ERYTHROLEUKEMIA IN A CAT

Erythroleukemie bij een kat

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ABSTRACT

A 3-year-old neutered male domestic cat was presented with anorexia and weight loss. Clinical examination also revealed fever and pale mucosae. The blood smear showed an abnormal presence of both erythrocytic and leukocytic precursors in the circulation. The cat also tested positive for feline leukemia virus (FeLV). Due to the poor prognosis, the cat was euthanized and presented for autopsy. Bone marrow smears also revealed the presence of immature erythrocytic and leukocytic cells. This findings corresponded well with erythroleukemia, an uncommon form of leukemia.

SAMENVATTING

Een 3 jaar oude, gecastreerde huiskat werd aangeboden met anorexie en vermagering. Bij het klinisch onderzoek werden koorts en bleke mucosae waargenomen. Het bloeduitstrijkje toonde een abnormale aanwezigheid van erythrocytaire en leukocytaire precursors in de algemene circulatie. De test voor het feliene leukemie virus (FeLV) was positief. Omwille van de slechte prognose werd de kat geëuthanaseerd en aangeboden voor autopsie. Een beenmerguitstrijkje toonde ook immature erythrocytaire en leukocytaire cellen aan. Deze bevindingen wijzen sterk op erythroleukemie, een zeldzame vorm van leukemie.

INTRODUCTION

Erythroleukemia, as the name implies, is a leukemia of both red and white cell lineages. Both erythrocytic and leukocytic precursors are present in the circulation (Harvey *et al*., 1978; Harvey, 1981; Reagan *et al.*, 1998; Smith *et al.*, 2003). A key feature that distinguishes acute erythroleukemia from other types of acute leukemia is that the erythroid precursors comprise more than 50% of nucleated bone marrow cells with a myeloid/erythroid ratio of less than one. Prominent megaloblastic or atypical erythroid precursors are common. Myeloblasts and monoblasts are < 30% of all nucleated cells in the bone marrow (Grindem, 2000). Erythroleukemia and erythremic myelosis are considered different manifestations of the same illness. In erythremic myelosis there is a predominance of immature erythroid cells in peripheral blood, which can progress to a mixture of neoplastic myeloid and erythroid cells in the peripheral blood in acute erythroleukemia (Jain, 1986; Harvey, 1981). In fact the distinction is mostly arbitrary and is based on the finding of myeloblasts admixed with abnormal nucleated erythrocytes in peripheral blood (Jain, 1993). However, erythremic myelosis has historically been classified as a leukemia of the erythrocytic lineage. This disorder has recently been renamed as either myelodysplastic syndrome with erythroid predominance or erythroleukemia with erythroid predominance (Reagan *et al.*, 1998).

Descriptive case reports of erythroleukemia are very limited in the literature. Herz and others (1969a, 1969b) described a case with successive stages of myeloproliferative disorders, including erythroleukemia. Shimada and others (1995) described erythroleukemia in two cats in the same household. Comazzi and others (2000) described a case of erythremic myelosis. However, various forms of hematologic appearances of myeloproliferative disease in the cat have been described, each with a specific terminology. Nowadays hematologists prefer simply to use the term "erythroleukemia" to encompass the various forms of this disease, as in humans (Harvey *et al.*, 1978). The present report is a description of an erythroleukemia case via hematology, biochemistry, serology, cytology, autopsy and histopathology.

CASE REPORT

Case history

A 3-year-old neutered male domestic cat (*Felis vulgaris*), which lived indoors as well as outdoors, was presented with signs of anorexia and weight loss, which had started 2 weeks before and were the reason for the consultation. The cat had been vaccinated annually against feline panleukopenia and rhinotracheitis (Felocell 3 ®, Phizer). There was no history of previous illnesses or travel history. Clinical examination also revealed fever and pale mucosae. Blood (clotted, EDTA and fluoride tube) was colected for hematology and extended general, liver and kidney screening. Feline leukemia virus (FeLV), feline immunodeficiency virus (FIV) and feline infectious peritonitis (FIP) rapid tests were also requested. Meanwhile the cat was treated with antibiotics and corticosteroids. There was a mild to moderate response to this treatment, i.e. weight gain and return of appetite. Because the FeLV test was positive and the condition of the cat deteriorated one week after presentation, euthanasia was requested.

Hematology, biochemistry and infectious serology

The results of hematology, biochemistry and infectious serology can be found in Table 1. There was leukocytosis, mild non-regenerative anemia, mild hyperglycemia, hypergammaglobulinemia, slightly increased levels of creatinin, and markedly increased levels of AST, ALT and (total) bilirubin.

The Bio Vet Test Speed® Duo FeLV / FIV and the Speed® FIP are rapid immunochromatographic tests for the detection of FeLV antigen, FIV antibody and FIP (feline coronavirus) antibody, respectively, in feline blood.

The principle of the tests is as follows: as the sample (whole blood, serum or plasma) flows through the absorbent pad, the labelled FeLV antibody-dye conjugate binds to any P27 FeLV antigen present; the labeled synthetic FIV peptide (GP40) dye conjugate binds to any FIV antibodies present; and the labeled antigen dye conjugate (a unique recombinant protein specific to coronavirus) binds to the FIV/feline coronavirus antibodies. The antigen/antibody complexes move by capillary action along the path and are captured within the test regions of each device, which are indicated by a pink line in those areas.

Cytology

The blood smear (Modified Wright stain, Sigma Aldrich) showed an abnormal presence of both erythrocytic and leukocytic precursors in the circulation, such as prorubricytes, rubricytes, metarubricytes and promyelocytes (Figure 1), characterized by a marked anisocytosis.

The bone marrow (Modified Wright stain) was very cellular and characterized by the presence of a population of large immature cells. The immature cells with intensely staining cytoplasm resembled erythroid precursors. The blasts with the pale staining cytoplasm appeared to be promyelocytes (Figure 2). The maturation of the erythroid and myeloid forms was abnormal, meaning that appropriate numbers of cells in various stages of maturation were absent. The percentage of erythroid precursors was 57% of the nucleated bone marrow cells, with a myeloid/ erythroid ratio of 0.85.

Autopsy

At autopsy, a pale (anemic) aspect of the carcass, an enlarged, pale and thickened spleen, and an enlarged, pale colored liver were noticed. No abnormalities were observed in other organ systems. Samples of the liver, spleen, and bone marrow were collected for histopathology.

Histopathology

Histopathology (Hematoxylin-eosin) of the liver revealed moderate to severe centrolobular to midzonal vacuolar degeneration, marked centrolobular fibrosis and diffusely spread foci of extramedullary hematopoiesis (Figure 3). The spleen showed a loss of normal architecture and a massive proliferation of blood cells, especially erythroid cells (extramedullary hematopoiesis).

According to the hematological (erythrocytic and leukocytic precursors in circulation, nonregenerative anemia) and bone marrow (abnormal maturation of erythroid and myeloid cells) cytological findings, together with the other data (such as case history, FeLV positive), the most likely diagnosis was erythroleukemia.

DISCUSSION

As in humans, the hematologic appearance of cats with erythroleukemia may change with time (Harvey, 1981). Dameshek (1965) and Harvey (1981) stressed the existence of three successive stages of myeloproliferative disorders in cats, initially involving the erythrocytic series and later the granulocytic precursors, as follows: (1) a period of erythremic myelosis characterized by striking erythroid hyperplasia of the bone marrow; (2) a stage of mixed erythroid and myeloid proliferation, namely erythroleukemia, and (3) the eventual termination of some cases in myeloblastic leukemia. Each phase is generally

Table 1. Results of hematology, biochemistry and serology.

Hematology			**Reference values**	
Erythrocytes	5.14	x 10^{12}/l	5.5 – 10.0	-
Leukocytes	37.6	x 10^{9}/l	5.5 – 15.5	+
	%banded neutro	0	0 – 7	
	%segmented neutro	3	42 – 73	
	%lympho	34	14 – 52	
	%atypical lympho	62		
	%mono	1	0 – 4.0	
	%eos	0	2 – 6	
	%baso	0	0 – 0.7	
	%nucleated red cells	28		
Hemoglobin	3.9	mmol/l	5.4 – 9.9	-
Hematocrit	207.0	ml/l	260 – 460	-
MCV	40	fl	40 – 55	
MCH	7	fmol	8.00 – 10.6	-
MCHC	19	mmol/l	18.6 – 23.6	
%RETIC	0.52	%	<1	
#RETIC	27.0	x 10^{9}/l	15.0 – 81.0	
Platelets	159	x 10^{3}/µl	190 – 430	
Biochemistry				
Glucose (fasting)	6.9	mmol/l	3.50 – 6.00	+
Total proteins	84.0	g/l	55.0 – 85.0	
PR. electrofor. alb	51.0	%	45.0 – 60.0	
Alfa1	3.1	%	3.0 – 7.0	
Alfa2	13.7	%	6.0 – 15.0	
Beta	10.8	%	10.0 – 20.0	
Gamma	21.4	%	8.0 – 18.0	+
Albumin	37.8	g/l	31 – 40	
Ureum	7.3	mmol/l	5.9 – 12.50	
Creatinin	133.48	µmol/l	70 – 130	+
ALT (GOT)	365	U/l	< 60	+
ALT (GPT)	132	U/l	37 – 75	+
Bilirubin total	8.89	µmol/l	2.50 – 3.50	+
Bilirubin direct	< 0.51	µmol/l	1.50 – 2.50	
gammaGT	< 2	U/l	0 – 8	
Alc. Phosph.	7	U/l	10 – 50	
Bile acids	9	µmol/l	< 20	
Amylase	884	U/l	260 – 1040	
Lipase	24	U/l	< 250	
Cholesterol	2.9	mmol/l	1.80 – 3.90	
Sodium	155	mmol/l	146 – 158	
Potassium	4.1	mmol/l	3.40 – 5.20	
Chloride	110	mmol/l	105 – 112	
Calcium	2.7	mmol/l	1.80 – 3.00	
Phosphorous	1.6	mmol/l	1.10 – 1.60	
Infectious serology				
FeLV	Positive	Bio Veto Test Speed® Duo FeLV-FIV (France)		
FIV	Negative			
FIP	Negative			

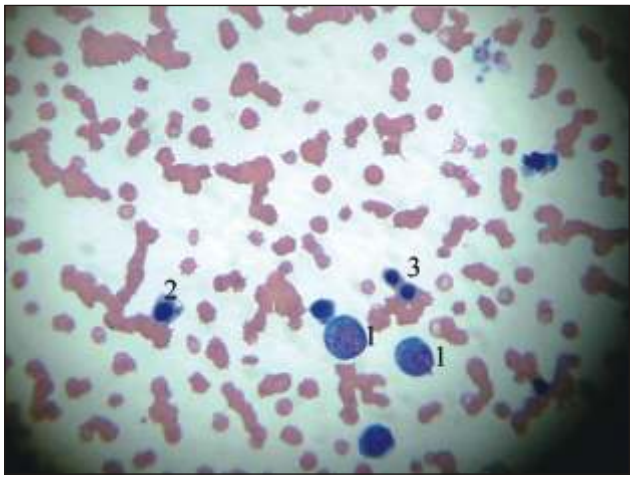

Figure 1. Microphotograph of blood smear with an abnormal presence of both erythrocytic and leukocytic precursors in the circulation, such as large immature cells, probably early granulocytic precursors (1), metarubricytes (2) and nucleated red blood cells (3) (Modified Wright stain – objective 100x).

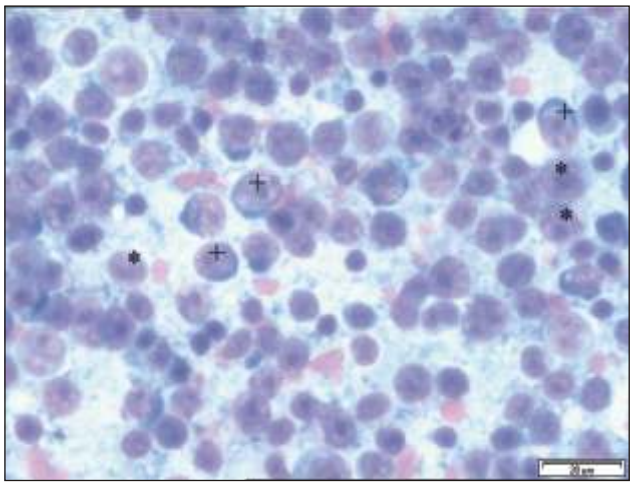

Figure 2. Microphotograph of bone marrow. Notice a large population of large immature cells. The immature cells with intensely blue staining cytoplasm (+) resemble erythroid precursors. The blasts with the pale blue staining cytoplasm (*) appear to be promyelocytes (Modified Wright stain).

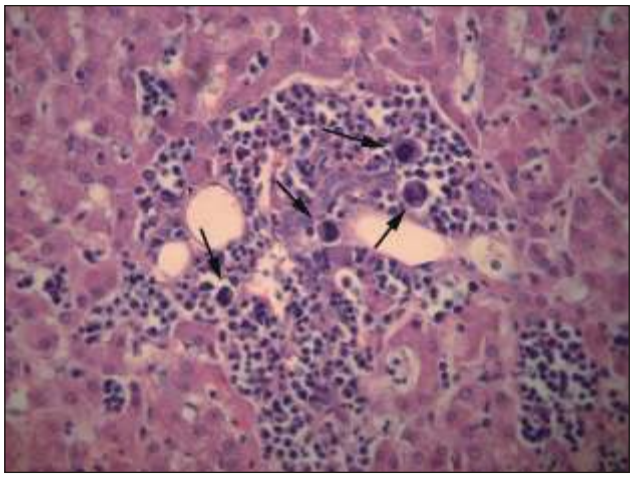

Figure 3. Microphotograph of liver showing a focus of extramedullary hematopoiesis with megakaryocytes (arrows) (HE staining – objective 40x).

observed for a few weeks or a few months. Myeloblasts are generally present in low numbers, even in stages of the disease when abnormal erythroid cells predominate. If the patient does not die or is not euthanized, immature myeloid cells tend to increase in numbers until there is a clear mixture of neoplastic myeloid and erythroid cells. Finally, some cases may progress to the appearance of a "pure" granulocytic leukemia (Harvey, 1981). However, it is not known how consistently individual cases of erythroleukemia in animals follow the course outlined above (Harvey, 1981). It is believed that the present case showed a mixed erythroid and myeloid proliferation and can therefore be diagnosed as erythroleukemia. The cat was euthanized before the disorder could develop into another stage.

This type of leukemia almost always occurs in FeLV positive cats (Gaskell and Bennett). The present case and all reports of erythroleukemia in the literature tested FeLV positive. This is a condition that primarily affects cats infected with FeLV subgroup C, a mutation of the infective form of the virus, i.e. type A (Gaskell and Bennett, 1996). FeLV-C is the least common subtype encountered (Gaskell and Bennett, 1996) and is more pathogenic than FeLV-A (Ramsey and Tennant, 2001).

Feline leukemia virus (FeLV) can cause neoplasia of lymphoid or myeloid tissue, although the most common hemopoietic malignancy in the cat is lymphosarcoma, which accounts for 90% of the hemopoietic tumors and around one-third of all feline neoplasia. Most cases of lymphosarcoma in the cat are associated with FeLV (Gaskell and Bennett, 1996). However, feline lymphoma has historically been associated with FeLV infection. Nowadays there is a significant decrease in the importance of FeLV-associated types of lymphoma in cats due to mass testing and vaccination programs (Louwerens *et al*., 2005).

The symptoms most commonly noticed are progressive anemia, intermittent pyrexia and weight loss (Jain, 1993). The abnormal values of the red blood cell count may be due to a deficient formation of new mature red blood cells and an increased production of immature red blood cells and erythroid precursors. The abnormal white blood cell count and formula is a consequence of the neoplastic changes in the bone marrow, which produce and release immature blood cells into the circulation. The slight hyperglycemia may have been due to excitation prior to the blood sampling. The hyperglobulinemia can be explained by the neoplastic change of the white blood cells. The high AST, ALT and bilirubin (total) levels are due to liver cell necrosis (centrolobular and midzonal degeneration and the infiltrative neoplastic leucemic intra-hepatic metastases). The presence of neoplastic changes in the bone

marrow results in release of neoplastic immature erythroid and myeloid cells into the circulation and blood smear. On histopathology, the centrolobular and midzonal areas of the liver lobuli are the most sensitive to noxes, resulting in degeneration and fibrosis (in chronic cases). In both the liver and the spleen, there were metastatic foci of neoplastic extramedullary hematopoiesis. The primary lesion is in bone marrow, with possible secondary lesions in liver, spleen and lymph nodes (Gaskell and Bennett, 1996), as was also demonstrated in the present case in the liver and spleen.

The diagnosis of erythroleukemia is usually made by biopsy findings in bone marrow and hematology. The hematological and bone marrow cytological findings of the present case were similar to those described by Perman *et al.* (1979).

At this time, there is no cure for erythroleukemia and the long-term prognosis is grave (Wellman and Radin, 1999).

In conclusion, the most common tumor associated with FeLV infection is lymphoma/lymphosarcoma (Ramsey and Tennant, 2001). Occasionally, FeLV infection is associated with leukemia, such as erythroleukemia as in the present case.

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