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CASE REPORT

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Cutaneous adverse drug reaction in a dog following firocoxib treatment

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Abstract

A 9-year-old intact female toy poodle was presented with oedema around the neck, including pus and cutaneous necrosis, 2 days after starting firocoxib treatment and placement of a cervical collar for intervertebral disc disease. Cytology of the pus revealed predominantly mature neutrophils with fewer macrophages and lymphocytes, indicating sterile inflammation. Although a skin biopsy could have provided more diagnostic information, it was not performed at presentation. Firocoxib treatment was discontinued, and immunosuppressive therapy including cyclosporine was initiated, which significantly alleviated the skin lesions. The dog recovered fully in 7 weeks. The final diagnosis was a possible cutaneous adverse drug reaction to firocoxib based on history, clinical signs and response to therapy.

KEYWORDS
cutaneous adverse drug reaction, dog, firocoxib

1 | INTRODUCTION

A cutaneous adverse drug reaction (CADR) or simply 'drug eruption' is any unintended effect of drug administration in which the skin is primarily affected (Miller et al., 2013). A CADR can resemble virtually any dermatosis and is often mediated immunologically or related to genetic differences in drug metabolism (Miller et al., 2013). The incidence of CADRs in dogs and cats with skin diseases was 2% and 1.6%, respectively, following treatment with drugs, such as topical agents, sulfonamides, penicillin and cephalosporins (Scott & Miller, 1998, 1999). Non-steroidal anti-inflammatory drugs (NSAIDs) have also been associated with skin eruptions in both human and veterinary patients, although the major side effects tend to be gastrointestinal (GI) and renal (Stringer et al., 2012; Johnson et al., 2009; Young et al., 2018). Firocoxib, a selective cyclooxygenase (COX)-2 enzyme inhibitor, is an NSAID routinely used to treat veterinary cases of osteoarthritis (Hanson et al., 2008). GI issues, including vomiting, are the common side effects of firocoxib (Hanson et al., 2008), while allergic reactions associated with cutaneous lesions have been rarely reported. A dermatological case report is presented here to discuss the diagnosis and management of adverse drug reactions possibly induced by firocoxib in a dog, although a histopathologic evaluation of skin biopsy was not included.

2 | CASE REPORT

A 9-year-old intact female toy poodle was referred to our clinic with upper motor neuronal signs involving all limbs. The animal was tentatively diagnosed with cervical intervertebral disc disease (IVDD) based on neurological examination, radiology and haematological test findings. On physical examination, the dog was alert with normal pulse rate and body temperature. Laboratory studies revealed thrombocytosis (647 K/μl; reference range, 148–484 K/μl), hyperglobulinemia (4.7 g/dl; reference range, 2.5–4.5 g/dl) and mildly elevated alkaline phosphatase (340 U/L; reference range, 23–212 U/L)

and gamma-glutamyl transpeptidase (20 U/L; reference range, 0–11 UL). Other serum biochemistry parameters were unremarkable.

Firocoxib (5 mg/kg, PO, BID; Previcox; Merial, Toulouse, France) was prescribed for cervical IVDD. The treatment also included pentoxifylline (15 mg/kg, PO, BID; Trental; Handok, Eumseong, Chungbuk, Korea) and vitamin B complex (0.25 T/dog, PO, BID; Beecom; Yuhan, Cheongju, Chungbuk, Korea). Pentoxifylline and vitamin B were administered to improve microcirculation and reduce oxidative stress or inflammation in the intervertebral disc. These two drugs were administered continuously throughout therapy for skin lesions and also after their resolution. A neck brace made of mouldable splint was worn for neck support but taken off a few hours later by the owner on the first day (day 0). The neck brace was cautiously adjusted to prevent oedema.

Two days after starting the treatment, the owner detected oedema around the dog's neck, which felt firm and partially soft the next day. The soft part of the skin lesion ruptured a day before the clinical presentation. The skin lesions involved three large ulcers measuring approximately 1–2 cm dorsally on the head and neck, with a pink purulent discharge and white necrotic tissue (Figure 1a). The dorsal neck muscle around the oedema felt partially firm. Pruritus could not be assessed due to tetraplegia caused by IVDD, without prominent symptoms of pain. Vital signs including body temperature were within the normal range even though the skin lesions were severely ulcerated and necrotising in a toy poodle weighing 2.6 kg.

Impression cytology of the neck discharge revealed numerous neutrophils with fewer macrophages and lymphocytes (Figure 2a). Mature neutrophils were predominantly observed without signs of primary infection (Figure 2b). No skin biopsy was performed because of severe ulceration and secondary purulent lesions. However, sample collection along the periphery of the lesions would have been appropriate for diagnostic evaluation.

The owner reported that the dog had no known history of drug allergies or underlying dermatosis. Based on previous reports describing CADRs to NSAIDs routinely used in veterinary medicine, firocoxib was suspected to induce dermatological reactions in the affected areas. In this case, clinical signs started 2 days after the drug administration and the patient had no history of previous exposure to firocoxib, which was not typically seen in drug hypersensitivity reactions. The Naranjo scale was used to estimate the probability of adverse drug reaction to firocoxib (Naranjo et al., 1981). The total score of four indicated that firocoxib was a possible cause of skin reactions. Other drugs were prescribed for their antioxidant, hepatoprotective and gastrointestinal protective effects, which were less likely to be related to the reaction and were continued even beyond the resolution of cutaneous lesions.

The firocoxib therapy was discontinued, and cyclosporine (7 mg/kg, PO, BID; Cipol-N; Chong Kun Dang Pharm, Cheonan, Chungnam, Korea) and amoxicillin/clavulanate (22 mg/kg, PO, BID; Lactamox; Aprogen Pharm, Hwaseong, Gyeonggi, Korea) were included in the treatment. The use of glucocorticoids was avoided because of suspected hyperadrenocorticism based on physical and laboratory examinations. Clinical signs included a pot-bellied appearance, thin skin that bruises easily, alopecia and hepatomegaly. Blood tests revealed elevated levels of alkaline phosphatase, gamma-glutamyl transpeptidase and platelet counts. The diagnosis of pituitary-dependent hyperadrenocorticism was established after the resolution of the skin eruption. Adrenocorticotropic hormone (ACTH) stimulation test revealed hypercortisolemia based on a pre-ACTH cortisol concentration of 7.4 μg/dl (reference range, 2–6 μg/dl) and a post-ACTH cortisol concentration of >30 μg/dl (reference range, 6–18 μg/dl). Immunosuppressive therapy combined with antibiotic treatment immediately reduced inflammation and stopped the purulent drainage, which was no longer observed after the initial cleansing and bandaging.

After a week, the crusts appeared on the surface, covering one of the large ulcerative lesions behind the left ear. The size of each of the three ulcerative lesions was reduced by 80%, and no oedema around the neck was detected. No adverse events were observed during the entire immunosuppressive therapeutic period. The ulcerative lesions were entirely covered with crusts 4 weeks after initiating immunosuppressive treatment (Figure 1b). Cyclosporine

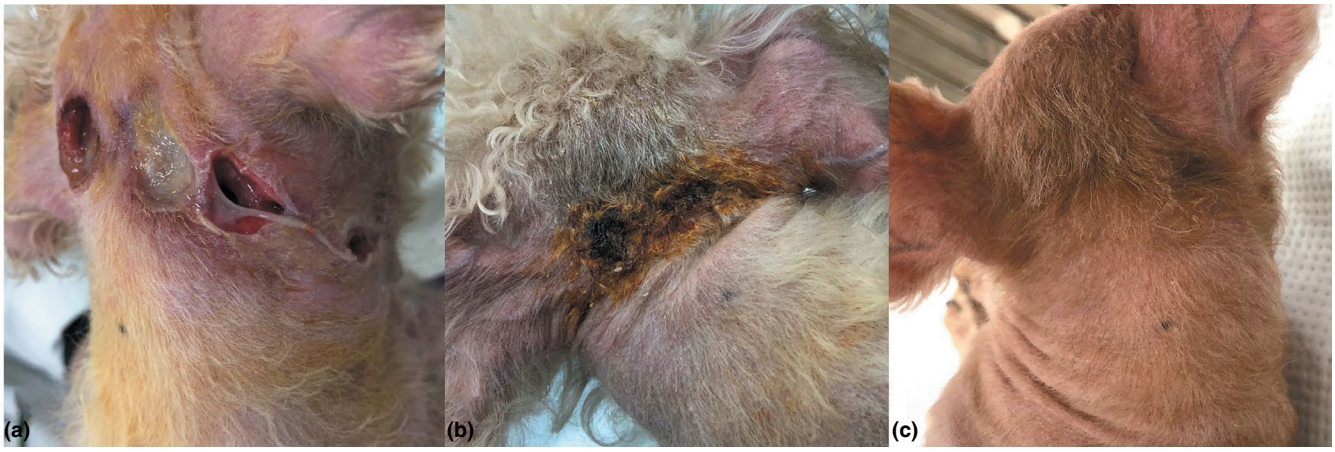

FIGURE 1 Photographs of the dorsal neck of the dog. A: Purulent discharge and ulcerative lesions at presentation. B: The lesions were entirely covered with crusts 4 weeks after the treatment initiation. C: Neck fully recovered from crusts after 7 weeks of treatment

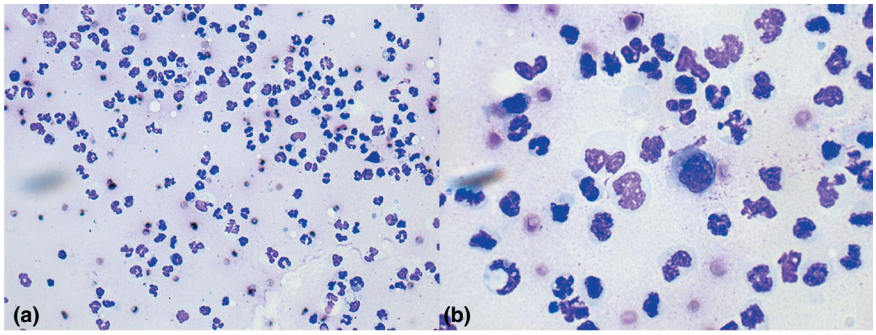

FIGURE 2 Photomicrographs showing impression cytology of neck discharge. A: Aseptic exudative inflammation. Numerous neutrophils and a few macrophages were detected (Diff-Quick stain, microscopic magnification view, ×400). B: Several non-toxic neutrophils and some macrophages (Diff-Quick stain, microscopic magnification view, ×1,000)

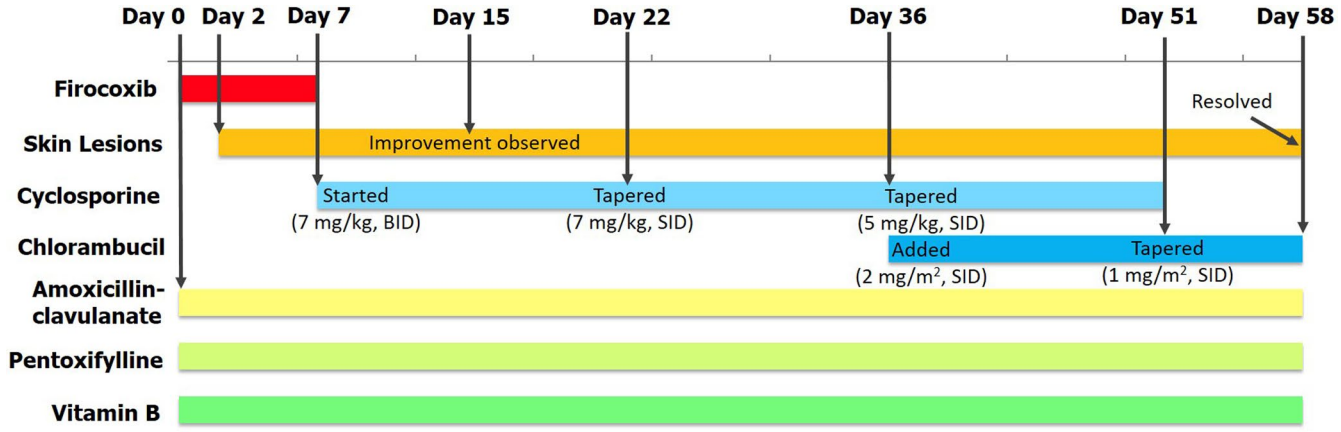

FIGURE 3 Timeline of drug administration, the onset of skin lesions and treatment

therapy was tapered and stopped over the following 5 weeks, while chlorambucil (2 mg/m^2, PO, SID; Leukeran; Aspen, Feucht, Germany) was first co-administered for 2 weeks and then substituted for cyclosporine (Figure 3). As cyclosporine was tapered down, a slow improvement in skin lesions was observed without other clinical signs. Chlorambucil was substituted for cyclosporine to accelerate the improvement of skin lesions. Three weeks later, the skin lesions resolved completely (Figure 1c), and chlorambucil was tapered off. No clinical signs, other than soft stool, were observed for the entire 7 weeks of therapy.

3 | DISCUSSION

This report describes the successful management of a possible CADR to firocoxib in a dog. Immunosuppressive therapy, including cyclosporine and chlorambucil, effectively ameliorated the inflammation, and the skin lesions fully resolved after 7 weeks of treatment.

In field trials, vomiting and other GI problems were reported as common adverse effects of firocoxib treatment (Hanson et al., 2008), while cutaneous reactions were rarely observed. Only two cases of suspected firocoxib skin reactions were reported previously: a white rhinoceros with vesiculobullous skin lesions and a standard poodle with fatal Sweet's syndrome (Johnson et al., 2009; Stringer et al., 2012). Although hepatotoxicity following NSAID administration has been widely recognised in both humans and dogs (Trepanier, 2013), skin eruptions have also been associated with NSAIDs used in veterinary medicine, including carprofen, meloxicam and piroxicam. Three dogs diagnosed with neutrophilic dermatosis, resembling Sweet's syndrome, died following treatment with carprofen (Mellor et al., 2005; Vitale et al., 1999). Meloxicam induced cutaneous and ocular reactions in a dog, and piroxicam was reported as a probable cause of ulcerated lesions in a cat (Niza et al., 2007; Young et al., 2018).

During the evaluation of immune-mediated skin reactions, the interval between drug administration and the reaction is critical to distinguish immediate drug hypersensitivity mediated by IgE (Type I hypersensitivity) from non-immediate reactions, which suggest IgG, IgM, complement or T cell involvement (Pourpak et al., 2008; Voie et al., 2012). A number of diagnostic tests for each type of drug hypersensitivity exist, such as lymphocyte transformation test for delayed hypersensitivity, although the overall practical value is limited (Pourpak et al., 2008).

In this case, the skin reaction started 2 days after the first exposure to the suspected drug, which was atypical for a delayed drug hypersensitivity reaction that usually involves previous sensitisation. However, it is also worth indicating that immune-mediated adverse drug reaction can occur any time the drug is administered (Voie et al., 2012). A previous case report described a similar onset of cutaneous drug reaction in a dog that developed oedema and pruritus of the limbs 2 days after the first exposure to meloxicam (Niza et al., 2007).

Some limitations of this case report are notable. First, no skin biopsy was performed due to the severity of the ulcerative lesions at presentation although the case was appropriate for a biopsy. A skin biopsy may have provided useful information regarding the specific histopathologic changes possibly induced by firocoxib. Further, the skin lesions were considered deep and severe enough to warrant immediate initiation of immunosuppressive therapy. Nonetheless, drug withdrawal and local care without other systemic treatment facilitate the evaluation of the reaction for diagnostic purposes.

Furthermore, drug challenge for a definitive ADR diagnosis was not possible due to recurrent reactions, which may have triggered severe and life-threatening events (Young et al., 2018). However, the causality of ADRs was assessed using the Naranjo scale, a standardised method to establish a causal association between drugs and adverse events in human medicine (Naranjo et al., 1981). Based on the history and clinical outcomes, a score of 4 was assigned to this case, suggesting 'possible' cutaneous reactions triggered by firocoxib administration.

Sweet's syndrome, a sterile neutrophilic dermatosis, was not included in the differential diagnosis in the current study. Clinical signs of Sweet's syndrome mainly include fever and painful skin lesions such as papules and diffuse erythematous nodules or plaques (von den Driesch, 1994). However, the current case presented with deep ulcerating skin lesions limited to the neck without symptoms of pain, and the body temperature was normal. Therefore, a histopathological evaluation of skin biopsy may have been essential for differential diagnoses including other sterile dermatoses, such as vasculitis, panniculitis, sterile pyogranuloma and pyoderma gangrenosum.

4 | CONCLUSION

Firocoxib may induce severe CADRs in dogs, causing immune-mediated inflammation and ulcerative lesions. Therefore, CADR should be considered when cutaneous lesions develop after firocoxib therapy. While discontinuing firocoxib treatment, immunosuppressive therapy with cyclosporine is effective for the management of skin lesions. To our knowledge, this is the first report of a canine case that describes the diagnosis and management of possible CADRs following firocoxib administration. If a skin biopsy had been properly performed, it could have provided more useful diagnostic information.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTION

Migyeong Geum: Conceptualization; Formal analysis; Investigation; Writing-original draft. Hui-Yeon Ko: Investigation. Yeon-Joo Na: Validation; Writing-review & editing.

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