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CUTANEOUS ADVERSE DRUG REACTIONS

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INTRODUCTION

Of all adverse drug reactions, cutaneous manifestations are one of the most common. Cutaneous adverse drug reactions (CADRs, also loosely termed “drug eruptions”) are difficult to diagnose with certainty and often go unreported. Therefore, their true prevalence in domestic animal species is not well established, though empirically they represent 1-2% of all patients examined at specialty dermatology clinics. Since CADRs appear sporadically and are quite variable in presentation, there is a paucity of CADR “collections” reported in the literature, with perhaps only a dozen references in the veterinary literature over the past 20 years, and most of these being single case reports.

Any drug may cause a CADR, though most cases in small animals appear to be related to antibiotics (in particular, potentiated sulfonamide and beta-lactam drugs), phenothazines, levamisole, and nonsteroidal anti-inflammatory drugs. Reactions have been seen with topical, oral, or parenteral formulations. In addition, several specific and unique syndromes are associated with particular drugs such as itraconazole, methimazole, and doxorubicin (see below).

Generally, CADRs can be divided into two types: *Predictable* reactions are related to a known pharmacologic action of a drug and are usually dose-dependent; familiar examples include alopecia associated with immunosuppressive or antineoplastic drugs, or an allergic contact dermatitis from neomycin-containing topical formulations. In contrast, the *idiosyncratic* reactions are unrelated to the primary pharmacologic effect, are independent of dose, and occur related to immunologic and/or genetic factors in the host. This review will concentrate on this latter group of CADRs.

CLINICAL FEATURES OF CUTANEOUS ADVERSE DRUG REACTIONS

The dermatologist’s rule of thumb is that “drug eruptions can look like anything,” and in human medicine they are thought to be able to mimic nearly any dermatosis. Certain patterns are more common in domestic animals, including:

1. Maculopapular eruptions (“red rashes”)
2. Urticaria and/or angioedema (“hives”)
3. Blistering, pustular, and/or ulcerative patterns (“autoimmune-like”) – includes erythema multiforme, Stevens-Johnson type reactions, toxic epidermal necrolysis, pemphigus-like, vasculitis, etc.
4. Exfoliative (scaling) dermatoses
5. Pruritus with self-induced excoriations
6. Erythroderma (marked cutaneous erythema which may extend over large areas of the body).

In diagnosing CADRs, bear in mind that they can occur in any age, breed, or sex of animal, but certain syndromes have a strong association with a breed, for example sulfonamide sensitivity in Dobermans. Interestingly, though human beings with HIV infection are at increased risk for a CADR, such an association has not been made for FeLV-positive cats. Drug eruptions usually occur within 1 to 3 weeks after starting drug

therapy, often appear rather suddenly, and persist for 1 to 3 weeks after discontinuation of the offending medication; however these are only generalizations. Because CADRs can “look like anything” it is important to obtain a thorough drug history from any patient with a recent onset, unexplained skin disease of any type. Unfortunately, many patients experiencing a drug eruption often have serious diseases that are being treated with a variety of drugs concurrently or in sequence, which makes incriminating any particular drug difficult. There is no specific diagnostic test that is uniformly helpful for establishing the diagnosis of drug reaction. Biopsy findings vary widely, and include perivascular dermatitis, interface dermatitis, vesicopustular dermatitis, panniculitis, granulomatous dermatitis, and vasculitis. Thus, there is really no specific histologic pattern that uniformly suggests the presence of a CADR.

The clinical pleomorphism seen in CADRs perhaps reflects that they may occur through a variety of mechanisms, most of which are incompletely understood. Reactions are sometimes related to the parent compound, and sometimes related to a metabolic intermediate. Clearly, some CADRs are “classical” Type I, II, III, or IV hypersensitivity reactions. 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 destroy keratinocytes directly, and other types may induce pathology through their release and induction of a variety of cytokines that promote cutaneous inflammation or even apoptosis.

SPECIFIC DRUG ERUPTION SYNDROMES

The Erythema Multiforme/Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis “Group”

Much confusion and debate has centered on these uncommon diseases, even over how to differentiate them from each other by clinical appearance. At one time, they were considered variants of a single disease “group,” but recent immunohistologic evidence suggests that they are probably separate entities. In some cases they are clearly related to a drug reaction, but it must be emphasized that they may also be secondary to infection, neoplastic disease, or idiopathic in origin.

Erythema multiforme (EM) is the most common of the group. It is perhaps best characterized as an acute, usually self-limiting, symmetrical eruption of the skin (and possibly mucous membranes) with appearance of flat to raised “target” lesions (central clearing, peripherally spreading), along with an erythematous or purpuric macular to patchy eruption occurring on up to 50% of the skin surface. Ulcerations or epidermal detachment may occur, on the skin or in the oral mucosa, but is limited to less than 10% of the body surface. Mild systemic signs may be present, usually relating to the severity of the skin disease. Assuming that relatively early (non-ulcerated) skin biopsy specimens can be obtained, the histopathologic findings are unique and often diagnostic, and include interface dermatitis with edema of keratinocytes, prominent areas of individually necrotic keratinocytes, with “satellitosis” or adjacent adherence of lymphocytes and/or macrophages to the apoptotic keratinocytes. Though patients with EM have a rather dramatic appearance, it is a “relatively mild” disease in that if the underlying precipitating cause can be found and stopped, most cases recover with supportive care within 1-3 weeks. The pathogenesis of EM is not understood, but it is thought to represent some type of immunologic reaction against a foreign antigen, which could be an organism, a food, a drug,

or an autoantigen. As part of this reaction, the keratinocytes are stimulated to express large quantities of adhesion molecules (such as ICAM-1) which “holds” the inflammatory reaction within the epidermal tissues and creates a “cell-rich” cutaneous inflammatory infiltrate, particularly of T-lymphocytes. Despite the presumed immunopathology of this disease, there is controversy about whether therapy with glucocorticoids or other immunosuppressive therapies are helpful.

In **Stevens-Johnson syndrome**, classical “target” lesions are NOT present, but the erythematous eruption occurs over more than 50% of the body surface and mucosal involvement is generally severe. Systemic signs are often prominent. Epidermal ulceration and detachment is still less than 10% of the total body surface. Some authors believe Stevens-Johnson syndrome is merely a mild manifestation of toxic epidermal necrolysis.

Toxic epidermal necrolysis (TEN) is the most severe of these diseases, has the highest association with being caused by a drug reaction, and has the greatest risk for mortality. In addition to mucosal involvement and greater than 50% of the body surface involved in the erythematous eruption, at least one-third of the body surface becomes subject to complete detachment of the epidermis with resultant ulceration. Systemic signs and pain are prominent. Histopathology of skin biopsy specimens shows large, contiguous areas of epidermal cell necrosis, including full-thickness necrosis and detachment in many places. Surprisingly, the dermal inflammatory cell infiltrate in TEN is relatively cell-poor, and dominated by macrophage-like cells. In human beings, evidence points to sudden and massive induction of keratinocyte apoptosis as a major mechanism.

Syndromes Associated with Antifungal Drugs

Itraconazole has been associated with sudden development of vasculitis in canine patients, typically after a month or more of therapy for systemic mycoses such as coccidioidomycosis or blastomycosis. Cutaneous ulcerative lesions caused by this drug eruption can be misinterpreted as worsening of the primary disease, and skin biopsy is useful to differentiate the drug reaction from recurring mycosis. Treatment with amphotericin B is occasionally associated with development of calcinosis cutis in dogs.

Methimazole and Propylthiouracil Reactions in Cats

These antithyroid drugs have been associated with alopecia and scaling/crusting reactions of the head and face in cats. Severe pruritus with excoriations may be present, making the disease similar to 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.

Injection Reactions

A focal area of vasculitis with alopecia has been reported in some small-breed dogs after administration of rabies vaccine. This reaction has been reported mostly in small, long-haired dogs such as Poodles, Bichons, Yorkshire, Silky, and Maltese Terriers, and Pekingeses, and is unassociated with

any other signs of “vaccination reaction.” Interestingly, vaccine antigens have been demonstrated via immunohistology in biopsy specimens of these 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.

Palmoplantar Erythrodysesthesia (PPES; “Hand-Foot Syndrome”) with Doxil

Doxil, a liposome-encapsulated form of doxorubicin, has been associated with this unique 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. The reaction can be dose-limiting and thus limit treatment success with this antineoplastic drug. Though the pathomechanism is unclear, the effect can be partially mitigated through concurrent use of oral pyridoxine supplementation.

Hepatocutaneous Syndrome from Hepatotoxic Drugs

Hepatocutaneous disease is a syndrome of unknown pathogenesis in which liver pathology (of apparently any type) appears concurrent with skin lesions and necrosis of epidermal cells. The “metabolic connection” that causes keratinocyte death has not been established, though the hepatopathy is considered to be the primary cause, and the skin disease a secondary effect. Several dermatologists have seen this syndrome secondary to chronic administration of hepatotoxic drugs, including phenobarbital. The clinical picture is very striking, and includes ulcerative and crusting lesions of the inguinal and axillary regions and footpads, often with severe cracking and fissuring of the latter. There is frequently pain in standing or walking, and systemic illness related to the hepatopathy. The finding of this unusual pattern of skin lesions should always prompt a search for evidence of concurrent liver disease.

DIAGNOSING AND TREATING CUTANEOUS ADRs

The prognosis for a CADR is generally good, providing that the offending drug can be withdrawn, that there is not extensive epidermal necrosis, and that other organ systems are not involved; the latter two situations create a less optimistic scenario. The general treatment approach involves discontinuation of the drug, treating with supportive care as necessary, and avoiding use of chemically related drugs in the future. Cutaneous adverse drug reactions are notoriously unresponsive to corticosteroid therapy, though such therapy is widely used as part of treatment. Pentoxifylline has been valuable for patients with clinical or histological evidence of vasculitis and may be of some use in EM/TEN. Recently, human intravenous immunoglobulin was used for treatment of a cat with severe erythema multiforme, with dramatic improvement. This therapy, which is beneficial for similar types of CADRs in humans, bears further study in domestic animals for treating CADRs of the EM/SJ/TEN “group.”