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Abstract

Case summary A female neutered domestic longhair cat, aged 1 year and 5 months, presented with lymphadenomegaly and anaemia following therapy with phenobarbital for idiopathic epilepsy. Physical examination revealed pale pink mucous membranes and peripheral lymphadenomegaly. Haematology showed a regenerative anaemia (haematocrit 19.3%, reticulocyte count $118.08 \times 10^9/l$), and saline agglutination was positive. Infectious disease screening was negative and lymph node cytology was consistent with reactive lymphoid hyperplasia. A diagnosis of phenobarbital-induced reactive lymphoid hyperplasia and immune-mediated anaemia was suspected. Complete resolution of the lymphadenomegaly and anaemia was documented within 4 weeks of phenobarbital discontinuation.

Relevance and novel information There are limited case reports of phenobarbital-induced haematological changes and lymphadenomegaly; however, the combination has not previously been reported in cats and is similar to the rare but significant syndrome in humans known as ‘anticonvulsant hypersensitivity syndrome’. Anticonvulsant hypersensitivities should be considered as a potentially serious, yet reversible, sequela to phenobarbital treatment that may be mistaken for more severe illness such as neoplasia.

Keywords: Phenobarbital; anaemia; lymphadenomegaly; adverse reaction; hypersensitivity; pseudolymphoma

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Introduction

In humans, anticonvulsant hypersensitivity syndrome (AHS) occurs after treatment with carbamazepine, phenytoin, phenobarbital or valproic acid. This syndrome mainly manifests as skin lesions but is accompanied by pseudolymphoma in 70% of cases and haematological abnormalities, including leukocytopenia, anaemia and thrombocytopenia, in 50% of cases.¹

Although lymphadenomegaly^{2,3} and pancytopenia⁴ have been previously recorded separately in cats receiving phenobarbital, the combination of these findings, as described in AHS, has not been described.

Case description

A female neutered domestic longhair cat aged 1 year and 5 months and weighing 3.5 kg was presented with

a 3-day history of reduced appetite and lethargy. The cat had a recent history of generalised tonic–clonic seizures treated with 3 mg/kg PO q12h phenobarbital (Epiphen; Vetoquinol) for 2 weeks prior to presentation. Haematology, biochemistry, bile acid stimulation,

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toxoplasma serology, serum ammonia, MRI, cerebrospinal fluid cytology and protozoal PCR were all normal/negative at the time of seizure investigation, leading to a diagnosis of idiopathic epilepsy. Echocardiography was performed by an American and European diplomate to investigate a grade II/VI systolic heart murmur, and was structurally normal. No further seizures had been noted after the initiation of treatment with phenobarbital.

On presentation, the cat was quiet, alert and responsive. Physical examination revealed pale pink mucous membranes and peripheral lymphadenomegaly. Rectal temperature was 38.4°C. Haematology (VPG) showed a regenerative anaemia (haematocrit 19.3%; reference interval [RI] 24–45) reticulocyte count $118.08 \times 10^9/l$ and thrombocytopenia ($51 \times 10^9/l$; RI 170–650). All other parameters were within normal limits. Blood film examination performed by a resident in clinical pathology showed polychromasia and anisocytosis. Giant platelets and platelet clumps were noted, although the count appeared reduced. Saline agglutination was positive. Biochemistry showed hyperglobulinaemia (61 g/l; RI 28.0–51.0 g/l) and mild hypokalaemia (3.3 mmol/l). Testing for feline immunodeficiency virus antibody (FASTest FIV; Megacor) and feline leukaemia virus antigen (FASTest FeLV; Megacor) and haemoplasma PCR on whole blood were negative. Phenobarbital serum levels were within the RI (59.5 $\mu\text{mol/l}$; RI 40–160 [VPG]). Lymph node cytology showed reactive lymphoid hyperplasia; no atypical cells or infectious agents were seen. Abdominal ultrasonography revealed hepatic lymphadenomegaly, measuring 6.55 mm, with no free abdominal fluid. A single lateral thoracic radiograph was unremarkable.

An adverse drug reaction causing reactive lymphoid hyperplasia and immune-mediated anaemia was suspected. Phenobarbital was tapered over 3 days and levetiracetam (Levetiracetam 100 mg/ml oral solution; Beacon Pharmaceuticals) was initiated (20 mg/kg PO q8h). The cat was anorexic in hospital and a nasogastric feeding tube was placed, allowing enteral nutrition.

The cat remained clinically stable until 6 days after admission, when its packed cell volume (PCV) decreased to 11%. The cat was blood typed A (Rapid Vet-H; dms laboratories) and a fresh whole-blood transfusion was given. Owing to the concern of immune-mediated destruction a single dose of dexamethasone (Duphacort Q; Zoetis) was administered at 0.4 mg/kg IV.

Post-transfusion, there was progressive improvement in the PCV (Table 1) and appetite. Two short seizures occurred on day 8 of hospitalisation, and the dose of levetiracetam was increased to 40 mg/kg PO q8h. A mild transient pyrexia was noted 5 days post-transfusion. Eleven days after initial presentation, PCV was 21% and no further seizures had been noted since the

Table 1 Serial monitoring of packed cell volume (PCV)

Day	1	3	4*	5	6	7	8	9	10	11	17	32	RI
PCV (%)	15	15	20	13	11	13	14	15	16	21	24	34	31–48
Notes		Phenobarbital weaned 2 mg/kg	Phenobarbital weaned 1 mg/kg	Phenobarbital stopped	Transfusion								Discharged

*PCV recorded on day 4 was presumed to be spurious but was, unfortunately, not rechecked
RI = reference interval

Table 2 Serial monitoring of haematology in a cat with anaemia following phenobarbital discontinuation on day 5 (VPG)

	Day 1	Day 17	Day 32	RI
HCT (%)	19.3	26.5	34.8	27–50
Absolute reticulocyte count ($\times 10^9/l$)	118.08	98.40	54.11	
Platelets ($\times 10^9/l$)	51	461	486	170–650
Globulins (g/l)	61	52	44	27–50

RI = reference interval; HCT = haematocrit

levetiracetam dose increase. The cat was discharged on 40 mg/kg q8h levetiracetam and 2 mg PO q24h mirtazapine, as required.

One week later the cat was clinically well with mild lymphadenomegaly of the right prescapular lymph node; the clinical examination was otherwise normal. Complete blood count showed a mild regenerative anaemia and resolution of the thrombocytopenia (Table 2). Serum biochemistry showed an improved hyperglobulinaemia (52 g/l; RI 27.0–50.0).

One week later the owner reported three seizures of 10s duration on different days with a quick recovery. Levetiracetam was increased to 50 mg/kg PO q8h.

On final examination 3 weeks after discharge there had been two further seizures, 4 days after the previous dose increase, but otherwise the cat was clinically well. Clinical examination revealed complete resolution of the peripheral lymphadenomegaly. The anaemia, thrombocytopenia (Table 2) and hyperglobulinaemia (44 g/l; RI 27–50) were resolved.

Discussion

Phenobarbital is a common first-line antiepileptic drug in both human and veterinary medicine. Phenobarbital-associated side effects can be split into types A and B.⁵ Type A side effects have known pharmacological mechanisms, and hence are often dose dependent and predictable. Type B side effects are idiosyncratic and unpredictable. Peripheral lymphadenomegaly and haematological abnormalities are type B reactions and are part of AHS.⁶

AHS is rare in humans and typically appears 1–12 weeks after starting anticonvulsant treatment. Fever and rash are the most common signs (90–100% cases) variably accompanied by lymphadenomegaly/pseudolymphoma (70%) and hepatitis (50–60%). Haematological abnormalities, including leukocytopenia, anaemia and thrombocytopenia, are reported in 50% of cases.¹ Haemolytic anaemia has been reported to occur in 0.4/100,000 anticonvulsant prescriptions in human medicine.⁷

Phenobarbital-induced AHS is incompletely understood. Cases do not appear to be linked simply to serum concentrations of phenobarbital above the target range; reported cases in the veterinary literature of adverse

effects associated with phenobarbital,^{2,3,8} and the cat reported here had measurably normal serum phenobarbital concentrations. Aromatic antiepileptic drugs are metabolised to toxic metabolites and hydroxylated aromatic compounds (arene oxides), which are thought to be cytotoxic and may initiate an immune reaction via T-cell activation.^{6,9} Epoxide hydroxylase and glutathione transferase are enzymes required for arene oxide detoxification. Deficiency or abnormalities in these enzymes could cause an accumulation of arene oxides, leading to a secondary immune response by acting as antigens which stimulate T cells, and possibly a direct toxic effect on cells due to the covalent binding to cell macromolecules.^{8,10}

Several veterinary case reports document signs suggestive of AHS following phenobarbital administration. Phenobarbital-associated pseudolymphoma has been reported in two cats^{2,3} and one dog;⁸ however, no haematological changes were noted in these cases. In this case, and these previous cases, it is likely that the lymphadenomegaly was due to reactive lymphoid hyperplasia, and nodal effacement might not have been present. Therefore, while this presentation might resemble lymphoma clinically, the pathological criteria for pseudolymphoma used in humans were not met. Phenobarbital-associated pancytopenia has been reported in a cat where haematological changes resolved after treatment was stopped.⁴ No lymphadenomegaly was noted in this case. To our knowledge, this is the first report of phenobarbital-associated pseudolymphoma and haematological abnormalities concurrently in the same cat.

In our case report, a regenerative anaemia with positive saline agglutination, alongside a mild thrombocytopenia, were reported. Regenerative anaemia can have haemorrhagic or haemolytic aetiology. In this case, there was no evidence of haemorrhage in the clinical history, clinical examination or imaging findings. Differential diagnoses for haemolysis in cats include infectious disease, oxidative injury and immune-mediated haemolytic anaemia. A positive saline agglutination is suggestive of immune-mediated destruction. Apart from phenobarbital there was no history of toxin or drug ingestion, and infectious disease testing was negative. An adverse reaction to phenobarbital causing a secondary immune-mediated anaemia was the diagnosis of exclusion, which

was supported by the resolution of anaemia when phenobarbital was discontinued.

Hyperglobulinaemia has been reported in one other veterinary case of phenobarbital-induced pseudolymphoma³ but was not present in two others.^{2,11} Hyperglobulinaemia may represent immune stimulation, which resolved after phenobarbital treatment was stopped. Other differential diagnoses include neoplasia and infectious disease, such as feline infectious peritonitis, although lymph node cytology was not consistent with either of these diagnoses. Serum protein electrophoresis could have been performed to distinguish between a mono- and polyclonal gammopathy,¹² and coronavirus PCR could have been performed on lymph node aspiration samples.¹³ However, resolution of clinical abnormalities following discontinuation of phenobarbital, in the absence of other treatment modalities, supports an idiosyncratic response to phenobarbital.

Phenobarbital-induced pyrexia has been reported in one cat¹⁴ and resolved promptly on the cessation of treatment. While the cat in our case report developed transient pyrexia, it started several days after phenobarbital treatment was stopped and followed administration of a blood transfusion. A delayed transfusion reaction was considered most likely.

The mainstay of therapy in AHS is discontinuation of anticonvulsants. Clinical signs typically improve within 10–14 days. In our case, a similar response was seen, with partial resolution 12 days after discontinuation of phenobarbital and full resolution noted at 4 weeks.

Treatment with prednisolone, intravenous methylprednisolone and human intravenous immunoglobulin has been reported in severe cases of AHS in humans.^{6,15} One dose of dexamethasone was given in this case when the PCV reduced to 11%. However, the improvements seen clinically over the following days were likely related to discontinuing phenobarbital rather than an effect of dexamethasone. The case report of pancytopenia secondary to phenobarbital reported resolution of clinical signs with withdrawal of the drug alone;⁴ hence, the use of dexamethasone may not have been warranted in our case.

Conclusions

To our knowledge, this is the first report of concurrent peripheral lymphadenomegaly and haematological abnormalities secondary to phenobarbital administration in a cat. The combination of anaemia, hyperglobulinaemia and lymphadenomegaly can be seen with neoplastic processes such as lymphoma and in infectious diseases, such as feline infectious peritonitis. A misdiagnosis of a neoplastic syndrome or systemic infection might lead to unnecessary financial expenses, prolonged suffering for the patient or euthanasia. This drug

reaction should be considered in any cat that presents with lymphoma-like signs and haematological abnormalities that is receiving phenobarbital; phenobarbital administration should be discontinued before more invasive treatments, such as chemotherapy or euthanasia, are considered.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained, it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). For any animals or people individually identifiable within this publication, informed consent (either verbal or written) for their use in the publication was obtained from the people involved

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