Original Article

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Feline non-regenerative immune-mediated anaemia: features and outcome in 15 cases

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Abstract

Objectives Pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA) are uncommon causes of non-regenerative anaemia affecting the bone marrow in the cat. This retrospective study aimed to describe the clinical features, treatment and outcome (remission and survival) of cats with these disorders.

Methods Cases of PRCA and NRIMHA presenting between 2009 and 2013 were retrieved. Clinical features including signalment, history, clinical signs and diagnostic investigations were recorded, as well as treatment(s) used and outcome (remission and survival). Outcome was compared for PRCA and NRIMHA.

Results Fifteen cats met inclusion criteria: seven with PRCA and eight with NRIMHA. The majority (12/15) were younger than 3 years of age. Volume overload was common (8/11). Treatment with whole blood transfusions with or without Oxyglobin was necessary in most cats (14/15) and resulted in congestive heart failure in one cat. Most cats (11/15) achieved remission 12–42 days after starting immunosuppressive treatment. Treatment protocols associated with remission were glucocorticoids alone (remission in 6/7 cats), glucocorticoids and chlorambucil (remission in 3/6 treated cats), glucocorticoids and ciclosporin (one cat only) and ciclosporin alone (one cat only). Relapse was observed in 3/11 cats, and 8/11 cats were still receiving treatment at the time of follow-up. Outcome (remission and survival) did not differ between PRCA and NRIMHA.

Conclusions and relevance PRCA and NRIMHA are uncommon causes of anaemia in predominantly young cats. The prognosis is reasonable, with a mortality rate of 27%, and it can take at least 6 weeks before remission is observed. Following clinical remission, gradual withdrawal of immunosuppressive treatments should be attempted, with close monitoring for relapse; some cats may require long-term treatment. This study is the first to report the use of chlorambucil as an adjunctive immunosuppressant in these cases. Outcome did not differ for PRCA and NRIMHA.

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Introduction

Immune-mediated haemolytic anaemia (IMHA) arises due to antibody-mediated erythrocyte destruction[1] and is less common in cats than dogs.[2] It can arise as a primary (idiopathic) condition, or secondarily to a stimulus for the immune-mediated destruction, such as feline leukaemia virus (FeLV), *Mycoplasma hemofelis*, drugs or neoplasia.[2,3]

Although primary IMHA is typically associated with a reticulocytosis, evidence of regeneration is sometimes not found. This may be due to the IMHA being in the pre-regenerative phase[4,5] or due to immune-mediated destruction of erythrocyte precursors.[5,6]

Primary IMHA with immune-mediated destruction of erythrocyte precursors occurs in two conditions: pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA).[5,7,8] PRCA is characterised by bone marrow erythroid aplasia or hypoplasia,[6,8,9] whereas NRIMHA is associated with bone marrow erythroid hyperplasia and/or erythroid maturation arrest.[6,9] Both PRCA and NRIMHA are

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speculated to represent a spectrum of the same disease process, and may reflect immune-mediated destruction of different stages of erythrocyte cell maturation.[5] Prednisolone alone, or in conjunction with other immunosuppressive drugs, is used to treat PRCA and NRIMHA.[10–12]

Little information is available describing cats with PRCA and NRIMHA, particularly regarding outcome.[9,10,12,13] The aim of the study was to describe the clinical features, treatment and outcome (remission and survival) of cats with PRCA or NRIMHA.

Materials and methods

Case selection

A retrospective study was undertaken across two referral centres (The Feline Centre, Langford Veterinary Services, University of Bristol, and the Queen Mother Hospital for Animals, The Royal Veterinary College). Computerised medical records between 2009 and 2013 were searched for cats with PRCA or NRIMHA diagnosed on bone marrow analysis. The records that met the following additional inclusion criteria were used: ⩾5-day history of clinical signs, moderate or severe non-regenerative anaemia (haematocrit [HCT] <20%[14] with absolute aggregate reticulocyte count $<15 \times 10^9$/l)[5] and an absence of identified triggers for the anaemia on investigations. Minimum investigation to screen for triggers included the absence of recent toxin or drug exposure, feline leukaemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody testing (Petcheck microwell ELISA; IDEXX), serum biochemistry and abdominal ultrasonography. Additional investigations performed at the discretion of the clinician included bone marrow FeLV provirus PCR, haemoplasma (*M haemofelis*, *Candidatus* Mycoplasma haemominutum and *Candidatus* Mycoplasma turicensis) PCR testing, Coombs' testing, thoracic radiography and echocardiography.

Data recording

Case records were evaluated and signalment, historical findings and clinical examination findings recorded. Haematological data at presentation were recorded including: HCT, aggregate reticulocyte, neutrophil and platelet counts. Results for haemoplasma PCR, Coombs' testing, blood typing and bone marrow sample type (aspirate and/or core) were recorded. Any blood products (whole blood transfusions and Oxyglobin) and immunosuppressive drugs administered were also recorded, together with any adverse effects seen.

Outcome

Each case was defined as having gone into remission (defined as HCT >25% with an absence of clinical signs) or having a failed response if remission did not occur. The time between diagnosis and any remission was recorded. Survival data was obtained by recording whether the cat survived to discharge (euthanasia or death). For those cats that survived to discharge, referring veterinarians were contacted for follow-up information regarding survival time (from diagnosis), treatment and any relapses.

Statistical analysis

Descriptive statistics were prepared for the recorded data, with continuous variables reported as a median and range. Remission and relapse data were evaluated for any significant association with PRCA or NRIMHA diagnosis by Fisher's exact test using SPSS Statistics for Windows v21 (IBM Corp). Significance was defined as $P \leqslant 0.05$.

Results

Seventeen cases were initially retrieved. Two failed to meet the inclusion criteria (one had paracetamol toxicity and one had recent methimazole treatment), leaving 15 cases in the study: seven with PRCA and eight with NRIMHA.

Signalment, history and clinical signs

Breed was known for all 15 cats: 12 domestic shorthair, one domestic longhair, one Maine Coon and one Bengal. They ranged in age from 7 months to 15 years (median 1.5 years); 12 cats were younger than 3 years of age. All cats were neutered; 10 were male. All cats presented with lethargy ranging in duration from 5 days to 3 months (median 7 days). Other clinical signs reported included inappetence (n=12), weight loss (n=4) and pica (n=3). All cats had pallor. Clinical examination findings included tachypnoea (n=13), gallop rhythm (n=9) and a grade II–III/VI systolic heart murmur (n=9).

Diagnostic investigations

All cats underwent haematology at presentation, with results summarised in Table 1. Thirteen of the 15 cats had severe anaemia (HCT <15%), and the remaining two cats had moderate anaemia (HCTs of 18% and 19%). Neutropenia was identified in 7/15 cats. In 12/15 cats, platelet clumping precluded accurate machine platelet counts, but blood smear estimates indicated that the platelet count was adequate. Accurate machine platelet counts with which smear examinations agreed were available in three cats. Severe thrombocytopenia ($<30 \times 10^9$/l) was present in two of these three cats.

Table 2 outlines serum biochemistry results. Increases in urea were considered pre-renal in all affected cases (10/15 cats) due to concurrent urine concentration (data not shown). Hypokalaemia was common (12/15 cats) and considered likely to be due to reduced food intake,

Table 1 Haematology results at presentation in 15 cats with pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA)

Haematological variable (unit)	Median	Range	Reference interval
HCT (%)	7.8	5.6–19.0	25.0–45.0
Haemoglobin (g/dl)	2.4	1.8–6.3	8.0–15.0
Red blood cells ($\times 10^{12}$/l)	1.9	1.3–4.6	5.5–10.0
MCV (fl)	45	35.1–54.1	40.0–55.0
MCHC (g/dl)	33	27.7–39.2	30.0–35.0
Aggregate reticulocyte count ($\times 10^9$/l)	0	0.0–10.0	
White blood cells ($\times 10^9$/l)	6	3.6–18.2	4.9–19.0
Bands ($\times 10^9$/l)	0	0–0.05	0.0–0.3
Segmented ($\times 10^9$/l)	3.1	0.94–6.95	2.4–12.5
Lymphocytes ($\times 10^9$/l)	3.1	0.5–11.6	1.4–6.0
Monocytes ($\times 10^9$/l)	0.2	0–0.43	0.1–0.7
Eosinophils ($\times 10^9$/l)	0.1	0.0–1.4	0.1–1.6
Platelets ($\times 10^9$/l) (n = 3)*	13	8–709	200–700

*Accurate platelet count only available in three cats
HCT = haematocrit; MCV = mean cell volume; MCHC = mean cell haemoglobin concentration

Table 2 Serum biochemistry results at presentation in 15 cats with pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA)

Biochemical variable	Median	Range	Reference interval
Urea (mmol/l)	14.6	5.4–22.1	6.5–10.5
Creatinine (μmol/l)	109	48.0–215.0	133–175
Albumin (g/l)	30.7	22.4–39.4	24.0–35.0
Globulin (g/l)	39.6	26.4–69.2*	21.0–51.0
Alanine aminotransferase (IU/l)	64	0–757	15–45
Alkaline phosphatase (IU/l)	21	0–29	15–60
Bilirubin (μmol/l)	3.5	0–10.0	0.0–10.5
Potassium (mmol/l)	3.5	2.4–3.9	3.8–5.0

*Serum protein electrophoresis was performed in the cat that had a globulin concentration of 69.2 g/l, which revealed a polyclonal gammopathy

or renin-angiotensin-aldosterone system (RAAS) activation secondary to renal hypoperfusion. Increased alanine aminotransferase activity (ALT) was a common finding and was considered most likely to reflect hepatic hypoxia due to the anaemia.

All cats were blood typed; 13 were blood type A and two were blood type B. Six cats were Coombs' tested, and three were positive.

Ten cats had FeLV provirus PCR performed on bone marrow samples, and all were negative. Ten cats had haemoplasma PCR performed with negative results in all.

Thoracic radiography, performed in 13 cats, revealed cardiomegaly in nine. Abdominal ultrasonography findings were either normal or revealed findings consistent with immune-mediated disease including mild hepatomegaly with extramedullary haematopoiesis on fine-needle aspiration, and prominent mesenteric lymph nodes with reactive lymph nodes on fine-needle aspiration. Echocardiography was performed in eight cats and revealed generalised mild to moderate cardiomegaly with enlargement of all four chambers and volume overload presumed secondary to the anaemia in seven cats. The remaining cat had a previous diagnosis of hypertrophic cardiomyopathy, and no evidence of chamber enlargement was noted in this cat, although there was mild hypertrophy of the interventricular septum.

Six cats had both bone marrow aspirates and core biopsies performed, and in all cases both yielded results that agreed. In seven cats only aspirates were performed, and in two cats only core biopsies were performed. Bone marrow analysis revealed PRCA in seven cats, with erythroid aplasia in five cats and erythroid hypoplasia in two cats, and NRIMHA in eight cats, with erythroid hyperplasia in all eight cats and maturation arrest in two cats. Erythrophagocytosis was identified in two cats with PRCA and three cats with NRIMHA, consistent with the immune-mediated aetiology of the disorders. Megakaryocyte numbers were normal in 12 cats. The two severely thrombocytopenic cats had low megakaryocyte numbers, and both had PRCA. Myeloid numbers

and maturation were normal in seven cats, including 1/7 neutropenic cats. Myeloid hypoplasia was found in eight cats (6/8 had NRIMHA, 2/8 had PRCA), including 6/7 neutropenic cats. One cat (PRCA) had neutropenia and thrombocytopenia on haematology. Bone marrow cytology showed normal megakaryocyte and myeloid numbers. Nine cats showed lymphoid hyperplasia (4/9 had NRIMHA, 5/9 had PRCA). Myelofibrosis was present in two cats both in the NRIMHA group; in both cats, the myelofibrosis was described as mild, and the marrow was judged to be hypercellular.

Treatment

Blood products were given to 14/15 cats. Fourteen cats received at least one whole blood transfusion; 11 cats received one, two cats received two and one cat received three. Oxyglobin was given to five cats, all of which also received one whole blood transfusion. Median post-transfusion packed cell volume (PCV) was 12% (range 8–18%).

Immunosuppressive therapy and outcomes are summarised in Table 3. Immunosuppressive glucocorticoids were given to 14/15 cats. Eleven cats received oral prednisolone (range 2–4 mg/kg q24h, median 3 mg/kg q24h), two cats received oral methylprednisolone (2 mg/kg q24h) and one cat received a single intravenous injection of dexamethasone (0.6 mg/kg). One cat received oral ciclosporin alone (10 mg/kg q24h) due to pre-existing hypertrophic cardiomyopathy, which was considered a contraindication to glucocorticoid therapy. Adjuvant oral immunosuppressive therapy was used with glucocorticoids in seven cats (either immediately in four, or following a failed response to glucocorticoids alone for 6–10 days in three); one cat received ciclosporin (10 mg/kg q24h) and six received chlorambucil (2 mg every other day).

Five cats received doxycycline while awaiting haemoplasma PCR results. Additional therapies given included furosemide (n = 3), pimobendan (n = 2), benazepril (n = 1) and famotidine (n = 1).

One cat developed a pleural effusion, suspected to be due to volume overload following Oxyglobin administration; this resolved with furosemide administration. One cat developed recrudescence of herpesvirus infection following immunosuppression with prednisolone and chlorambucil. The same cat also then developed an acute hepatopathy, presumed to be a drug reaction to the chlorambucil or doxycycline, and withdrawal of both drugs resulted in resolution.

Outcome

Two cats failed to survive to discharge. Both were euthanased during hospitalisation (days 2 and 9) due to a failed response and owner finances precluding further treatment. Of the 13 cats that survived to discharge, two showed a failed response and were euthanased 28 and 112 days after discharge. Thus, a total of four (two PRCA, two NRIMHA) showed a failed response resulting in euthanasia, giving an overall mortality rate of 27%.

The remaining 11 cats went into remission in a median of 28 days (range 12–42 days). Follow-up was available for all 11 cats with a median follow-up of 532 days following discharge (range 84–1512 days). The shortest follow-up of 84 days was in a cat that was euthanased due to anorexia and weight loss. Three of the 11 cats had relapse of anaemia during follow-up at 56, 71 and 280 days following diagnosis. Relapse occurred when reducing prednisolone dosage from 3 mg/kg q24h to 2 mg/kg q24h in one cat and from 1 mg/kg q24h to 0.5 mg/kg q24h in another, and after 10 months off all medications in the remaining cat. All relapses resolved with increasing dosages of glucocorticoids and cats remained stable on maintenance treatment. Three cats were on maintenance/tapering treatment at the time of follow-up (168, 560 and 1344 days). Two were receiving prednisolone (1 mg/kg q24h, 1.5 mg/kg q24h) and chlorambucil (2 mg q48h), and one was receiving prednisolone (0.5 mg/kg q24h) and ciclosporin (10 mg/kg q24h) with no relapse of anaemia occurring. Four cats were not receiving any medications and had not displayed any evidence of relapse (median follow-up 532 days, range 502–1008 days). Tables 3 summarises the outcomes of cats when divided into treatment group, and Table 4 summarises outcome according to diagnosis.

Discussion

PRCA and NRIMHA were uncommon diagnoses with only 15 cats meeting inclusion criteria identified in the

Table 3 Response, relapse and survival in 15 cats with pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA) according to treatment group

Immunosuppressive therapy	Number of cats	Remission	Failed response	Relapse	Alive at follow-up
Glucocorticoids	7 (2*5†)	6 (2* 4†)	1 (1†)	3 (3†)	6 (2* 4†)
Glucocorticoids and ciclosporin	1 (1†)	1 (1†)	0	0	1 (1†)
Glucocorticoids and chlorambucil	6 (5* 1†)	3 (3*)	3 (2* 1†)	0	3 (3*)
Ciclosporin only	1 (1†)	1 (1†)	0	0	0
Total	15 (7* 8†)	11 (5* 6†)	4 (2* 2†)	3 (3†)	10 (5* 5†)

*PRCA on bone marrow analysis
†NRIMHA on bone marrow analysis

Table 4 Response, relapse and survival in 15 cats with pure red cell aplasia (PRCA) and non-regenerative immune-mediated haemolytic anaemia (NRIMHA)

Diagnosis	Remission	Failed response	Relapse	Not receiving medications
PRCA	5/7	2/7	0/5	2/5
NRIMHA	6/8	2/8	3/6	1/6
Total	11/15	4/15	3/11	3/11

4-year study period. Consistent with previous reports,[10,12,13] this study found that PRCA and NRIMHA predominantly affected young cats, implying that older cats with this diagnosis should be thoroughly screened for an underlying trigger. A higher incidence of primary IMHA has previously been described in male cats,[3,10] and two-thirds of the cases of presumed immune-mediated bone marrow disease in the current study were male. This contrasts with the female bias reported in dogs with PRCA and NRIMHA.[6]

In common with previous reports, most cats presented with non-specific signs. Pica was only reported in three cats, and has previously been associated with immune-mediated anaemia in cats.[14] Clinical examination commonly identified cardiac auscultation abnormalities (gallop rhythm, heart murmur). However, underlying cardiac disease was identified in one cat only.

Most cats were severely anaemic at the time of presentation, and the majority required at least one whole blood transfusion. Five cats also received Oxyglobin. However, it should be noted that Oxyglobin was not available for the majority of the study period (2010–2013), and thus this figure may have been higher had Oxyglobin been available.

Concurrent neutropenia and/or thrombocytopenia was not uncommon at presentation (8/15 cats), and in most of these cases, bone marrow analysis revealed myeloid and megakaryocyte hypoplasia. Myeloid hypoplasia was identified in 6/8 cats with NRIMHA and 2/7 cats with PRCA. Megakaryocyte hypoplasia was identified in 2/7 cats with PRCA. The presence of these did not appear to affect outcome. As previously described in dogs,[6,15] the identified neutropenia and thrombocytopenia responded rapidly to immunosuppressive therapy in all cats. Myelofibrosis was identified in two cats, but both cats achieved clinical remission and were alive at follow-up. The latter suggests that myelofibrosis, which is suggestive of marked bone marrow pathology,[5] was not associated with a negative outcome in this study. Idiopathic myelofibrosis rather than myelofibrosis as a pathological alteration secondary to immune-mediated disease was considered unlikely given the presence of a hypercellular marrow on histopathology in both cats.

Half of the cats tested were Coombs' positive, consistent with previous studies,[6,12] and this is considered to reflect immune-mediated attack directed at epitopes found on immature erythrocyte progenitors in the bone marrow and mature erythrocytes in the circulation.[6]

Cardiomegaly and volume overload were common findings on thoracic radiographs and echocardiography. This has previously been well described in cats with non-regenerative anaemia[12,13] and the underlying mechanism is thought to be volume overload due to neuroendocrine compensatory mechanisms, including RAAS activation.[16] Despite this, blood products, including Oxyglobin, a product known to potently increase circulating volume,[17] were administered to 13 cats in the study, with only one cat developing circulatory overload after Oxyglobin, which resolved with furosemide treatment.

Remission was seen with all treatment regimens in this study (Table 3). Blood transfusion resulted in an increase in PCV of up to 18% in this study. Therefore, no cat was inappropriately defined as in remission based upon our definition of an increase in HCT to >25% following blood transfusion alone. Outcome could not be statistically compared amongst the treatment groups, as cats were not randomly assigned to the group. Indeed, some cats received adjunct therapy due to a failure to respond to glucocorticoids alone, thereby confounding analysis. This study is the first to describe the successful use of chlorambucil as an adjunct in cats with PRCA or NRIMHA, with half of the cats receiving adjunct chlorambucil showing remission. Ciclosporin has been previously used as successful adjunct treatment in PRCA.[12] The only cat in the current study that received ciclosporin alone achieved remission but was euthanased at 84 days due to a poor appetite and weight loss.

The majority of cats achieved remission following immunosuppressive therapy, resulting in a failed response rate of 27% (3/11 cats), with all of these cats undergoing euthanasia. This is similar to previous studies, which report a 23.5–33% mortality rate.[6,10–12] Time to clinical remission was 12–42 days. This is similar to Stokol et al[9] who reported 8–42 days. This highlights the importance of an extended treatment period before assuming non-response to treatment and therefore a poor prognosis.

Relapse was observed in 3/11 (27%) cats that underwent remission, similar to that reported by Kohn et al[10] in cats with primary IMHA where 5/16 cats relapsed (relapse rate of 31%), but lower than that described by both Stokol and Blue[9] who reported 3/4 cats relapsed

(75% relapse rate) and Viviano et al[12] who reported 4/6 cats relapsed (66% relapse rate). Interestingly, of the three cats that relapsed, two were receiving tapering glucocorticoid therapy, with only one cat being off all treatment during relapse. Of the seven cats that survived and did not relapse, only three were still being given immunosuppressive treatment and four were off treatment. Thus, relapse does not appear to be consistently prevented by ongoing treatment in these cases, although reintroduction of immunosuppressive dosing regimens was effective in all cases. The diagnosis of PRCA or NRIMHA did not affect the remission or relapse rate.

Conclusions

PRCA and NRIMHA are uncommon causes of anaemia in predominantly young cats. Most cats required at least one blood transfusion. Treatment is immunosuppression, and remission was associated with treatment with glucocorticoids alone, or in combination with ciclosporin or chlorambucil. Relapse was common (3/11 cats; 27%), and ongoing drug therapy was not protective of relapse. Cats that relapsed responded well to reintroduction of immunosuppression. Therefore, following remission, attempts to taper and withdraw immunosuppressive treatments should be made. The majority of cats remained on glucocorticoids with or without adjunctive treatments at follow-up. Outcome in this study did not differ between PRCA and NRIMHA.

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