Erythema multiforme minor in a dog following inappropriate intranasal *Bordetella bronchiseptica* vaccination: a case report

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ABSTRACT: A one-year-old, intact female, Yorkshire terrier dog was presented with a six-month history of multifocal, polycyclic erythematous lesions with epidermal collarette formation at the axillae, the trunk and ventral abdomen. The dog had a history of an inappropriate vaccine administration one day prior to the onset of clinical signs. The histopathology of the lesions revealed apoptosis of keratinocytes in the overlying epidermis, hydropic degeneration and lymphocytic exocytosis. The clinical signs and histopathology of the lesions were compatible with erythema multiforme. The skin lesions resolved after treatment with prednisolone combined with azathioprine for one month. No recurrence of clinical signs occurred during the follow-up period (four months). This is the first case report of erythema multiforme associated with an accidental subcutaneous injection of a *Bordetella bronchiseptica* vaccine.

Keywords: *Bordetella bronchiseptica* vaccine; dog; erythema multiforme

Erythema multiforme (EM) is an acute self-limiting eruption of the skin and mucous membranes characterized by distinctive target shaped lesions, with an erythematous central area surrounded by an area of clearing (Scott et al., 1983; Mcmurdy, 1990; Medleau et al., 1990; Fritsch and Elias, 1993). Erythema, papules, macules, vesicles or a combination of these lesions may be present anywhere on the body (Mcmurdy, 1990; Rosenbaum and Kerlin, 1995). The pathogenesis of EM is multifactorial and not fully understood, but it is generally thought to be a host-specific cell (T lymphocyte)-mediated hypersensitivity reaction to various antigens (Mcmurdy, 1990; Fritsch and Elias, 1993; Rosenbaum and Kerlin, 1995; Scott and Miller, 1999). Although not all of the causes have been identified and many cases appear idiopathic, the known causes include infections, drug eruptions, neoplasia, connective tissue diseases, radiation therapy, contactants, or endocrine abnormalities (Scott et al., 1983; Mcmurdy, 1990; Fritsch and Elias, 1993; Rosenbaum and Kerlin, 1995; Scott and Miller, 1999). In this report, we describe a dog with EM associated with inappropriate subcutaneous injection of intranasal *Bordetella bronchiseptica* (*B. bronchiseptica*) vaccine.

Case description

A one-year-old, intact female, Yorkshire terrier dog presented with generalized chronic polycyclic lesions. The dog had a history of an inappropriate vaccine (Novibac® KC, Intervet Korea Ltd., MDS animal health) administration one day prior to the onset of clinical signs. This patient showed acute clinical signs (local pain and redness) on the next day after the vaccination. Other side effects apart from local pain on the skin overlying the site of vaccine depot after injection were not noted. In a local animal hospital, referring veterinarians treated this dog as suffering from bacterial or fungal

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skin disease and administered empirical antibiotic and/or antifungal agents (amoxicillin-clavulanate 12.5 mg/kg, twice daily, orally and itraconazole 5 mg/kg, twice daily, orally). However, there was no improvement in clinical signs and the patient was referred. The abnormal physical findings at presentation were non-pruritic, alopecic skin disease characterized by multifocal erythematous lesions with epidermal collarettes. The condition affected the axillae, trunk, dorsum and ventral skin symmetrically (Figure 1A). No other abnormalities were noted on physical examination except dermatological problems. Complete blood cell count and serum biochemistry profiles were unremarkable. The dog had no history of systemic illness or recent drug therapy prior to the onset of skin disease. The differential diagnosis of this case included bacterial folliculitis, demodicosis, dermatophytosis, vesiculobullous disease, and toxic epidermal necrolysis (TEN). To rule out bacterial, fungal and parasitic skin diseases, we performed bacterial and fungal culture, and multiple skin scrapings (superficial and deep). Skin scrapings for Demodex and hair pluckings for dermatophyte culture proved to be negative. In addition, bacterial culture was also negative. Skin biopsy was performed on a right truncal polycyclic lesional margin (two areas that had an intact epidermis) for histopathological evaluation. A local anaesthetic, 2% lidocaine (1 ml, subcutaneous tissue directly under the lesion, Daehan Pharm, Seoul, Korea) was injected into the skin. A biopsy sample was obtained using a 6-mm biopsy punch (KAI Sterile Dermal Biopsy Punch; Kai industries Co., Ltd. Seki City, Japan), which was fixed in 10% neutral formalin and processed for paraffin embedding. The resulting sections were stained with hematoxylin and eosin (HE) for histologic examination. An interface infiltrate of lymphocytes and macrophages, with vacuolation of the basal epidermal cells, was identified in the biopsy samples. Individual to confluent apoptotic keratinocytes were observed within the epidermis (Figure 2). The infundibular region of the hair follicle was also similarly affected. Based on the history, the skin lesions and histological findings, the dog was diagnosed with EM. Prednisolone (Solondo®; Yuhan Medica, Seoul, Korea) (1 mg/kg, twice daily, orally) and azathioprine (Azaprine®; Korea United Pharm Co., Ltd, Seoul, Korea) (2.2 mg/kg, once daily, orally) immunosuppressive treatment was initiated for four weeks. After one month of treatment the lesions were completely resolved without side effects. Administration of the drugs continued with gradual tapering for two further months; at four months of follow-up the dog was well with no recurrence and hair had returned six months later (Figure 1B).

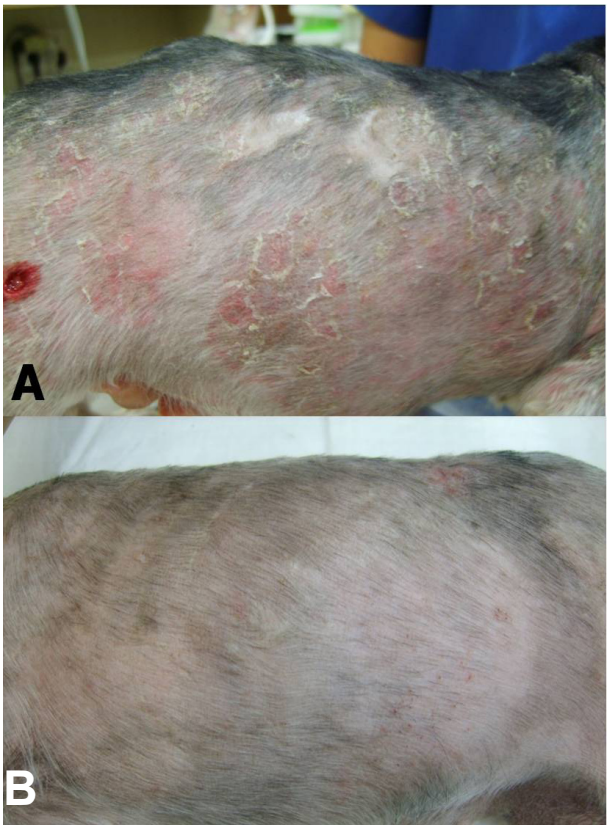

Figure 1. Nonpruritic, multifocal erythematous coalescing lesions of erythema multiforme in a one-year-old, intact female, Yorkshire terrier. Note the affected trunk lesions (A). Four weeks after therapy with prednisolone and azathioprine, the gross lesions of the patient had completely resolved without side effects (B)

DISCUSSION AND CONCLUSIONS

EM was originally described in dogs and cats in 1983 (Scott et al., 1983) and 1984 (Scott, 1984), respectively. Although the exact pathogenesis is not completely understood, it is currently hypothesized that cytotoxic T lymphocytes are involved in the disease process in response to antigenic stimulation. It has also been shown that epidermal and follicular keratinocytes markedly express the adhesion and activation molecules (ICAM-1 and MHC II) which are upregulated through the production of IFN-α/TNF-β by CD8+ and CD4+ T lymphocytes. The upregulated molecules then attract lymphocytes

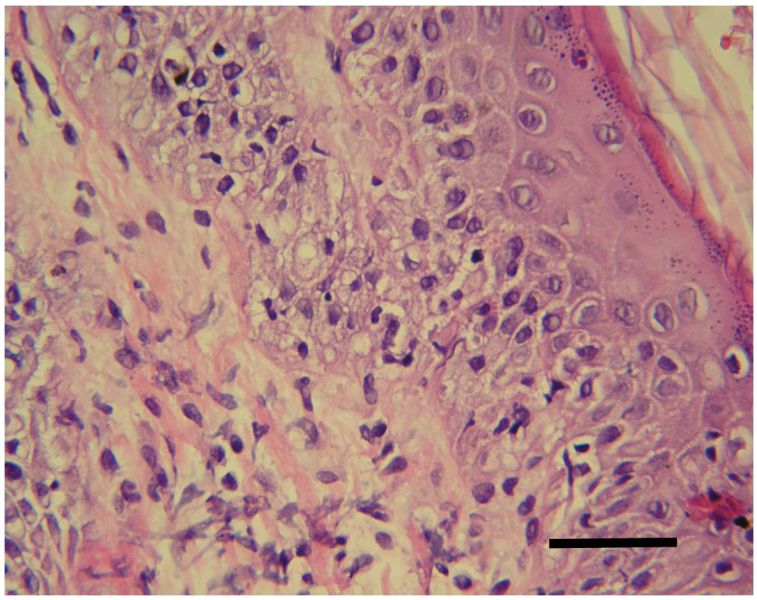

Figure 2. H&E photomicrograph of EM minor lesion highlighting the interface dermatitis reaction. Note the hydropic degeneration, occasional apoptosis (asterisk), and superficial interstitial infiltrates of lymphocytes (H&E, ×400). Bar = 50 µl

into the epithelium, where signals from intraepithelial CD8+ T lymphocytes trigger apoptosis of the keratinocytes, resulting in epidermal damage and the progressive development of clinical signs (Scott and Miller, 1999).

The acute onset of skin lesions after subcutaneous injection of intranasal *B. bronchiseptica* vaccine suggests an etiology of EM in this case. There are a few case reports of EM following vaccination in humans (Milstein and Kuritsky, 1986; Frederiksen et al., 2004; Kaur and Handa, 2008); the exact incidence of such cutaneous reactions has not been determined. The majority of adverse events following vaccinations are fever and pain with reaction at the injection site. According to a previous veterinary report (Toshach et al., 1997), vomiting, pyrexia, irritation of the injection site and hepatic failure could be induced by subcutaneous injection of vaccine to *B. bronchiseptica*. However, liver failure and pyrexia were not noted in this case except for local pain after injection. The skin lesions were nonpruritic, symmetrical erythematous patches with epidermal collarettes. The lesions affected the lateral trunk and ventral abdomen more severely. Alopecia was also noted. Based on the recently proposed classification of canine EM, the skin lesions exhibited by this patient fit the criteria for the clinical diagnosis of EM minor (erythematous patchy lesions with ulcerations on less than 10% of the body surface, and with less than one mucosal surface affected) (Bastuji-Garin et al., 1993; Assier et al., 1995; Hinn et al., 1998;). Histopathologically, this case was characterized by an interface infiltrate of lymphocytes and macrophages with vacuolation of the basal epidermal cells and apoptosis of keratinocytes within the epidermis, which is commonly noted in cases with EM (Scott et al., 1983; Scott, 1984; Mcmurdy, 1990; Medleau et al., 1990; Fritsch and Elias, 1993; Rosenbaum and Kerlin, 1995; Hinn et al., 1998; Scott and Miller, 1999). Although vaccination has not been previously implicated in published cases of EM in dogs, all of the gross and histological features of the lesions were consistent with those previously reported for canine EM (Scott et al., 1983; Scott, 1984; Mcmurdy, 1990; Medleau et al., 1990; Fritsch and Elias, 1993; Rosenbaum and Kerlin, 1995; Hinn et al., 1998; Scott and Miller, 1999).

Treatment of EM involves correction of the factors triggering the reaction if possible (Fritsch and Elias, 1993). Most cases of EM in dogs are caused by drug reactions or underlying infections (Table 1). Drug-induced EM markedly improves within one to two weeks of discontinuation of the offending drug while antigen-triggered EM needs immunosuppressive medication of various periods (Scott et al., 1983; Fritsch and Elias, 1993; Scott and Miller, 1999). The use of immunosuppressive drugs, especially systemic glucocorticoids, for the treatment of EM remains controversial in human medicine (Fritsch and Elias, 1993); however, immunosuppressive therapy has been accepted in veterinary dermatology practice because of the presumed immune-mediated pathogenesis of the disease (Fritsch and Elias, 1993; Scott and Miller, 1999). Appropriate symptomatic care including

Table 1. Causes of canine erythema multiforme

Drugs	
Amoxicillin	Scott and Miller, 1999
Cephalexin	Scott et al., 1983
Chloramphenicol	Scott and Miller, 1999
Chlorpyriphos	Medleau et al., 1990
Diethylcarbamazine	Fritsch and Elias, 1993
D-limonene	Rosenbaum and Kerlin, 1995
Enrofloxacin	Scott and Miller, 1999
Erythromycin	Fritsch and Elias, 1993
Gentamicin	Fritsch and Elias, 1993
Ivermectin	Fritsch and Elias, 1993
Levamisole	Scott and Miller, 1999
Lincomycin	Scott and Miller, 1999
Tetracycline	Fritsch and Elias, 1993
Trimethoprim-potentiated sulfonamides	Mcmurdy, 1990
Infections	
Parvovirus infection	Favrot et al, 2000
Pseudomonal otitis externa	Scott and Miller, 1999
Staphylococcal folliculitis	Scott et al., 1983
Miscellaneous	
Diet	Scott and Miller, 1999
Idiopathic	Scott and Miller, 1999
Thymoma	Tepper et al., 2011

systemic antibiotics, bathing and parenteral nutrition can be provided as needed and usually lesions improve more rapidly in mild cases if the underlying causes can be found. Only rare cases require long-term medication and are characterised by refractory lesions, and mostly the prognosis of EM is fair to good (Scott et al., 1983; Mcmurdy, 1990; Fritsch and Elias, 1993; Scott and Miller, 1999). In the case reported here, treatment with systemic corticosteroids and azathioprine appeared to be necessary for the resolution of the EM. Improvement of the lesions was noticed within a few days after the initiation of treatment and the dog was in complete remission by four weeks after the start of treatment. Therefore, in cases with severe symptoms of EM or when the disease persists after elimination of potential underlying causes, treatment with immunosuppressive drugs may provide excellent results.

In conclusion, this could represent the first case report of iatrogenic EM that developed after inappropriate subcutaneous injection of intranasal *B. bronchiseptica* vaccine. Knowledge of the medical history and rapid initiation of treatment resulted in an excellent outcome.

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