Use of human immunoglobulin for treatment of severe erythema multiforme in a cat

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- ➤ Cutaneous drug reactions may cause serious life-threatening disease, and satisfactory treatment has not been available.
- ➤ When lesions persist after withdrawal of the inciting cause and use of supportive care measures, treatment to halt the aberrant immune response is necessary.
- ➤ Human intravenous immunoglobulin appears to be a promising treatment for severe cutaneous drug reactions that acts by blocking binding of Fas ligand to Fas receptors on keratinocytes.

A 5-month-old sexually intact female domestic shorthair cat was referred to the **Veterinary Hospital of the University of Pennsylvania (VHUP)** for evaluation of pruritus and severe crusting and ulcerative skin lesions of 10 days' duration. The cat was found as a stray at 5 weeks of age and adopted by the owners at approximately 12 weeks of age. The owner reported that before adoption the cat had received a feline rhinotracheitis virus-calicivirus-panleukopenia virus combination vaccine, had negative results of tests for FeLV, and had been given a medication for intestinal parasites. Sixteen days prior to rabies vaccination, the cat had received another feline rhinotracheitis virus-calicivirus-panleukopenia virus combination vaccine[a] and pyrantel pamoate[b] (5 mg/kg [2.3 mg/lb] of body weight, PO). At the time of administration of a killed rabies vaccine[c] (right hind limb, SC), pyrantel pamoate (6.7 mg/kg [3.0 mg/lb], PO) for potential intestinal parasites and a single application of an otic preparation[d] containing neomycin, thiabendazole, and dexamethasone (both ear canals) were administered by the owner's primary veterinarian.

One day later (day 1), skin lesions developed rapidly and were characterized by the owner as crusting scabs. Lesions first appeared on the face and head and progressed to the trunk, limbs, and feet during a 5-day period. Results of a dermatophyte culture and skin scrapings for mites obtained by the primary care clinician 2 days after the onset of skin lesions were negative. Prednisone acetate (1.4 mg/kg [0.6 mg/lb], SC) was administered and prednisone (1.8 mg/kg [0.8 mg/lb], PO, q 12 h) was dispensed for 20 days. However, the owner discontinued administration of the prednisone after a few days because of perceived lack of response; the cat was lethargic, and the crusts and hair loss worsened, but its appetite remained normal.

During initial examination at VHUP (day 10) the cat was lethargic, febrile (rectal temperature, 39.7 C [103.5 F]), stunted, and thin (weight, 1.4 kg [3.1 lb]). Respiratory and heart rates were within reference ranges, but a grade II/V systolic murmur was auscultated. Skin turgor could not be evaluated because of extensive skin lesions. Dermatologic examination revealed crusts ≤ 0.6 cm thick that involved > 50% of the body surface area and were confluent on the head, neck, and shoulder areas. Smaller lesions (1 to 2 cm) were visible on the ventrum, and 1 ulcerated fissure with purulent exudate on the left side of the trunk was detected. Extensive involvement of the coat within crusts accentuated the alopecia (**Fig 1**). The footpads and perionychial areas of all 4 feet were also severely crusted. There were no visible lesions in the oral cavity.

Abnormalities detected via CBC were mild leukocytosis (23,300 WBC/µl; reference range, 5,500 to 19,500 WBC/µl) attributable to mild neutrophilia (14,000 cells/ml; reference range, 2,500 to 12,500 cells/µl) and marked eosinophilia (4,400 cells/µl; reference range, 0 to 1,000 cells/µl). There was a mild normocytic-normochromic anemia (Hct, 32%). Serum biochemical abnormalities included hypernatremia (164 mmol/L; reference range, 148 to 157 mmol/L]), hyperchloremia (130 mmol/L; reference range, 115 to 128 mmol/L]), and hyperproteinemia (7.7 g/dl; reference range, 5.5 to 7.1 g/dl) associated with increased serum albumin and globulin concentration; BUN (25 mg/dl; reference range, 15 to 29 mg/dl) and creatinine concentrations (1.3 mg/dl; reference range, 0.5 to 1.4 mg/dl) were near the upper limits of the reference range, which was suggestive of dehydration most likely attributable to insensible water loss because of extensive skin damage. We decided not to obtain a urine sample by use of cystocentesis because of the severity of skin lesions.

Results of multiple skin scrapings for mites and a dermatophyte culture of hair samples were again negative. Cytologic examination of exudates from ulcerated areas of the trunk revealed marked neutrophilic inflammation with small numbers of coccoid bacteria and few yeast organisms. Because of the temporal relationship between the development of skin lesions and administration of the rabies vaccine, anthelmintic, and otic preparation, **erythema multiforme (EM)** appeared likely. Severe pemphigus foliaceous, bacterial dermatitis, and ectoparasitism were also considered. Because the owners reported

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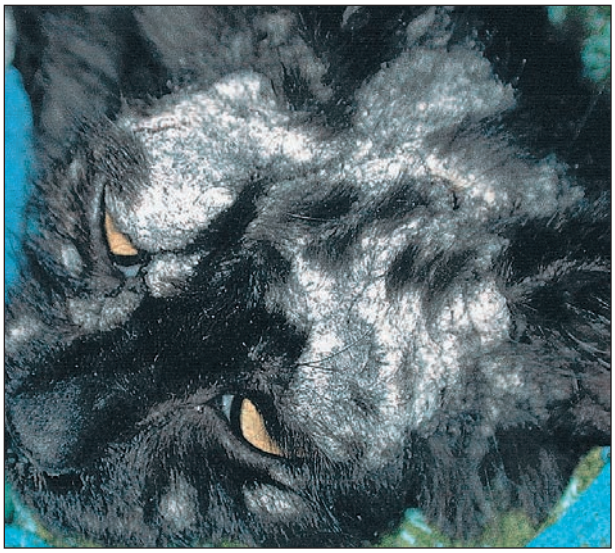

Figure 1—Photograph of a cat with severe erythema multiforme. Notice crusting and ulcerative skin lesions.

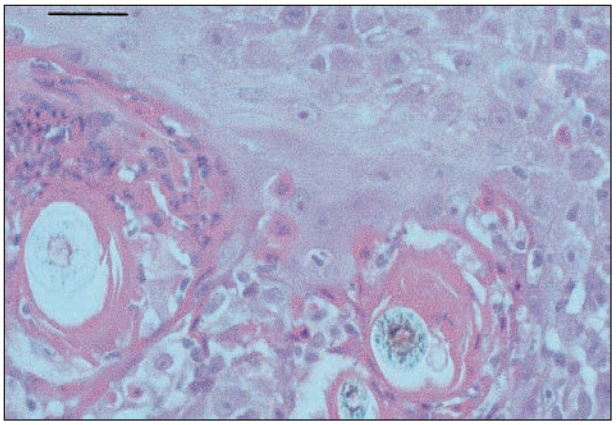

Figure 2—Photomicrograph of a section of skin from the cat in Figure 1. H&E stain; bar = 50 µm.

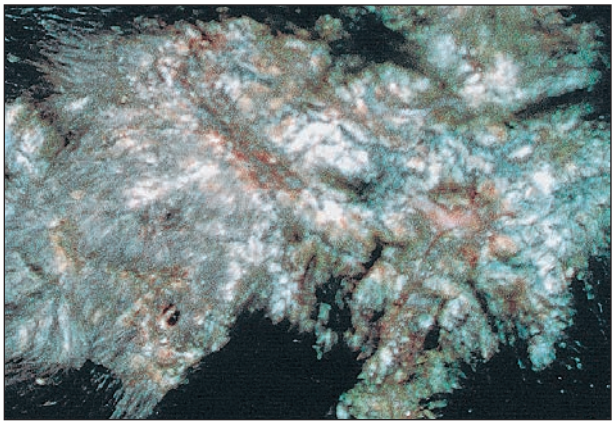

Figure 3—Photograph of the skin of the shoulder region of a cat with severe erythema multiforme. Notice persistence of severe ulceration and crust formation 25 days after initiation of various treatments.

that the cat continued to eat and drink at home, treatment for dehydration was not given. The owners were instructed to administer cefadroxil[e] (11.5 mg/kg [5.2 mg/lb], q 12 h) orally and lime sulfur[f] (3% in water, q 7 d) and a moisturizer[g] (q 12 h) topically.

Skin biopsy specimens were obtained from the dorsal portion of the trunk with a 6-mm skin biopsy punch and processed for routine histologic examination. Degenerating granulocytes were evident in the stratum corneum and follicular infundibulum. Apoptotic keratinocytes were seen at all levels of the epidermis and in the external root sheath of the hair follicles **(Fig 2)**. A dermal infiltrate composed of moderate numbers of mast cells and eosinophils was also evident. The histopathologic findings confirmed a diagnosis of EM.

Fourteen days later (day 25), the cat was returned to the VHUP because of progressive lethargy and lack of improvement of skin lesions **(Fig 3)**. The cat was afebrile (rectal temperature, 38.3 C [100.9 F]), pulse and respiratory rate were within reference ranges, and body weight and heart murmur remained unchanged from day 10. The extent and severity of skin lesions appeared to be slightly worse than previously. Cytologic examination of exudate from ulcerated areas of the trunk revealed small numbers of coccoid bacteria and few yeast organisms. Mild anemia (Hct, 31%) and leukocytosis (18,500 WBC/µl) attributable to slight monocytosis (1,100 cells/µl; reference range, 0 to 900 cells/µl]) and marked eosinophilia (4,500 cells/µl) were detected. Serum biochemical analysis again revealed mild hypernatremia (162 mmol/L) and hyperchloremia (131 mmol/L) attributable to dehydration, but BUN (15 mg/dl) and creatinine concentrations (0.4 mg/dl) were within reference ranges. Total protein and albumin concentrations had decreased to 7.0 and 2.7 g/dl, respectively. Further diagnostic tests included fecal examination for intestinal parasites and ELISA for FeLV antigen; these results were negative.

Because of the extent and severity of the EM, lack of improvement with supportive treatment, and the known resistance to conventional treatment and progressive nature of EM, a recently proposed alternative treatment for drug reactions in humans was considered. After informed consent was received from the owner (required because the product is of human origin and not approved for use in cats), human **intravenous immunoglobulin (IVIG)** was administered. A 6% solution of human IVIG[h] in saline (0.9% NaCl) solution was prepared according to manufacturer's recommendations and infused IV at a dose of 1 g/kg (0.45 g/lb) during a 4-hour period on day 26 and again on day 27. During the infusion, no other medications were given, and food was withheld to avoid possible gastrointestinal tract disturbances attributable to infusion of human IVIG. There were no apparent adverse effects during or after administration, and the cat was alert and eating well thereafter. Twenty-four hours after the second infusion, CBC abnormalities persisted, including mild leukocytosis (22,000 WBC/µl) attributable to slight monocytosis (1,300 cells/µl), eosinophilia (5,300 cells/µl), and mild basophilia (440 cells/µl; reference range, 0 to 200 cells/µl]); mild hypernatremia (162 mmol/L) and increased total protein concentration (8.0 g/dl) were also detected. Serum biochemical analysis revealed slightly increased BUN (57 mg/dl) and creatinine (1.9 mg/dl) concentrations. A cystocentesis for urinalysis

was not performed because of concerns of bacterial contamination through skin crusts. The cat was discharged to the owners on day 28 with the instructions to administer cefadroxil[c] (18 mg/kg [8.2 mg/lb] PO, q 12 h) and topical moisturizer as before.

According to the owners, the cat's demeanor improved dramatically 4 days after initiation of human IVIG therapy (day 30), and the skin was healing rapidly. Eight days after initiation of human IVIG therapy (day 34) the cat was reevaluated. The cat was bright, alert, and afebrile (38.6 C [101.5 F]). Pulse and respiratory rate were within reference ranges, and body weight was unchanged. There was > 90% resolution of crusts on the skin of the head, trunk, and proximal portion of the limbs. The skin in these areas was now intact, pliable, and nonexudative, with no erythema (**Fig 4**). There was cutaneous hyperpigmentation, and some areas had a small amount of new hair growth. There was at least 60 to 70% reduction in crusting at the perionychial areas, and only a single crust (0.5 cm) was found over the right eye. Abnormalities revealed by use of a CBC included mild anemia (Hct, 25%; reference range, 33.0 to 45%), leukocytosis (23,000 WBC/µl), neutrophilia (16,000 cells/µl), mild monocytosis (2,500 cells/µl), and eosinophilia (3,000 cells/µl). Serum creatinine (0.4 mg/dl) and BUN concentrations (15 mg/dl) were within reference ranges, but slight hypernatremia (160 mmol/L) and mild hyperchloremia (130 mmol/L) persisted. Mild hypoalbuminemia (2.3 g/dl; reference range, 2.7 to 3.9 g/dl]) was also detected. The owners declined any further diagnostic tests, and the cat was discharged to the owners for observation.

Fifty-seven days later (day 117), the cat was returned to VHUP for routine ovariohysterectomy. The cat was afebrile (38.7 C [101.6 F]), and pulse and respiratory rate were within reference ranges. Body weight had increased to 2.8 kg (6.2 lb), and the heart murmur was still evident. A benign flow murmur was suspected, because results of thoracic radiography, echocardiography, and Doppler echocardiography were all unremarkable. No skin lesions were found, and the cat had a normal coat. There was no evidence of anemia (Hct, 39%) or leukocytosis (4,880 WBC/µl), and abnormalities of the differential cell count and serum biochemical values were completely resolved. Results of urinalysis were within reference ranges. Routine ovariohysterectomy was performed uneventfully.

Erythema multiforme is a rare disease of the skin in humans and other animals[1-4] and is thought to represent a host-specific cell-mediated hypersensitivity reaction induced by various antigens that alter keratinocytes, making them targets of an aberrant immune response.[4] In humans, almost all cases of EM are associated with herpesvirus infections. Erythema multiforme has been more commonly reported in dogs than in cats, but in both species it is typically associated with drug administration (eg, ampicillin, cephalexin, trimethoprim-sulfonamide, griseofulvin, acepromazine, neomycin, chloramphenicol, enrofloxacin, and lincomycin),[1,5] although many cases in dogs remain idiopathic.[5] One dog appeared to develop EM secondary to otitis caused by *Pseudomonas* sp, which resolved after appropriate antimicrobial therapy. In another dog, EM appeared to

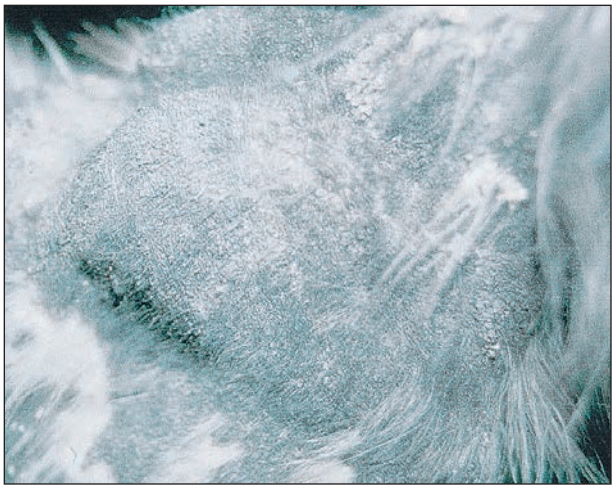

Figure 4—Photograph of the skin of the shoulder region of a cat with severe erythema multiforme 8 days after IV administration of human immunoglobulin. Notice resolution of ulcers and crusts, although scaling is evident and the areas that were ulcerated are hyperpigmented.

be triggered by exposure to beef, soy, or both.[5] Administrations of vaccines, anthelmintics,[1] and otic medications[4] have been suggested as a possible causes of cutaneous drug reactions in various animals. In humans, a small number of cases of **toxic epidermal necrolysis (TEN)**, a closely related drug reaction, are associated with vaccination[2] or administration of measles-mumps-rubella vaccines.[6] Lesions of EM usually develop after 7 to 18 days of exposure to the offending agent,[5] although lesions may develop as soon as 1 day after exposure if the animal has been previously exposed.[7] Often, more than 1 drug has been administered shortly before the development of lesions, making it difficult to determine which was the offending agent. Challenge studies with single agents may determine the causative agent in these cases but would be risky and therefore unethical.

In the cat reported here, lesions developed 1 day after administration of the first killed rabies vaccine, second administration of pyrantel, and first known application of an otic preparation; this incriminated the anthelmintic that the cat had received previously. Pyrantel has not been associated with EM in dogs and cats. The cat had not received rabies vaccination previously but had received a vaccine for feline rhinotracheitis virus-calicivirus-panleukopenia virus produced by the same manufacturer. It is possible that the 2 vaccines contained a similar ingredient that initiated EM upon reexposure. There was no history of prior use of the otic preparation, although previous exposure could not be completely ruled out, because it is so commonly used. Additionally, the otic preparation contains neomycin, an antimicrobial that has been associated with EM in dogs and cats. Use of these medications should be avoided in the cat reported here. Avoidance of reexposure to rabies vaccine may also need to be considered as far as regulatory organizations permit. A different vaccine against rabies (eg, canary pox vaccine)[i] could be tried.

Gross lesions of EM in dogs and cats may appear as erythematous papules and plaques that may have central clearing and coalesce to form serpiginous and arciform shapes. Some lesions, especially in cats,

become bullous, with detachment and necrosis of the epidermis as observed in the cat reported here. The principal histopathologic finding in EM is necrosis or apoptosis of individual keratinocytes, which usually develops at all levels of the epidermis and may also involve epithelium of the hair follicles. Some affected animals have full-thickness necrosis of the epidermis, a finding typical of TEN, which is clinically more severe than EM.[4,8,9] Abnormalities such as leukocytosis, eosinophilia, and abnormalities associated with dehydration may be evident in both diseases. In our cat, peripheral eosinophilia persisted through day 117. Eosinophilia has been occasionally reported in humans with TEN and in 3 dogs with EM.[2,5,10,11]

Regardless of classification of a drug reaction as EM or TEN, apoptosis or keratinocyte necrosis is characteristic of both conditions. Induction of apoptosis or keratinocyte necrosis may be triggered by a number of factors, including infiltrating CD8+ T lymphocytes, **tumor necrosis factor α (TNF α)**, and activation of a "death receptor" such as Fas on the keratinocyte cell surface.[2,5,12-15] When **Fas ligand (FasL)** expression was analyzed in skin samples, there was marked upregulation of FasL in keratinocytes in all skin samples from humans with TEN but not in control samples. Furthermore, skin sections from humans with TEN but not skin sections from healthy controls induced 3- to 4-fold more cell death in Jurkat cells (a Fas-sensitive cell line). This cytotoxicity was completely abrogated by incubation with FasL-blocking monoclonal antibody.[14] In dogs and cats, infiltrating CD8+ T lymphocytes also appear likely to be responsible for the induction of apoptosis in EM, whereas TNF α may be important in induction of apoptosis or keratinocyte necrosis in TEN[4]; however, FasL expression in the skin of dogs or cats with EM has not been studied.

In human and veterinary medicine, management of cutaneous drug reactions includes withdrawal of suspect drugs administered within the 2 weeks prior to development of lesions, as well as any related drug or drug with a similar chemical structure. A thorough search for underlying infectious disease or neoplasia is warranted if there is no history of drug administration. Supportive care to prevent dehydration is necessary if lethargy results in decreased fluid intake or if damage to the skin results in increased insensible water loss. Prevention of bacterial skin infections and management with systemic antimicrobial that are unrelated to any suspect drugs are necessary when erosion and ulceration leaves the skin susceptible to secondary infections. Erythema multiforme in dogs and cats that is triggered by administration of a drug often improves within 2 weeks after supportive care, control of secondary infections, and avoidance of the suspect drugs are instituted.

In humans, treatment options for drug reactions other than withdrawal of the offending agent and supportive care are controversial, as there are no controlled studies documenting efficacy of different treatment protocols.[16,17] Prompt withdrawal of the offending drug in humans suspected of having TEN is key and greatly reduces mortality rate.[18] The use of systemic glucocorticoids for treatment of EM is not recommended, and the use of systemic glucocorticoids for treatment of TEN is controversial. At 1 hospital, the mortality rate of human patients with TEN declined when the routine use of glucocorticoids was discontinued.[19]

Treatment with glucocorticoids may have some benefit for dogs with idiopathic EM; lesions in 2 dogs worsened when administration of glucocorticoid was discontinued, then improved when treatment was reinstituted.[5] A dog and cat with EM appeared to improve only after being treated with chlorambucil and the immunosuppressive drug azathioprine.[5] In the cat reported here, lesions persisted 3 weeks after exposure to suspect drugs and appeared to worsen during administration of prednisone.

A novel therapeutic option has been proposed in humans with severe cutaneous drug reactions. Human IVIG is a highly purified polyvalent antibody product containing all the IgG antibodies that regularly occur in the human donor population. It contains trace amounts of fragments of IgM and IgA and is approved for treatment of human hepatitis infections, some primary immunodeficiencies such as Kawasaki syndrome, and certain immune-mediated disorders, including idiopathic thrombocytopenia purpura and dermatomyositis.[h] Proposed mechanisms for the in vivo immunomodulatory effects of IVIG include blockade of Fc receptors on macrophages, inhibition of complement activity, modulation of cytokine synthesis, interference with T- and B-cell functions, neutralization of autoantibodies, and selection of immune repertoires such as suppression of autoantibody-producing clones of lymphocytes.[20,21] Because human IVIG contains antibodies against Fas and is able to block in vitro binding of FasL to Fas,[14] IVIG has been proposed as a promising treatment for TEN in humans. Recent reports indicate that the use of IVIG (0.4 to 0.75 g/kg [0.2 to 0.3 mg/lb] per day, 2 to 4 treatments) in humans with TEN led to rapid clinical improvement. In 1 report of 10 patients with TEN treated with IVIG, epidermal detachment ceased after 24 to 48 hours, and complete skin healing occurred after 4 to 10 days. All 10 patients recovered completely, although, on the basis of mortality rates for TEN, 1 would have been expected to die.[14] Similar results were observed in an additional 7 patients with TEN,[15] and 2 children with severe TEN rapidly improved after administration of human IVIG.[22]

To the authors' knowledge, use of IVIG in cats has not been previously reported. Because of the protracted course (> 3 weeks), lack of response to drug withdrawal, treatment with prednisone and supportive care, worsening of skin lesions, and deteriorating overall status, human IVIG was administered after informed client consent. Within days of human IVIG infusion, resolution of all skin lesions and laboratory abnormalities began and was complete within 2 months. The infusion was well tolerated with no major adverse effects; the increased BUN and creatinine concentrations were unexplained. These findings may suggest a beneficial effect and may support the judicious use of IVIG in severe EM and TEN before serious morbidity or mortality develop.

Since the successful management of EM with IVIG in this cat, a dog with severe acute skin necrosis, hepatopathy, anemia, thrombocytopenia, and a histologic diagnosis of severe necrotizing epidermitis compatible with TEN was also successfully treated with the same IVIG regimen.

[a]FeloVax PCT, Fort Dodge, Overland Park, Kan.
[b]Nemex, Pfizer Animal Health, New York, NY.
[c]Rabvac 1, Fort Dodge, Overland Park, Kan.
[d]Tresaderm, Merial Ltd, Iselin, NJ.
[e]Cefa Drops, Fort Dodge Animal Health, Overland Park, Kan.
[f]Lym dip, DVM Pharmaceuticals, Miami, Fla.
[g]Aquaphor, Beiersdorf-Jobst Inc, Norwalk, Conn.
[h]Sandoglobulin, Sandoz Pharmaceuticals, East Hanover, NJ.
[i]PureVax feline rabies vaccine, Merial, Iselin, NJ.

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