare "dermatologic emergency" and have a worse prognosis.

Skin biopsy with histopathologic evaluation is *always* the diagnostic test of choice. Assuming that relatively early (nonulcerated) skin biopsy specimens can be obtained, the histopathologic findings are unique and often diagnostic. A histopathology report mentioning *any* of these diseases should prompt immediate concern, search for a drug-related cause, and consultation with a dermatologist on current treatment recommendations.

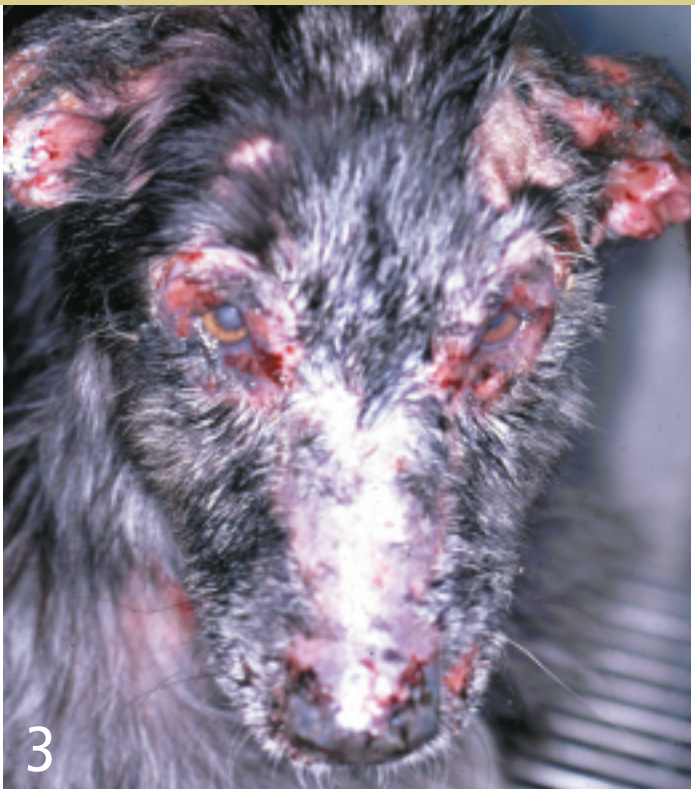
Despite the presumed immunopathology of these diseases, most authorities state that therapy with glucocorticoids or other immunosuppressive therapies is not helpful.



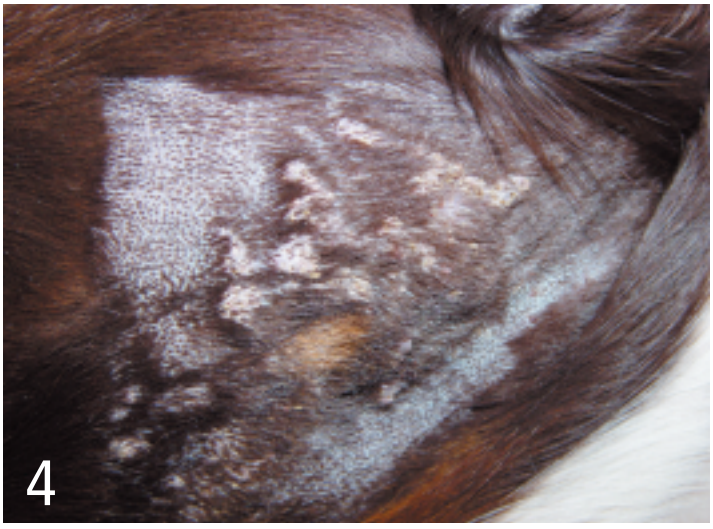
Allergic contact dermatitis induced in the skin of a dog after repeated application of neomycin-containing "triple antibiotic" ointment near the eye. Sudden, unexpected worsening of erythema and inflammation on a region of skin to which such a product has been applied (including *in* the eye or *in* the ear) should prompt the clinician to consider a cutaneous adverse drug reaction.



Target lesions appearing on the truncal skin of a dog with erythema multiforme related to cephalexin.



Massive, sudden epidermal ulceration occurring on the facial skin of a dog with toxic epidermal necrosis, presumably secondary to treatment with trimethoprim-sulfonamide.



Calcinosis cutis occurring on the face of a dog being treated for blastomycosis with liposome-encapsulated amphotericin B.

Syndromes Associated with Specific Drugs

Antifungal Drugs

Itraconazole is occasionally associated with sudden development of vasculitis in canine patients, typically after a month or more of higher-dose (10 mg/kg/d) therapy for systemic mycoses, such as coccidioidomycosis or blastomycosis.[7] Cutaneous ulcerative lesions caused by this drug can be misinterpreted as worsening of the primary disease, and skin biopsy is useful to differentiate a drug reaction from recurring mycosis.[8] Treatment with amphotericin B occasionally causes calcinosis cutis in dogs [9] (**Figure 4**).

Methimazole Reactions in Cats

This antithyroid drug has been associated with alopecia and scaling/crusting reactions of the head and face in cats (**Figure 5**). Severe pruritus with excoriations may be present, which makes the disease resemble food hypersensitivity in some patients. The reaction, once it begins, typically continues and worsens as long as the drug is administered and requires a change in therapeutic strategy for the hyperthyroidism.

Doxorubicin

Doxil, a liposome-based form of doxorubicin, has been associated with a unique syndrome termed palmoplantar erythrodysesthesia ("hand-foot syndrome") in a substantial number of human, canine, and feline patients. Along with scaling, crusting, alopecia, and/or ulcerative lesions of the axillary and inguinal regions, distal extremities, and pads, discomfort (pain, pruritus, or paresthesia) leads to difficulty in walking or self-mutilation in some patients. These side effects can be dose-limiting, thereby reducing the success of treatment with this antineoplastic drug. Although the pathophysiologic mechanism is unclear, the effect can be partially mitigated through concurrent use of oral pyridoxine supplementation.[10]

Superficial Suppurative Necrolytic Dermatitis from Medicated Shampoos

This unique syndrome has been reported in adult miniature schnauzers. It begins rather acutely, 48 to 72 hours after use of a medicated (often insecticidal) shampoo.[1] An erythematous, papular-pustular reaction develops, often over large areas of the body, and is initially interpreted as "shampoo irritation" by the owner. The lesions progress and become painful, weeping, ulcerative, and necrotic over several days. Pyrexia, anorexia, and depression are often present. Lesions regress spontaneously after 1 to 2 weeks of supportive care. The mechanism is unknown.

Alopecia, scaling, and crusting on the ears and face of a cat being treated for hyperthyroidism with methimazole.

Localized Cutaneous Reactions to Injections

Although these reactions are not technically drug eruptions, clinicians should be alert to their existence. A focal area of vasculitis with alopecia has been reported in some small-breed dogs at the injection site of rabies vaccine[11]

continues

(**Figure 6**). This reaction has been reported mostly in small, long-haired dogs, such as poodles; bichon frises; Yorkshire, silky, and Maltese terriers; and Pekingese, and is not associated with any other signs of systemic vaccine reaction. Interestingly, vaccine antigens have been demonstrated via immunohistologic evaluation of skin biopsy specimens from affected patients, leading to the speculation that it represents some type of abnormal immunologic reaction to the vaccine material. Focal panniculitis with formation of nodules and/or draining tracts has been reported at subcutaneous injection sites in both cats and dogs, related to several routine vaccinations as well as medications, such as repositol glucocorticoids (e.g., methylprednisolone acetate).[1]

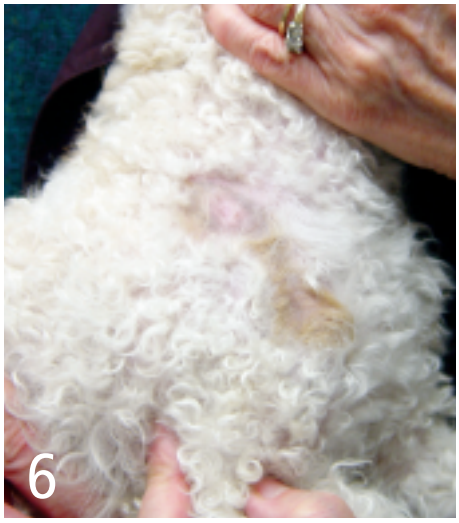
"Hepatocutaneous Syndrome" from Hepatotoxic Drugs

Hepatocutaneous disease is a syndrome of unknown pathogenesis in which liver disease (apparently of any type) appears concurrently with skin lesions and necrosis of epidermal cells. The "metabolic connection" that causes keratinocyte death has not been established, although the hepatopathy is considered to be the primary disorder and the skin lesions a secondary one. Thus, this syndrome is not a classic CADR, but it is important to be aware that drugs can cause such "indirect" skin reactions. Several dermatologists have seen this syndrome secondary to long-term administration of hepatotoxic drugs, including phenobarbital. The clinical picture is striking and includes ulcerative and crusting lesions of the inguinal and axillary regions and footpads, often with severe cracking and fissuring of the latter (**Figure 7**). Pain frequently occurs on standing or walking, and systemic illness is present because of the hepatopathy. The finding of this unusual pattern of skin lesions should always prompt a search for comorbid liver disease.

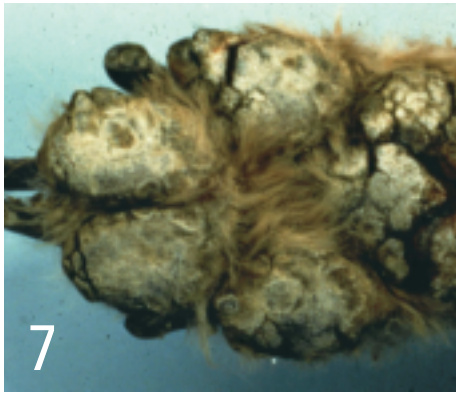
Miscellaneous Drug Eruption Syndromes

Irritant (or Allergic) Contact Dermatitis

This type of dermatitis, which is related to application of topical medications, may also be considered a "drug reaction," although it is generally considered separate from idiosyncratic CADRs. In the author's experience, allergic contact dermatitis to topical medications is rare but



Focal area of alopecia on the shoulder, ventral to the site of injection of a rabies vaccine, 2 months after injection. The alopecia may be permanent.



Cracking, fissuring footpads in a dog with hepatocutaneous syndrome. In this case, the syndrome resulted from phenobarbital hepatotoxicity due to treatment of a seizure disorder.

is most commonly associated with neomycin-containing topical or otic products (**Figure 1**).

Fixed Drug Eruption

This type of CADR is an unusual syndrome, in which systemic administration of a drug results in circumscribed, edematous to erythematous lesions that may eventually progress to ulceration. The characteristic and unusual feature is that the lesions reappear at exactly the same site each time the drug is readministered.[1] Withdrawal of the offending drug prevents further occurrence.

Prevention

Because CADRs occur idiosyncratically and are unpredictable, no specific measures can be taken to prevent their occurrence. However, it is critical that clinicians always maintain a high degree of suspicion when *any sudden, unexplained skin condition occurs in a pet being treated with a drug*. This event should prompt consideration of a drug eruption, and immediate discontinuation of the drug, if possible. It is also important to routinely advise clients of the possibility of a CADR and the clinical signs thereof, particularly when treating a patient with a drug known to be associated with CADR.

Prognosis

The prognosis for a CADR is generally good as long as the offending drug can be withdrawn, that TEN has not occurred, and that other organ systems are not involved. The latter 2 situations create a much less optimistic scenario—the prognosis for recovery from TEN is poor.

Treatment

The general treatment approach involves discontinuing the drug, treating with supportive care for 1 to 3 weeks as necessary, and avoiding use of the same or structurally related drugs in the future. Cutaneous adverse drug reactions are notoriously unresponsive to corticosteroid therapy, even at immunosuppressive doses, although such therapy is widely used as part of treatment.

The author has found pentoxifylline (10 mg/kg PO Q 8 H) to be valuable for patients with clinical or histologic evidence of vasculitis, and this drug may be of some use in erythema multiforme and TEN. More recently, concentrated human IV immunoglobulin (IVIG) infusions have been shown to be remarkably beneficial for treatment of severe reactions in the erythema multiforme/TEN group in both humans and animals. Such treatment may represent a life-saving advance in managing severe TEN. A few dogs and cats[12] with TEN have been treated with dramatic success using a single slow intravenous infusion of human IVIG at 1 g IVIG/kg patient weight. Unfortunately, human IVIG can be difficult to obtain and costs over U.S. $100/g. There has been speculation that equine IVIG, which is more readily available and less expensive, may have similar benefit. Attempting such treatment is probably warranted, considering the otherwise-poor prognosis.

See Aids & Resources, back page, for references, contacts, and appendices.