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CASE REPORT
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Acute Erythroid Leukemia in a Cat Infected with Feline Leukemia Virus

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ABSTRACT

***Background*:** Erythroid leukemia is a myeloproliferative hematopoietic disorder considered acute when there is a predominance of blasts in the bone marrow. It is frequently reported in cats infected with feline leukemia virus, but it is unclear whether this virus is involved in the oncogenesis. The clinical signs in cats are anorexia, apathy, weight loss, with evolution from 2 weeks to 2 months, pale mucous membranes, hemorrhages, ascites, salivation, and dyspnea due to pleural effusion. This affection responds little to chemotherapy with an unfavorable prognosis. The aim of this study is to report a case of a feline leukemia virus infected cat with the onset of severe hemolytic anemia.

***Case*:** A 8-year-old male mixed breed cat was attended with a history of anorexia, oligodipsia, apathy, progressive weight loss, and yellowish color of urine for 7 days. Laboratorial exams showed anemia (with metarubricytes, acanthocytes and ghost cells), leukocytosis and FeLV reagent test. The cat underwent treatment with methylprednisolone acetate and supportive care. One day later, the animal returned with icteric mucous membranes, and emesis. A blood count was performed that found worsening anemia, increased leukocytosis, and lymphocytosis. Abdominal ultrasound showed cholangiohepatitis and lymphadenomegaly in mesenteric lymph nodes. Treatment was started with ondansetron, metronidazole, and amoxicilin with potassium clavulanate. The cat returned after 3 days and laboratorial exams revealed worsening of blood parameters, so blood transfusion was performed. After 2 days, the patient started with dyspnea and hypothermia, that evolved to cardiorespiratory arrest. The body was sent to necropsy and histopathology, where blast cells and rubricytes were found in blood vessels of various organs. The bone marrow was markedly cellular with complete disappearance of adipose tissue. Most of the cells were blasts with abundant and eosinophilic cytoplasm, central nucleus with finely dotted chromatin and a large nucleolus. There were rubricytes, which made possible to confirm acute erythroid leukemia as a morphological diagnosis.

***Discussion*:** The clinical signs observed in acute erythroid leukemia are lethargy, inappetence, fever, splenomegaly, mild lymphadenomegaly, associated with leukocytosis, severe anemia, and thrombocytopenia. The reported animal presented signs similar to those described in the literature except that there was no change in platelet counts. The diagnosis of leukemia was reached after histopathology, and it is made when is observed more than 30% of myeloblasts and monoblasts together or when the blast cells count including rubriblasts is greater than 30%. Although chemotherapy, the prognosis is usually poor. It is essential to perform the myelogram for the diagnosis of myeloid leukemias *in vivo*. In this report, we only achieve final diagnosis after the cat's death, due to the aggressive behavior of the disease. Clinicians must be aware of the likely development of acute erythroid leukemia whenever a feline leukemia virus infected cat presents hemolytic anemia to get an early diagnosis, since this is an extremely aggressive disease, to propose prompt chemotherapy and give the patient a longer survival period.

Keywords: hematopoietic disorders, hemolytic anemia, FeLV, leukemia, myeloneoplastic syndrome.

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INTRODUCTION

Hematopoietic disorders may originate from bone marrow, spleen, or thymus and may be classified as lymphoproliferative or myeloproliferative. The last ones include erythroid leukemia, which can be considered acute when there is predominance of blasts in the bone marrow [1]. It is a rare disorder that affects only the erythroid lineage; however, it has been frequently reported in cats infected with feline leukemia virus (FeLV), although it is unclear whether this virus is involved in the oncogenesis of this cell line [3,9].

The clinical signs in cats are mainly anorexia, apathy, weight loss or cachexia, pale mucous membranes, hemorrhages in the oral mucosa, ascites, dysphagia, salivation, and dyspnea due to pleural effusion [10]. Hematological changes include normochromic or hypochromic macrocytic anemia, neutrophilic leukocytosis, and in some cases leucopenia due to neutropenia, with metarubricytes, rods, metamyelocytes, and myelocytes. The diagnosis can be made by association of clinical signs, serial evaluation of hematological tests, clinicopathological alterations, with the conclusion of the diagnosis by myelogram or histopathological [1,7].

This type of leukemia has poor response to chemotherapy, and the prognosis is unfavorable. Survival varies from days to months, and euthanasia is often recommended soon after diagnosis [1]. The aim of this study was to report the case of a feline leukemia virus infected cat with the onset of severe hemolytic anemia that had *post morten* diagnosis concluded as acute erythroid leukemia by histopathology.

CASE

A 8-year-old neutered male mixed breed cat was attended with a history of anorexia, oligodipsia, apathy, progressive weight loss, and intense yellowish color of urine for 7 days. The cat had no vaccines and lived together with another cat with free access to outdoors.

During physical examination, the animal showed pale mucous membranes, body score index 3/9, and ulcer on the tongue, gingivitis, halitosis and sialorrhea, with the other parameters within the normal range.

A blood count was performed and showed macrocytic hypochromic anemia, with hematocrit 13.1% (ref.: 24-45%) and hemoglobin 3.9 g/dL (ref.: 8-15 g/dL), with metarubricytes (133/100 leukocytes, ref.: 0 to 5/100 leukocytes), presence of acanthocytes and ghost cells in erythrogram, leukocytosis (43,500 mm^3, ref.: 5,500-19,500 mm^3) due to neutrophilia (21,750 mm^3, ref.: 2,500-12,500 mm^3), with severe left deviation (band cell: 1,305 mm^3, ref.: 0-300 mm^3 ; metamyelocytes: 3,480 mm^3, ref.: 0 mm^3; myelocytes: 870 mm^3 ; ref.: 0 mm^3) and lymphocytosis (15,660 mm^3, ref.: 1,500-7,000 mm^3), with the presence of reactive atypical lymphocytes, lymphoblasts, toxic rods and toxic neutrophils in leukogram. There was no alteration in platelets number. In addition, immunochromatographic test[1] resulted reagent to feline leukemia virus (FeLV).

At that time, the cat underwent treatment for chronic gingivostomatitis with hexamidine isethionate with tetracaine hydrochloride[2] in spray (every 8 h for 10 days), methylprednisolone acetate[3] [Depo-Medrol® - 10 mg/animal I.M., single dose) and supportive care with fluid therapy[4] and hypercaloric diet[5].

One day after the first visit, the cat returned with anorexia, apathy, icteric mucous membranes and emesis. A blood count was performed that found normochromic macrocytic anemia, with hematocrit 10.8% (ref.: 24-45%), hemoglobin 3.6 g/dL (ref.: 8-15 g/dL), with metarubricytes (58/100 leukocytes, ref.: 0 to 5/100 leukocytes), intense leukocytosis (87,200 mm^3, ref.: 5,500-19,500 mm^3) by neutrophilia (65,400 mm^3, ref.: 2,500-12,500 mm^3) with severe left shift (band cell: 872 mm^3, ref.: 0-300 mm^3 ; metamyelocytes: 4,360mm^3, ref.: 0 mm^3; myelocytes: 3,488 mm^3, ref.: 0 mm^3) and lymphocytosis (12,208 mm^3; ref.: 1,500-7,000mm^3), with presence of reactive lymphocytes, toxic rods and hypersegmented neutrophils, no change in platelet count and reticulocyte count (16,200 cells/µL, ref.: minimum degree of regeneration 10,000-60,000 cells/µL). Also, biochemical exams revealed alanine aminotransferase (ALT) 64.1 IU/L (ref.: 28-83 IU/L), gamaglutamyltransferase (GGT) 1.0 IU/L (ref.: 1.3-5.1 IU/L), aspartate aminotransferase (AST) 140.6 IU/L (ref.: 6.7-11 IU/L), and total protein 6.19 g/dL (ref.: 5.4-7.8 g/dL).

Abdominal ultrasound showed signs of cholangiohepatitis and lymphadenomegaly in mesenteric lymph nodes. Treatment was instituted with ondansetron[6] [Nausedron® - 0.2 mg/kg, V.O., QID], metronidazole[7] [20 mg/kg, V.O., BID, for 10 days], amoxicilin with potassium clavulanate [Agemoxi CL® - 20 mg/kg, V.O., BID, for 10 days], and supplement for liver recovery[5] [Hepvet® - SID, for 30 days].

The cat returned after 3 days still without improvement, so another blood count was performed,

that revealed severe macrocytic hypochromic anemia, with hematocrit 9.3% (ref.: 24-45%), hemoglobin 3.0g/dL (ref.: 8-15g/dL), with metarubricytes (30/100 leukocytes, ref.: 0 to 5/100 leukocytes), still intense leukocytosis (84,300 mm^3, ref.: 5,500-19,500 mm^3) due to neutrophilia (62,382 mm^3, ref.: 2,500-12,500 mm^3) with severe left shift (band cell: 4,215 mm^3, ref.: 0-300 mm^3; metamyelocytes: 5,058 mm^3, ref.: 0 mm^3; myelocytes: 1,686 mm^3, ref.: 0 mm^3) and lymphocytosis (10,959 mm^3, ref.: 1,500-7,000 mm^3), with the presence of reactive lymphocytes, toxic rods and hypersegmented neutrophils on leukogram and without alteration in platelet count, so that blood transfusion was recommended.

The prescribed treatment was maintained, and blood transfusion was performed with 50 mL of whole fresh blood with addition of quelatated iron with vitamin complex[5] [Hemolitan Gold® - 0.3 mL, V.O., SID, 30 days]. The animal showed improvement in the clinical picture, presenting more active and interacting with the owner, but still presented hyporexia. After 2 days of blood transfusion, the patient started with intense dyspnea and hypothermia, and it was administered dexamethason[9] [0.5 mg/kg, I.V.] to reduce hemolytic anemia. However, the animal presented cardiorespiratory arrest and died before the myelogram could be performed, and his body was sent for necropsy.

In histopathology, blast cells and rubricytes were found in blood vessels of various organs such as liver, pancreas, lung, brain, spleen, stomach, and kidney (Figure 1). The bone marrow was markedly cellular with complete disappearance of adipose tissue. This proliferation was distributed in mantle form without noticeable stroma, most of the cells consisted of blasts with abundant and eosinophilic cytoplasm, central nucleus with finely dotted chromatin and a large nucleolus. Adjacent, there were also clusters of erythroid precursors with scarce cytoplasm and hyperchromatic nucleus, compatible with rubricytes (Figure 2), which made possible to confirm acute erythroid leukemia as a morphological diagnosis.

DISCUSSION

The present report describes a 8-year-old male feline reagent for FeLV that developed acute erythroid leukemia, one of the types of leukemia of the myeloid lineage. The relationship between FeLV and leukemia development in 37 cats over an 8-year period was evaluated and it was determined that myeloid leukemia occurred in 56.8% of the animals, being acute in 73% and among all these, 78.4% were positive for FeLV [3].

Two FeLV infected cats living in the same house for 1 year developed erythroid myeloid leukemia even though this is considered a rare disease, raising the possibility that this disease is related to the same strain of feline leukemia virus [9]. Besides, experiment with FeLV33 cloned of a cat with acute myeloid leukemia suggested that this variant was strongly associated with the induction of myelodysplastic syndromes (MDS) and acute myeloid leukemia [5]. On the other hand, another study found this hematopoietic neoplasia in a FeLV negative cat [4]. Nevertheless, considering that FeLV virus can be classified into several subgroups, the subgroups FeLV-A and B are the most associated with neoplasms, with FeLV-A having a greater tendency to develop myelodysplastic syndromes [2], and knowing that virus is easily transmitted, it is expected that positive FeLV cats that live in the same environment tend to have the same type and then develop the same syndromes.

The clinical signs commonly observed in acute erythroid leukemia are nonspecific and often are associated with other hematopoietic diseases, being lethargy, inappetence, fever, splenomegaly, mild lymphadenomegaly the most commons, associated with leukocytosis, severe anemia, and thrombocytopenia [1]. The reported animal presented signs similar to those described in the literature except that there was no change in platelet counts.

A prospective study observed only 10 cats among felines referred for necropsy in a period of 10 years, that, since they presented nonspecific signs, none had a suspicion of acute erythroid leukemia at the time of death, but other differential diagnoses such as hemotropic mycoplasmosis, lymphoma, feline infectious peritonitis, among other unrelated diseases [10]. The case described here started with signs of feline chronic gingivostomatitis, and after the results of the first tests, the suspicion of hemotropic mycoplasmosis and lymphoma was raised, with a diagnosis of leukemia reached after necropsy and histopathology.

This patient showed severe hypochromic macrocytic anemia with metarubricytes, leukocytosis due to neutrophilia and lymphocytosis, with the presence of reactive and atypical lymphocytes, lymphoblasts, toxic rods and toxic neutrophils, with no changes in

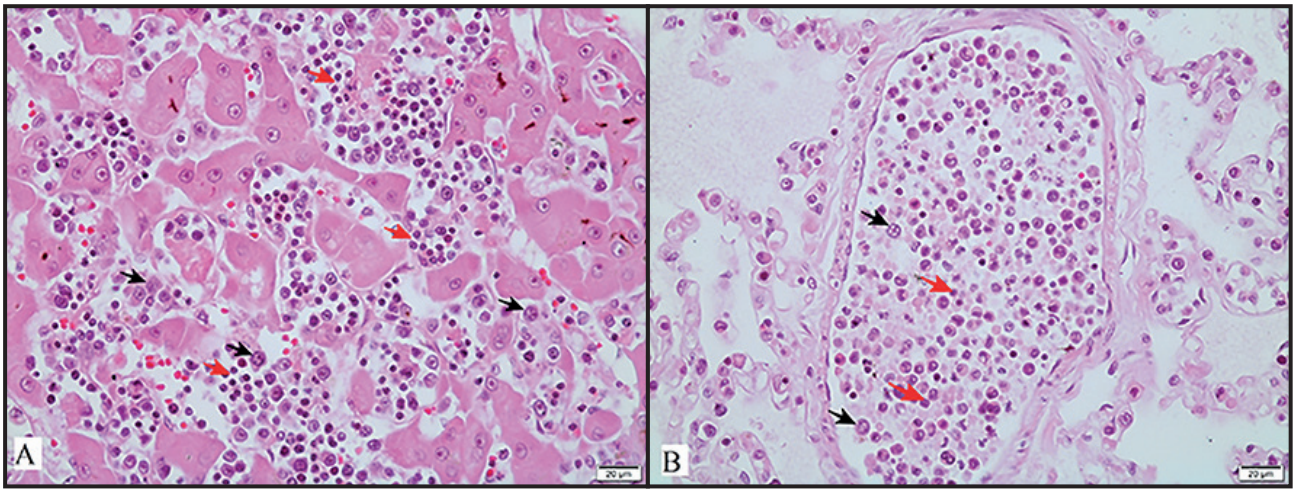

Figure 1. Blast cells (black arrows) and rubricytes (red arrows) in blood vessels in liver (A) and lung (B) [HE; 40x].

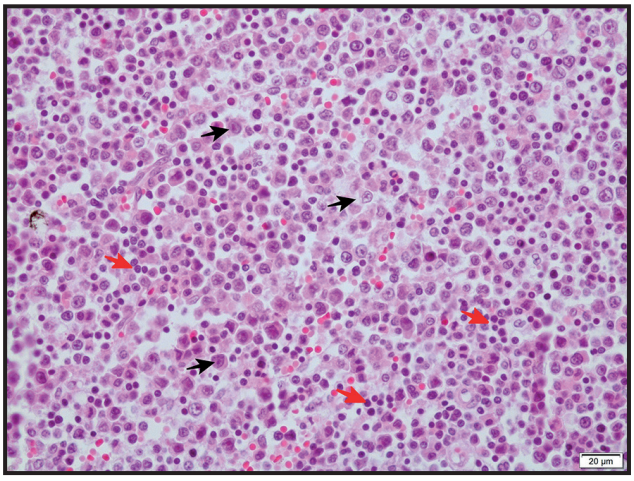

Figure 2. Bone marrow, markedly cellular with complete disappearance of adipose tissue, with most cells consisting of blasts (black arrows), characterized by the conspicuous eosinophilic nucleolus and presence of clusters of erythroid precursors, compatible with rubricytes (red arrows) [HE; 20x].

platelet counts in most tests. These findings were similar to hematological alterations in 10 animals analyzed previously [10]. Besides, leukocytosis, anemia and thrombocytopenia were also related [8,9]. Also, a study analyzed 16 cats with myelodysplastic syndromes, and of these, 15 were positive for FeLV, being only 31% with leukopenia and 25% neutropenia, emphasizing that intense anemia, followed by leukocytosis are the main changes found in acute erythroid leukemia in cats [6], just as in our report.

It is important to note that cats infected with FeLV tend to be diagnosed with pure red cell aplasia (PRCA), acute myeloid leukemia (AML), and aplastic anemia. When the diagnosis is made through the myelogram, leukemia in cats can be classified according to the adaptation of the classification French-American-British for the disease in humans [7] in acute myeloid leukemia with subtypes M1 to M5 and erythroleukemia M6 according to the cell lineage found, subtypes M1 and M2 are the most frequent in cats. The differentiation of AML and MDS subtypes is very difficult to be performed, requiring the association of cytological findings associated with clinical findings for a correct classification, which can be classified as MDS when there are less than 30% of blast cells and in AML when there are more than 30% blast cells [7].

The M6 classification (acute erythroid leukemia) occurs when there are more than 30% of myeloblasts and monoblasts together or when the blast cells count including rubriblasts is greater than 30%, being a progressive disease with manifestations myeloid or erythroid predominance, or both [7]. This differentiation is very important to be performed through the myelogram and is an indispensable exam for the diagnosis and classification of AML, in addition to determining prognostic factors and better therapeutic management. As the animal described died before the myelogram could be performed, this classification *in vivo* was not possible.

Chemotherapy protocol with low doses of cytosine-arabinosid has been shown to have good results for the treatment, however the prognosis is usually poor [9]. In the cat of this report, it was not possible to achieve the diagnosis *in vivo*, so that he received only supportive treatment but evolved to death in less than 7 days.

In the histopathological examination, it was possible to observe disappearance of adipose tissue in the bone marrow, with predominance of blasts and erythroid precursors compatible with rubricytes. The-

se findings are in accordance with a study [10] that described similar changes in bone marrow and also observed the presence of erythroid precursors such as rubricytes in various organs of the studied animals. This finding suggests an extramedullary hematopoiesis that can commonly occur in this type of leukemia. As the main differential diagnoses for AML and MDS in histopathology, it is important to always consider congenital hematological diseases, myeloid hyperplasia, toxicity due to the use of chemotherapy drugs, post-chemotherapy spinal regeneration and changes secondary to other neoplasms that may show different clinical and/or hematological alterations from acute erythroid leukemia [11].

Although acute erythroid leukemia is not common, it can be found in cats infected with leukemia virus, with signs suggestive of hemolytic anemia. In this report, we could only achieve final diagnosis after the cat's death, due to the aggressive behavior of the disease. Clinicians must be aware of the likely development of acute erythroid leukemia whenever a feline leukemia virus infected cat presents hemolytic anemia in order to get an early diagnosis, to propose prompt chemotherapy and give the patient a longer survival period.

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