Two Dogs with Juvenile-Onset Skin Diseases with Involvement of Extremities

Ji-Seon YOON\(^1\), Tomohiko MINAMI\(^1\), Yasuko TAKIZAWA\(^1\), Maiko SEKIGUCHI\(^1\), Atsushi YABUZOE\(^1\), Kaori IDE\(^1\), Koji NISHIFUJI\(^1\) and Toshiroh IWASAKI\(^1\)*

\(^{1}\) Laboratory of Veterinary Internal Medicine, Tokyo University of Agriculture and Technology, 3–5–8 Saiwai-cho, Fuchu, Tokyo 183–8509, Japan

NOTE


ABSTRACT: Two dogs of juvenile-onset skin diseases with involvement of extremities were examined by histopathological, immunohistochemical and ultrastructural analyses. Clinically, both cases showed alopecia and crusts on the face and extremities. Case 1 showed histopathology of dermo-epidermal separation. Ultrastructural analysis revealed that the clefts were recognized between hemidesmosomes and lamina densa. In case 2, histopathology showed follicular atrophy, vascular degeneration at lower epidermis and masseter muscle degeneration, without remarkable ultrastructural abnormalities in basement membrane zone of the skin. Thus, the findings in case 1 were compatible to those in junctional epidermolysis bullosa, while those in case 2 were compatible to dermatomyositis-like disease. Combination of histopathological and ultrastructural analyses was useful to distinguish the diseases in two dogs.

KEY WORDS: canine, dermatomyositis, epidermolysis bullosa, juvenile.

Congenital epidermolysis bullosa (EB) is a group of heritable mechanobullous diseases caused by structural irregularity of the basement membrane zone \([4, 8, 10, 11]\). Congenital EB in humans is divided into three disease groups, EB simplex (EBS), junctional EB (JEB) and dystrophic EB (DEB) based on the depth of the blisters in basement membrane zone of the skin \([3]\). JEB and dystrophic EB have been reported in dogs as blistering, erosive to ulcerative skin diseases \([4, 8, 11]\). Familial dermatomyositis (DM) is recognized exclusively in Shetland sheep dogs, collies and their crossbreds, while DM-like disease is recognized in any canine breeds, of which clinical and histopathological findings are identical to those in familial dermatomyositis \([2, 6, 12]\). Histopathology of skin in DM usually reveals vascular degeneration of basal cells, atrophy of hair follicle and dermo-epidermal separation \([2, 5, 6]\).

These 2 canine diseases develop in considerably young age and show crusting and ulceration shortly after blister formations \([4, 5]\). Thus, it may not be easy to differentiate them correctly solely by clinical findings. In this article, we describe histopathological and ultrastructural findings of 2 dogs with juvenile-onset skin diseases exhibited similar clinical findings.

Case 1 was an 8-month-old, intact female mongrel dog with 7-month history of vesicles, erosions, alopecia and crusts on her face (Fig. 1-A), paws (Fig. 1-B) and tail. Case 2 was a 6-month-old intact male mongrel dog. The dog showed clinical signs of alopecia, crust, erythema on face (Fig. 1-C) and ear pinnae (Fig. 1-C) which progressed to paws (Fig. 1-D) and tail tip starting from 3-month of age. There were no lesions on mucous membranes or mucocutaneous junctions in both dogs. Both dogs had poorly responded to antibiotics and antifungal drugs given prior to presentation.

Familial histories of the 2 dogs were investigated. Case 1 had 3 littermates, one survived without any skin lesions, another died at birth and the other died 3-month after birth exhibiting similar skin problems as seen in case 1. The familial history of case 2 was not recorded. Due to the juvenile-onset and exclusion of infectious diseases, congenital skin diseases such as epidermolysis bullosa, dermatomyositis, and juvenile cellulitis, were suspected in these two dogs.

Skin biopsies were performed from affected skin lesions in both cases. Common findings of the histopathology included follicular atrophy and dermal edema with minimal infiltration of inflammatory cells (Fig. 2). Additional histopathological finding in case 1 was a subepidermal blister in which the epidermis was separated from the underlying dermis at the basement membrane zone (Fig. 2-A). Periodic acid stain (PAS) revealed that the basement membrane remained at the bottom of a blister as well as epidermal hyperkeratosis (Fig. 2-B). In case 2, the histopathology revealed prominent vascular changes of basal cells with mild infiltration of inflammatory cells and follicular atrophy (Fig. 2-C). Further histopathological analysis of the masseter muscle revealed myofibril degeneration and atrophy in case 2 (Fig. 2-D). Next, ultrastructural examination was performed in both dogs. In subepidermal blister of case 1, cleft was located within a basement membrane and the lamina densa seen at the bottom of a blister (Fig. 3-A). Therefore, the blister in case 1 might have existed at the level of lamina lucida. On the other hand, in case 2, no marked changes were recognized in basement membrane zone ultrastructurally (Fig. 3-B).

In case 1, oral prednisolone and cyclosporine A was used to control edematous change on eyelids and extremities.
Fig. 1. Clinical features of case 1 (A, B) and case 2 (C, D). Note, similar clinical signs of erythema, crusts, alopecia on face and lower extremities in the 2 patients.

Fig. 2. Histopathological findings of case 1 (A and B) and case 2 (C and D). Case 1 (A) exhibited a subepidermal blister (asterisk). The basement membrane remains at the bottom of blister (asterisk) in case 1 (B). Follicular atrophy (C, arrow) and prominent vacuolar change of basal cells (right rectangular, arrowhead) are observed in the histopathological section from affected skin of case 2. Histopathological findings of the masseter muscle in case 2 include the myofibril degeneration and atrophy (D, arrow). (Hematoxylin and eosin stain: A, C, and D; Periodic acid-Shiff stain: B).
The skin lesions wax and wane, and the dog died at 1.7-year of age after surgery for ileus due to a foreign body in the small intestine. In case 2, the skin lesions gradually resolved without any treatment and no additional lesions developed from 7-month of age.

In case 1, clinical, histopathological, and ultrastructural findings were compatible to those in dogs with JEB as previously reported [1, 8]. Conversely, the ultrastructural findings did not support EBS or DEB, as the case did not show disruption of basal keratinocytes or subepidermal cleft beneath lamina densa, which are typical ultrastructural findings in humans with EBS or DEB, respectively [3]. Capt et al. reported that a German Shephard dog with non-lethal JEB showed reduced expression of laminin 5 caused by a homozygous insertion of repetitive satellite DNA (6.5 kb) within intron 35 of LAMA3 gene coding laminin 5 α3. The mutation induces premature termination codon (PTC) in the carboxy-terminal domain of α3 chain which leads to reduced expression of laminin 5. Therefore, PCR to amplify a part of intron 35 of LAMA3 gene were performed using whole blood of case 1. The primer pair for PCR was 5'-ACCACAGTAGATGGAGTTGTG-3' for forward primer, and 5'-GCTATAGACTTCTGTTGAGAAC-3' for reverse primer. As a result, genetic insertion of 6.5 kb nucleotides was not detected by PCR (data not shown). In humans, it is known that laminin 5 is defected by genetic mutations in several different genes, LAMA3, LAMB3, and LAMC2, each encoding the three chains of α3β3γ2 respectively [3, 7, 9]. To know the exact pathogenesis in the present case, further studies will be required to determine genetic mutation causing defect of laminin chains. Other differential diagnoses in case 1 might be autoimmune subepidermal blistering diseases (AISBD) and bullous systemic lupus erythematosus (BSLE). AISBD, a group of acquired blistering diseases in which circulating autoantibodies bind the components of basement membrane zone and cause dermo-epidermal separation, are further classified into bullous pemphigoid, mucous membrane pemphigoid, linear IgA bullous dermatosis and epidermolysis bullosa acquisita. However, both AISBD and BSLE are acquired skin diseases, and the onset at 1 month of age in case 1 is too young to be considered as acquired disease. On the other hand, signalments and the laboratory findings in case 2 were compatible to those in DM-like disease, which is currently classified into a group of ischemic dermatopathy.

The current two cases were each suspected of JEB and DM-like disease respectively, despite the cases shared similar clinical signs and age of onset. Our findings provide a suggestion that, when juvenile skin disease with congenital pathogenesis is suspected, extensive investigation for histopathological as well as ultrastructural analyses will help to diagnosis of these diseases.

REFERENCES


