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Hereditary epidermolysis bullosa

Hereditary epidermolysis bullosa (HEB) refers to a heterogeneous group of hereditary mechanobullous disorders of the skin and mucous membranes, characterised by spontaneous vesicle, erosion, and ulcer development. The condition follows minimal trauma and is caused by excessive fragility of the dermo-epidermal junction (DEJ)[1,2]. HEB is rare in the dog, but is an important differential in many skin disorders and important as a model for HEB in man.

The main criterion on which HEB is classified is the level of clefting in the DEJ. Simple EB (epidermolytic) (SEB) is characterised by intraepidermal clefting resulting from destruction of basal layer keratinocytes; junctional EB (JEB) is determined by clefting in the lamina lucida of the dermo-epidermal junction; dystrophic EB (dermolytic) (DEB) is characterised by intradermal clefting in the anchoring fibrils of the dermal sublamina densa. This clinico-anatomical classification scheme will gradually be replaced by a molecular classification in which each clinical phenotype will be associated with a characteristic molecular and genetic abnormality.

Only JEB and DEB have been reported in the dog.

Junctional epidermolysis bullosa

Epidemiology

JEB has been reported in the Poodle[3], possibly the Beauceron sheepdog (although the description in this breed is more like hereditary dermatomyositis than JEB)[4], a crossbreed[5] and the German pointer[6,9].

Lots of epidemiological data exist for the German Pointer, and JEB is the most common genodermatosis in this breed. The condition first appeared in the German Pointer in French breeding units in the early 1980s[9]. Since then, it has been regularly reported in France and also in Italy. Its incidence in France is high. Studies have shown that in 2000, about 13% of recommended breeding stock carried the mutation responsible. The mode of transmission is autosomal recessive in this breed. There is no sex predilection. Several puppies in the same litter are usually affected. Signs appear mostly between the age of 3 weeks and 6 months[9].

Aetiopathogenesis

JEB is associated with abnormalities of the hemidesmosome-anchorage filament complex, caused by mutations on genes encoding various proteins. These abnormalities have, to date, only been reported in the German Pointer.

In this breed, expression of hemidesmosome-anchorage filament complex proteins is defective. Collagen XVII expression is absent[6,7] and expression of the laminin 5 α3 chain, the main keratinocyte adhesion ligand, is defective[8,11]. It is currently thought that in cases of JEB in which defective collagen XVII has been demonstrated, only expression of the laminin 5 α3 chain is defective. Intronic insertion into the gene encoding the α3 chain results in aberrant mRNA and reduced wild laminin 5 production[12].

Clinical signs (Fig.33:1-5)

Dermatological signs usually start with paronychia and onychomadesis affecting several digits. Vesicles and bullae then burst to leave well-circumscribed ulcers on the medial pinnae, pressure points (footpads, elbows, carpi and tarsi) and mouth (gums and tongue). Dermo-epidermal detachment produces a positive Nikolsky's sign. In rare cases, mucous membranes (mouth, pharynx, oesophagus) are almost exclusively affected. If the dog is not euthanased at an early stage, ulcers around the pressure points spread and become very painful,

affecting locomotion. At this stage, onychodystrophy and onychogryphosis can affect many digits. Non-dermatological signs are often present including dental enamel dysplasia, persistent milk teeth, premature tooth wearing, prognathism, and growth retardation. Some adults develop a less serious form that makes life difficult but possible[8,11].

Diagnosis

Diagnosis is based on history, clinical appearance of skin lesions, and histopathological, ultrastructural and possibly immunohistochemical, examination of skin biopsies.

Histopathological examination of skin biopsies from the edge of ulcers or from rubbed skin reveals vacuoles in the basement membrane, which progress to form vast dermo-epidermal clefts, leaving the epidermis intact (Fig. 33:6). These lesions develop in the absence of inflammation. Histopathology does not reveal the level of clefting within the DEJ[8,11].

Ultrastructural examination of skin biopsies reveals dermo-epidermal clefting in the lamina lucida, and also hemidesmosomes that are normal in size and number[8,11].

Immunohistochemical procedures using antibodies to certain components of the hemidesmosome-anchorage filament complex also confirm the lamina lucida as the site of dermo-epidermal clefting. These techniques can be used to identify defective expression of proteins belonging to this complex (α3 chain of laminin 5)[10,11].

A mutation detection test (using heparinised blood) can identify genes carrying the mutation[9]. Eradication may then be possible.

Prognosis and treatment

Prognosis is very poor. Most affected dogs are soon euthanased.

There is no specific treatment. Hopes lie with gene therapy.

Genetic complementation experiments have produced phenotypic reversion of canine JEB keratinocytes allowing these cells to restart production of the defective α3 chain and functional laminin 5 products. In culture adhesion capacity, proliferation and clonogenicity of transduced keratinocytes have also been shown to be restored. The reconstitution of canine JEB epithelia expressing a laminin 5 hybrid has revealed durable expression of laminin 5 in the DEJ after a graft in SCID mice. Use of an autologous transgenic epithelial graft in immunocompetent JEB dogs allows evaluation of the immune response directed against the transgenic product[13].

Dystrophic epidermolysis bullosa

Epidemiology

A few cases of DEB have been reported in the Beauceron sheepdog[14] and Golden retriever[15] (although the diagnosis has been questioned). Typically, several puppies in the same litter are affected. Clinical signs usually appear between the age of 2 and 4 months.

Aetiopathogenesis

In the Golden retriever, a mutation on the gene encoding collagen VII has been identified[16].

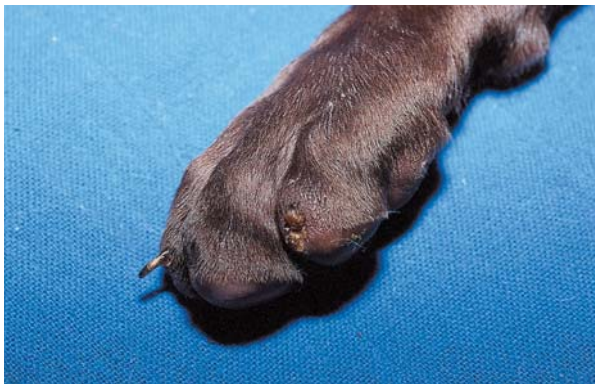
Clinical signs

Clinical signs have been studied in the Golden retriever (Fig. 33:7-8). Labial, periocular and oral ulcers are seen together with bullae, milium granules around the groin and axillae, growth retardation, prognathia and occasional loss of nails.

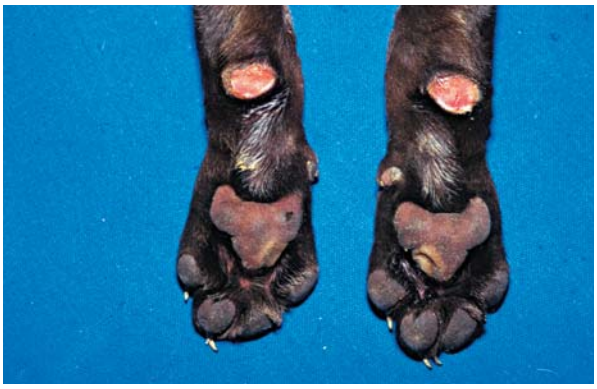
Oesophageal endoscopy reveals erosions. Growth retardation is apparent by the age of 7 months[15].

Diagnosis

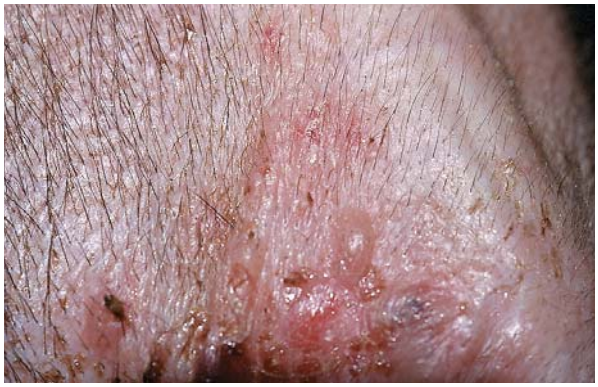
Diagnosis is based on history, clinical appearance of lesions, and histopathological, ultrastructural and possibly immunohistochemical examination of skin biopsies.



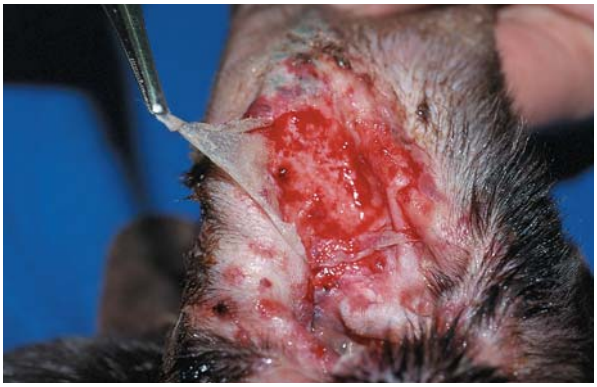
33.1: *Junctional epidermolysis bullosa in a German Pointer puppy: multiple onychomadesis.*



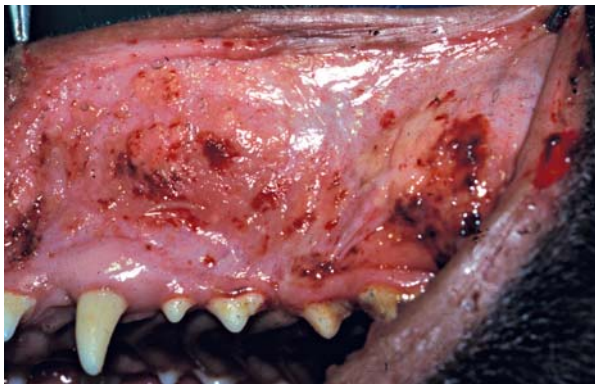
33.2: *Same animal as that in figure 33.2: well-defined ulcers on pads.*



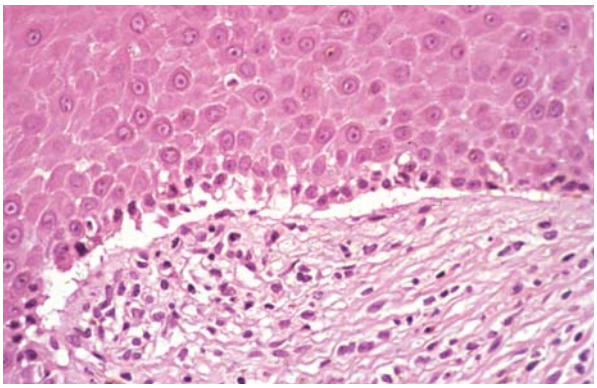
33.3: *Junctional epidermolysis bullosa in a German Pointer puppy: bullae and ulcers on the medial pinna.*



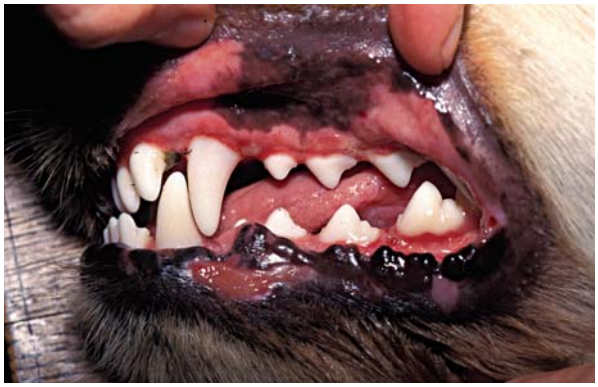
33.4: *Same animal as that in figure 33.3: dermo-epidermal detachment (positive Nikolsky's sign).*



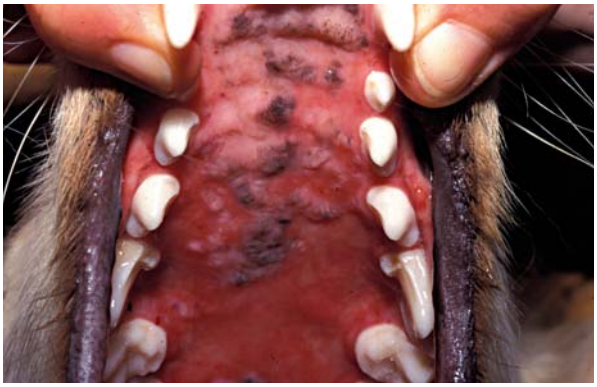
33.5: *Junctional epidermolysis bullosa in a German Pointer puppy: extensive ulceration of labial mucous membrane.*



33.6: *Skin histopathology: dermo-epidermal clefting (footpad) (H&E stain).*



33.7: *Dystrophic epidermolysis bullosa in a Golden retriever puppy: labial and gingival ulcers.*



33.8: *Same animal as that in figure 33.3: extensive ulcers on the hard palate.*

Histopathological examination of skin biopsies reveals dermo-epidermal clefting under the DEJ, and milium granules in the dermis[15].

Ultrastructural examination of skin biopsies reveals hypoplasia or reduced number of anchoring fibrils. Hemidesmosomes and anchoring filaments are, however, normal[15].

Histochemical and/or immunohistochemical techniques (PAS staining) using for example, anticollagen IV autoantibodies, confirm the presence of clefting under the DEJ. In the Golden retriever, immunohistochemical techniques using anticollagen VII autoantibodies have shown reduced collagen VII expression. This is more marked in mucous membranes than in skin[15]. Hence, the almost exclusive mucous membrane involvement in this breed.

Treatment

Prognosis is guarded although some animals manage to live more or less normally, avoiding secondary gastrointestinal infections[15].

There is currently no specific treatment and hopes lie with gene therapy. Genetic complementation experiments have produced phenotypic reversion of canine DEB keratinocytes allowing these cells to restart production of defective collagen VII[16].

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