Long-Term Management of Vaccine-Induced Refractory Ischemic Dermatopathy in a Miniature Pinscher Puppy

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ABSTRACT. A 2-month-old intact female Miniature Pinscher puppy presented with footpad swelling and crusted pustules of ear pinnae. The dog had been vaccinated with a polyvalent canine vaccine 5 days prior to the onset of clinical signs. With the history of recent vaccination, the clinical presentation and the histopathological observations were suggestive of ischemic dermatopathy. Treatment involved oral prednisolone, azathioprine, and other immune modulating drugs, which did not work. Chlorambucil plus cyclosporine therapy was initiated for vigorous immune suppression after rush therapy using intravenous immunoglobulin. Clinical signs again gradually improved with no relapse or side effects, even at a 4-month follow-up. The case report is suggested ischemic dermatopathy refractory to conventional therapy and suggests effective approaches to long-term management of the disease.

KEY WORDS: canine, intravenous immunoglobulin, ischemic dermatopathy, vaccine.

Ischemic dermatopathy is a syndrome that results from loss of blood supply from either vasculitis or vasculopathy [16]. It is often related to dogs with postrabies vaccination associated disease [5]. The lesions of ischemic dermatopathy subsequent to rabies vaccination are characterized by alopecia and focal vasculitis [5]. Meanwhile, reports have described vaccine-induced ischemic dermatopathy associated with not only rabies but also multivalent puppy vaccines [5, 20].

Management of the disease in veterinary medicine typically includes the use of glucocorticoids, dapsone, pentoxifylline, sulfasalazine and vitamin E with antibiotics [8, 9, 11]. However, some cases fail to be managed with these treatments and require long-term maintenance therapy [16]. This case report describes a dog with putative vaccine-induced canine ischemic dermatopathy that was refractory to conventional therapy.

A 2-month-old, intact, female Miniature Pinscher puppy presented with acute swelling of the feet and pustular lesions on ear pinnae. The dog had been vaccinated 5 days prior to the onset of clinical signs. The vaccine was a modified live combination product that included distemper, parainfluenza, parvo and rabies virus. The clinical signs worsened after 2 weeks following a second vaccination with the same vaccine.

On physical examination, severe swelling and crusts were present on the foot pads, ruptured pustules were present on ear pinnae and a necrotic ear margin was found (Fig. 1). There were no specific lesions on the site of vaccination. Hematology and serum biochemistry were within normal ranges. Radiographs of the swelled feet were unremarkable.

Skin scrapings were negative for ectoparasites. Cytological examination of the pustules on ear pinnae revealed sterile pyogranulomatous inflammation. Differential diagnoses included cutaneous vasculitis (ischemic dermatopathy), juvenile cellulitis, systemic lupus erythematosus, and pemphigus complex, infectious diseases, and histiocytic tumor. There were no proteinuria and a systemic clinical signs like fever, therefore, systemic lupus erythematosus was unlikely. Bacterial and fungal cultures of the pustules were negative. Skin biopsy was collected from foot pad for histological examination, which revealed severe diffuse vacuolation along the dermal-epidermal junction. There were accumulations of neutrophils and few mononuclear cells around the vessel (Fig. 2). Although histopathological findings were a little obscure, ischemic dermatopathy was likely.

Initially, human immunoglobulin (hIVIg) was administered at the dosage of 1 g kg⁻¹ over 4-hr on 2 consecutive days, followed by oral prednisolone at a dose of 1 mg kg⁻¹ twice daily and amoxicillin-clavulanic acid at a dosage of 12.5 mg kg⁻¹ twice daily. The dog’s condition moderately improved, with resolution of foot pad swelling within 24 hr. However, the ear pinnae lesion was not impressively responsive. After 1-week, oral azathioprine was added at a once-daily dosage of 2 mg kg⁻¹. However, the lesions progressively worsened and new lesions developed (Fig. 3). Ulceration on foot pads and swelling of the bridge of nose were noticed. Dapsone and pentoxifylline were also added for adjuvant therapy. But those drugs were withdrawn, for they did not work. For an immediate response, three additional injections of hIVIg were given. Severe refractory ischemic dermatopathy needed to be vigorously immune suppressed, which was accomplished by oral administration of chlorambucil at the dosage of 0.2 mg kg⁻¹ once daily along with cyclosporine instead of prednisolone. Clinical improvement was observed within 1 week with response to
Fig. 1. Photographs of this case at the first presentation. A: Foot pads were erosive and swollen. Erythema was also noted with crusts. B: Necrosis of the ear margin with a ruptured pustule was evident.

Fig. 2. Histological appearance of the foot pad biopsy specimen. A: Severe multifocal nodular to diffuse dermatitis in the footpad with a large pustule and focal ulcer (H&E stain, Bar=1 mm). B: High power magnification of A. There were accumulations of neutrophils and few mononuclear cells around the vessel (H&E stain, Bar=100 µm).

Fig. 3. Photographs of the dog after clinical relapse. The lesions had worsened, and development of new lesions had occurred. A: Foot pads with ulcerative depressions (pits). B: Papulopustular lesion on an ear pinna. C: Swelling of the nasal planum.
chlorambucil becoming gradually evident over the subsequent several weeks. The dog improved with no development of new lesions or worsening of existing lesions for 4-months (Fig. 4). Then chlorambucil have been tapered to 0.1 mg kg$^{-1}$ once daily. Side effects related to immune suppressive therapy in routine blood test profiles were not found at this follow-up.

The present case was likely associated with vaccination, which caused an immune complex-triggered hypersensitivity reaction. The second exposure to the boosted vaccination caused relapse of the skin lesions, providing defined evidence of the etiology.

Ischemic dermatopathy is the prototype for canine cell poor vasculitis, which includes five clinical subgroups: (1) canine familial dermatomyositis (DM), (2) juvenile-onset ischemic dermatopathy that is identical to DM (without breed predilection), (3) post-rabies vaccination panniculitis, (4) generalized vaccination-induced ischemic dermatopathy, and (5) adult-onset generalized ischemic dermatopathy (not vaccine-induced) [5]. Some group 2 dogs have temporal association with multivalent puppy vaccination [5]. Based on signalment of the puppy and historical evidence, the current case represents group 2.

In this case, the vascular lesions of cell poor vasculitis in ischemic dermatopathy were subtle on histopathologic examination. In particular, severe diffuse inflammation and the pus crust formation in both lesions may represent a secondary infection. However, in the rare cases of German shepherd familial cutaneous vasculopathy, even though the disease has been recognized as an inherited one, some cases show very similar patterns to the present case in clinical appearance and histopathology [21]. In the histopathology, the foot pad lesions displayed a pattern of nodular to diffuse dermatitis, and the inflammatory infiltrate was composed of mononuclear inflammatory cells and neutrophils [21]. The vessel lesion was not typical compared with other ischemic dermatopathies. According to a previous report, subtle histological changes often occur in cell poor vasculitis of ischemic dermatopathy [6]. Nevertheless, this case was suggestive of ischemic dermatopathy having a similar pattern to German shepherd familial cutaneous vasculopathy based on clinical features, patient history and histopathology. Therefore, the management focused on ischemic dermatopathy.

In humans, colchicine and dapsone have been used for mild limited cutaneous vasculitis [2, 13]. For moderate to severe cases, prednisone is considered the standard therapy [3, 4]. Meanwhile, IVIg is effective for refractory systemic and cutaneous vasculitis in humans [1, 10]. Recently, hIVIg was reported as effective and safe in the treatment of dogs with adverse cutaneous drug reactions and pemphigus foliaceus, which are severe immune-mediated skin diseases [12, 19]. In this case, clinical improvement was not maintained by only IVIg, necessitating the use of other immunosuppressive drugs. Cyclosporine has also been reported to be effective and to quickly induce remission in humans with recurrent or refractory cutaneous vasculitis [17, 18]. In veterinary medicine, conventional therapy for cutaneous vasculitis is often challenging; in addition, response to therapeutic manipulations can depend on the underlying or precipitating factors [16].

For vigorous immunosuppression, cyclosporine and chlorambucil were applied. Chlorambucil, a chemotherapy drug that is an alkylating agent affecting the cross-linking of DNA and is considered to be less toxic and slower acting than other alkylating agents, is a common therapeutic choice in animals with pemphigus [15]. Gradually improved clinical signs and no relapse was evident following the use of chlorambucil and cyclosporine. While myelosupression and gastrointestinal signs are side effects of chlorambucil [14], they had not developed as of the 4-month follow-up.

This case report describes the long-term management of refractory ischemic dermatopathy with cyclosporine and chlorambucil after rush therapy using hIVIg in a Miniature Pinscher puppy.

Fig. 4. Photographs of the dog after a 4-month treatment with cyclosporine and chlorambucil. The clinical signs were significantly improve.
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REFERENCES


