CASE REPORT

Presumed phenobarbital-induced Stevens–Johnson syndrome in a 4-year-old female Great Dane*

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A 4-year-old female Great Dane weighing 57 kg was evaluated for a 6-month history of cluster seizures. The referring veterinarian performed no further investigations, and no treatment was initiated. General physical examination at the time of presentation was unremarkable. On neurological examination, the dog was showing generalized tonic–clonic seizures with autonomic involvement (urination, defecation, salivation) only 5–10 minutes apart with regaining of consciousness in between seizures. Complete blood count and serum biochemistry profile were within normal limits. Diazepam (Valium, Roche, Basel, Switzerland) was administered intravenously (IV) (0.25 mg/kg bodyweight (BW)) successfully ending seizure activity after two boluses. The owner declined magnetic resonance imaging of the brain and cerebrospinal fluid examination. Due to the aggressive character of the dog, further hospitalization was impossible and the dog was discharged on phenobarbital treatment (Phenoleptil, Kela Veterinaria, Hoogstraten, Belgium) (5 mg/kg BW/12 h per os (PO)). Since initiation of treatment, no more seizures were witnessed at home. The dog was presented again after 6 weeks for an acute onset of skin lesions, which appeared to be rapidly progressive. At presentation, the dog was lethargic and was walking very slowly and cautiously, appearing markedly uncomfortable. General physical examination revealed a mild tachycardia and hyperemic mucous membranes. Multiple, symmetrical, painful, vesiculobullous lesions with an erythematous peripheral rim were present at the level of the groin, ventrum, axillae and sternum (Figures 1 and 2). These lesions had a positive Nikolskiy sign (the artiﬁcial extension of a blister or ulcer induced by digital pressure to adjacent mucous membrane or skin; Gross et al. 2005). A linear erosive lesion was present at the lateral canthus of the left eye, and there were multiple, ill-defined, painful ulcerative lesions on the footpads of the four paws (Figures 3 and 4, respectively). A single, well-delineated vesicle surrounded by an erythematous rim was seen at the left upper labial mucosa. Macroscopically, the main differential diagnoses were a drug reaction such as erythema multiforme (EM), Stevens–Johnson syndrome (SJS) or epidermolysis bullosa acquisita (EBA). However, EBA does not exhibit a positive Nikolskiy sign (Grando et al. 2003). The history, clinical distribution of the lesions, aspect of the flat lesions and the positive Nikolskiy sign leaded to a presumptive diagnosis of SJS. To establish this diagnosis, histopathological samples consisting of punch biopsies were obtained from three lesions on the ventrum. According to a previously established method for estimating the probability of an adverse drug reaction (ADR; Naranjo et al. 1981), a probable ADR to phenobarbital was diagnosed (Table 1) and phenobarbital treatment was therefore abruptly stopped. The dog was loaded orally with potassium bromide (Libromide, Dechra Veterinary Products, Bladel, the Netherlands) using a 5-day loading schedule according to Dewey (2008), consisting of 125 mg potassium bromide/kg BW/day, given in 6 doses for 5 consecutive days. Treatment was initiated with gabapentin (Neurontin, Pfizer, city, Belgium) (10 mg/kg BW/8 h PO) for additional seizure management. Prednisolone therapy (Prednisolone, Kela Laboratoria, Hoogstraten, Belgium) (0.3 mg/kg BW/day PO) was initiated for the skin lesions. After termination of the potassium bromide loading schedule, the dog was continued on a maintenance dose (20 mg/kg BW/12 h). The owner was advised to treat the skin lesions once daily topically with povidone-iodine (Iso-Betadine, Meda Pharma, city, Belgium), and the footpath lesions with chlorhexidine (Hibiscrub, Mölnlycke, city, Belgium) bathing.

All three skin samples demonstrated identical morphologic changes on histopathology. There was cytoxic interface dermatitis with the presence of multiple apoptotic keratinocytes in all the layers of the...
epidermis and follicular epithelium, sometimes with lymphocyte satellitosis. Vesicle formation was present, resulting in epidermal–dermal separation, and large areas of confluent necrosis were present over the blisters. A lymphohistiocytic perivascular inflammatory infiltrate was present in the dermis (Figures 5 and 6).

The use of phenobarbital in association with the rapidly progressive vesiculobullous lesions and demonstration of supportive but not pathognomonic histopathological lesions of panepidermal cytotoxic

### Table 1. Adverse drug reaction (ADR) probability scale according to Naranjo et al. (1981). For interpretation of the scores, a total score of ≥ 9 was associated with a definite diagnosis of ADR, a score of 5–8 with a probable ADR, a score of 1–4 with a possible ADR and a score of ≤ 0 with a doubtful ADR. The total score in the presented case was 6, revealing a probable ADR associated with phenobarbital.

| Questions                                                                 | Yes | No | Do not know | Score |
|---------------------------------------------------------------------------|-----|----|-------------|-------|
| Are there previous conclusive reports on this reaction?                   | +1  | 0  | 0           | +1    |
| Did the adverse event appear after the suspected drug was administered?  | +2  | −1 | 0           | +2    |
| Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1  | 0  | 0           | +1    |
| Did the adverse reaction reappear when the drug was readministered?      | +2  | −1 | 0           | +2    |
| Are there alternative causes (other than the drug) that could on their own have caused the reaction? | −1  | +2 | 0           | +2    |
| Did the reaction reappear when a placebo was given?                      | −1  | +1 | 0           | 0     |
| Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1  | 0  | 0           | 0     |
| Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1  | 0  | 0           | 0     |
| Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1  | 0  | 0           | 0     |
| Was the adverse event confirmed by any objective evidence?                | +1  | 0  | 0           | 0     |
interface dermatitis were indicative of SJS, most likely triggered by exposure to phenobarbital. After one week, the dog was presented for a reexamination. Lesions on the ventrum had become necrotic and ulcers had developed where previously vesiculobullous lesions were seen. No new lesions could be identified. Prednisolone dose was reduced and stopped after one more week. After the change from phenobarbital to potassium bromide, the dog showed recurrence of generalized tonic-clonic seizure activity with autonomic involvement 4–8 times weekly. Hospitalization at this point was declined by the owner and also prohibited by the aggressive character of the dog. One week later, another reexamination was performed, and no new skin lesions had developed. The existing lesions had regressed and the owner was advised to continue bathing the footpads. Blood was submitted for measurement of bromide concentration, which returned after 10 days, being 718 mg/l (reference range: 1000–3000 mg/l). Increasing the dose to try to achieve higher serum bromide concentrations was discussed with the owner. Two weeks after the last examination, the dog was admitted on emergency service for an acute onset of lethargy, progressive abdominal dilation and non-productive vomiting. An abdominal radiograph confirmed the presence of a gastric dilation and volvulus (GDV). Macroscopically, no more skin lesions were present on the mucosae, and all other lesions were reduced to multiple dry crusts and scar tissue. Because of the persistent poor seizure control at that time, together with a need for immediate surgery for the GDV, the owner elected euthanasia. A complete necropsy was performed, confirming the GDV and showing no other macroscopic and microscopic abnormalities. Histopathology of the brain revealed no abnormalities.

Cutaneous signs are the most common clinical manifestation of ADRs in dogs and cats (Voie et al. 2012). These ADRs can present with various skin lesions and can mimic other dermatological diseases. They can affect any part of the body, and specific clinical signs and lesions cannot be attributed to specific drugs (Voie et al. 2012). Most commonly, small animals present with angioedema/urticarial lesions, superficial pustular dermatitis, lupoid drug reactions, pemphigus foliaceus-like drug reactions, EM or SJS/toxic epidermal necrolysis (TEN) (Gross et al. 2005; Voie et al. 2012). For many years, the position in human dermatology has been that EM, SJS and TEN occupy a spectrum, with EM at the milder end and TEN at the severe extremity. The current position, however, is that EM is a separate disease, mostly triggered by infection with herpes simplex virus (Yager 2014). In contrast, SJS and TEN represent a spectrum of largely drug-induced disease. In veterinary medicine, confusion abounds around EM, SJS and TEN, still representing EM as a milder form of SJS/TEN as there are no universally agreements upon clinical criteria for EM in animals (Swartz et al. 2013; Yager 2014). In human dermatology, SJS can be distinguished from EM clinically as the lesions in SJS are almost always flat compared to raised lesions in EM (Bastuji-Garin et al. 1993). In this case, the clinical lesions were flat, evolved into ulcers and had a positive Nikolsky sign, as would be expected with SJS. Notably, SJS lesions can blister in the center, as was seen in this case, and this does not denote raised lesions (Banovic et al. 2015). Indeed, epidermal detachment, as seen in this case is a hallmark of SJS. The extent of the epidermal detachment on the body surface is the main criterium to differentiate SJS from TEN (Yager 2014; Banovic et al. 2015). SJS typically has epidermal detachment of less than 10% of the body surface, whilst TEN presents with epidermal detachment of more than 30% of the body surface. The distribution of the lesions was in accordance to what has been described in animals with SJS.

Figure 5. Microscopic image of the lesions in a 4-year-old female Great Dane, showing the presence of interface dermatitis (arrows pointing at apoptotic keratinocytes) and vesicle formation in the epidermis, with presence of confluent necrosis over the blisters. Haematoxylin and eosin stain.

Figure 6. Microscopic image of the lesions in a 4-year-old female Great Dane, showing the presence of interface dermatitis and vesicle formation in the epidermis (arrows pointing at roof of vesicle), with presence of confluent necrosis over the blisters. Haematoxylin and eosin stain.
lesions that become generalized especially involve the glabrous skin of the groin and axillae (Gross et al. 2005). Other common sites of involvement include the footpads and mucocutaneous junctions (Scott & Miller 1999; Gross et al. 2005). The present case had only oral mucosal involvement. Although this is present in the majority of SJS cases, and has been reported as one of the criteria to diagnose SJS, mucosal involvement is no longer required to make the diagnosis of SJS (Bastuji-Garin et al. 1993; Yager 2014). The dermatopathological changes reflected a cytotoxic lymphocyte response against altered keratinocytes, as can also be seen in EM. However, the keratinocyte cell death was more extensive than in classical EM, and there was some epidermal detachment present. However, it is not possible to differentiate accurately between EM, SJS and TEN using histological criteria alone (Bastuji-Garin et al. 1993; Yager 2014).

In dogs, the most common causes for ADRs are topical agents, trimethoprim-potentiated sulfonamides, penicillins, cephalosporins, levamisole, levothryoxine, chloramphenicol and diethylcarbazime (Miller et al. 2012), most commonly causing EM (Gross et al. 2005; Voie et al. 2012). TEN may be seen with the same drugs, and additionally with griseofulvine, 5-fluorocytosine and aurothioglucone in dogs, where quinolones, chloromezonean, nevirapine, lamotrigine, sertraline, anticonvulsant treatment for this dog when possible to differentiate accurately between EM, SJS and TEN using histological criteria alone (Bastuji-Garin et al. 1993; Yager 2014). In our case, the dog was diagnosed with SJS. The exact time frame and description of the evolution of the skin lesions add to a better understanding of this disease. Occurrence of withdrawal seizures can be a major problem when acute discontinuation of the offending drug (Scott & Miller 1999; Miller et al. 2012; Voie et al. 2012), which was also true for the presented case.

However, as superficial necrolytic dermatitis is known to be associated with chronic phenobarbital administration (March et al. 2004), this is the first case report describing presumed phenobarbital-induced SJS in a dog. The exact time frame and description of the evolution of the skin lesions add to a better understanding of this disease. Occurrence of withdrawal seizures can be a major problem when acute discontinuation of phenobarbital treatment is necessary, but nowadays some new treatment options consisting of oral loading schedule for potassium bromide (Gindidiousi et al. 2004) and the additional use of IV or oral leveteracetam (Hardy et al. 2012; Charalambous et al. 2014; Patterson 2014), can possibly help to overcome this issue.

Pitfalls of this case report are the lack of intravenous anticonvulsant treatment for this dog when possible withdrawal seizures were occurring, which could have positively influenced the outcome concerning seizure frequency. This frequency, combined with the expenses for surgery, made the owner elect euthanasia, and so no long-term follow-up is available in the present case. It was not possible to unequivocally prove that phenobarbital was the cause of SJS. However, the dog was not receiving any other medication prior to developing skin lesions, and the skin lesions resolved when treatment with phenobarbital was stopped. It is unclear whether the anti-inflammatory dose of glucocorticoids administered for two weeks, changed the evolution of the lesions, but the lesions went into regression and did not recur after the discontinuation of the glucocorticoids.
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