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Case Report
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Suspected Phenobarbital-Induced Pseudolymphoma in a Dog

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Pseudolymphoma is a drug reaction to anti-epileptics that is well recognized in humans; it has been reported in one cat but not dogs. In this report, lymphoma-like clinical signs are suspected to be secondary to phenobarbital administration in a dog. A 2.5-year-old male, neutered Shepherd mix presented for a 3-day history of progressive ataxia, dazed mentation, pyrexia, and lethargy. While hospitalized, the dog developed generalized lymphadenopathy and sustained pyrexia. The dog was receiving levetiracetam and phenobarbital for epilepsy, and serum concentrations of both were within standard therapeutic ranges. Abdominal ultrasound revealed hepatomegaly, splenomegaly, and generalized lymphadenopathy. Cytology of the peripheral lymph nodes was consistent with reactive lymph nodes, and aspirates of the liver and spleen revealed histiocytic-neutrophilic inflammation. Phenobarbital was discontinued and replaced with zonisamide. Within 24 hours, the dog was normothermic, and other clinical signs resolved within a week. This case highlights a potentially serious yet reversible adverse reaction to phenobarbital in a dog. This idiosyncratic reaction could be mistaken for neoplasia and is an important differential for lymphoma-like signs in any dog administered phenobarbital.

Key words: Adverse drug reactions; Epilepsy; Phenobarbital.

A 2.5-year-old (36.7 kg) male, neutered Shepherd mix presented for investigation of a 3-day history of lethargy, decreased appetite, dazed mentation, ataxia, and polyuria. He had no recent travel history or known tick exposure. He had initially presented to the hospital 4 months previously after his first generalized tonic-clonic seizure. Abnormalities were not detected on a CBC, chemistry, *Cryptococcus spp*. titer (antigen latex agglutination test), and brain MRI at that time. The dog was diagnosed with presumed idiopathic epilepsy and started on levetiracetam 750 mg PO q8h (20 mg/kg). Over the next few months, the dog's seizure frequency increased and the dog began to have cluster seizures. The dog's levetiracetam dose was increased to 1000 mg q8h (27 mg/kg), and phenobarbital of 60 mg q12h (1.6 mg/kg) was added 8 weeks before presentation. Three weeks before presentation, a phenobarbital serum concentration was measured below the therapeutic range, so the phenobarbital dose was increased to 90 mg q12h (2.5 mg/kg). At the time of presentation, the dog's seizure frequency was once every 7–10 days.

On examination, he was quiet to dull, tachypneic (respiratory rate of 44 breaths/min), and pyrexic (40.1°C/104.2°f), with no peripheral lymphadenopathy. Neurologic examination revealed mild ataxia and mild postural deficits in all four limbs. He did not guard his neck or show back pain. He was hospitalized and started on fluids administered IV and ampicillin (30 mg/kg IV q8h). Initial diagnostics included an in-clinic ELISA serology for vector-borne pathogens (Idexx 4dx), chest radiographs, urinalysis with aerobic culture, and repeat *Cryptococcus spp*. titer (antigen latex agglutination test), which did not detect any abnormalities. CBC and chemistry revealed mild nonregenerative anemia (hematocrit of 31%), monocytosis, lymphopenia, hypoalbuminemia, and mildly elevated bilirubin and ALP. Phenobarbital serum concentration was 100.5 umol/L (64–151), and levetiracetam serum concentration was 23.6 mcg/mL (5–45), both within the therapeutic range.

While hospitalized over the next 48 hours, the dog's pyrexia persisted despite administration of fluids and antibiotics. The dog developed peripheral lymphadenopathy and became more ataxic, lethargic, and dull. An abdominal ultrasound revealed hepatomegaly, splenomegaly, and generalized abdominal lymphadenopathy. Lymphoma was suspected, but fine needle aspirates of the dog's peripheral and abdominal lymph nodes revealed a reactive lymphatic population, while aspirates of his liver and spleen showed histiocytic-neutrophilic inflammation.

Phenobarbital administration was discontinued and zonisamide administered, based on one case report of pseudolymphoma previously reported in a cat.[1] Within 24 hours of discontinuing phenobarbital, the dog's temperature returned to normal and the dog's mentation improved. Within 2 days, the dog's ataxia had fully resolved, he remained normothermic, and the polydipsia and appetite improved. A week later, neurologic examination did not detect any abnormalities, and the dog's peripheral lymphadenopathy had resolved. The dog's owner reported that energy levels had improved, and the dog had an appropriate appetite. Repeat abdominal ultrasound, a week later, revealed resolution of the hepatomegaly, but persistent splenomegaly and abdominal lymphadenopathy. Three months later, the abdominal

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lymphadenopathy had resolved, but his spleen remained slightly enlarged on ultrasound. The dog's next seizure was 2 months after when phenobarbital was discontinued, which was the longest seizure-free interval since the dog's initial epilepsy diagnosis.

Phenobarbital is a commonly used anti-epileptic drug that has many known adverse reactions, both dose-dependent and idiosyncratic. A recent systematic review of the safety of anti-epileptics in dogs reported that over 50% of dogs receiving phenobarbital had an adverse reaction; however, these are usually mild and resolve with a lower dose or if the medication is withdrawn.[2,3] The most commonly reported adverse reactions to phenobarbital are dose-dependent (type 1) and include increased serum ALP and ALT activity, sedation, polydipsia/polyuria, ataxia, polyphagia, and chronic hepatopathy. Reported idiosyncratic (type 2) reactions to phenobarbital are much less common and include blood dyscrasias, pancreatitis, necrolytic dermatitis, and dyskinesia.[2] Due to the rare occurrence of these idiosyncratic reactions, they might go unrecognized for long periods of time. This combined with the high cost of a misdiagnosis (potential euthanasia), and the potential for reversible clinical signs, if the drug is withdrawn, makes it important to document new reactions.

Pseudolymphoma syndrome is a hypersensitivity reaction to anti-epileptic drugs that was first described in a human being after administration of phenytoin in 1950.[4] More recently, it has been associated with other anti-epileptic drugs having an aromatic structure including phenobarbital, carbamazine, and valproic acid.[5] This rare syndrome might be a subset of the better described anticonvulsant hypersensitivity syndrome (AHS), sometimes known as drug rash with eosinophilia and systemic symptoms (DRESS). This is a severe idiosyncratic acute drug reaction to aromatic anti-epileptic drugs. It typically presents initially with fever and malaise, followed a few days later by some combination of a skin rash, lymphadenopathy, and hepato- or splenomegaly. DRESS can also cause lymphocytosis, eosinophilia, and multiple organ involvement.[6–8] Pseudolymphoma is distinguished from DRESS by the absence of eosinophilia and prompt resolution after discontinuation of the medication without recurrence.[9]

The pathophysiology of pseudolymphoma syndrome is not well understood. Aromatic anti-epileptic drugs are metabolized to toxic metabolites and hydroxylated aromatic compounds (arene oxides) that can build up leading to a secondary immune response and might have a direct toxic effect on cells.[8] Clinical signs typically present 3–5 weeks after first administration of the medication and resolve 2–9 weeks after withdrawal of the inciting medication. Humans with severe signs are often treated with glucocorticosteroids, and recurrences and fatalities have been reported.[5,8]

Peripheral lymphadenopathy after phenobarbital administration in a cat is reported.[1] However, we were not able to find any published lymphoma-like signs after phenobarbital administration to a dog. Given the rapid improvement of all clinical signs after discontinuing the medication, we believe this is a phenobarbital-induced pseudolymphoma. This case presented similar to pseudolymphoma in humans, other than a lack of skin lesions that occurs in most humans. Other differentials would include infectious or immune-mediated disease; however, these seem unlikely given the timing of clinical signs 3 weeks after a dose increase in phenobarbital and prompt clinical improvement after ceasing phenobarbital administration without further medications.

This case report presents a probable rare adverse reaction to phenobarbital in a dog despite phenobarbital serum levels within the therapeutic margins. Clinical signs were reversible after discontinuing phenobarbital indicating an excellent long-term outcome if the reaction is recognized and the drug stopped. Given the severity of his clinical signs and similarity to lymphoma, the owners were given a guarded prognosis and euthanasia and chemotherapy options were discussed as we awaited the cytology results. This drug reaction should be considered in any dog that presents with lymphoma-like signs that is receiving phenobarbital; phenobarbital administration should be discontinued before more invasive treatments, such as chemotherapy or euthanasia, are considered.

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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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