Erythremic Myelosis

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ABSTRACT: Erythremic myelosis, a severe, nonregenerative anemia, occurs in cats that are infected with feline leukemia virus (FeLV) subgroup C. The condition is characterized by bone marrow proliferation of erythrocyte precursors up to the metarubricyte stage. Peripheral blood smears show increased numbers of nucleated erythrocytes without concurrent reticulocytosis. Bone marrow aspiration shows an increased erythroid:myeloid ratio with maturation arrest of the erythrocytes. Although several mechanisms have been suggested, the pathogenesis of erythremic myelosis is unknown. To date, there are few to no successful treatment options and the prognosis is grave.

Erythremic myelosis has historically been a poorly characterized disease. An association exists between severe, nonregenerative anemia and FeLV. However, several myeloproliferative diseases are associated with FeLV, and these may be distinct disease entities. This paper defines the different terms related to erythremic myelosis and explains the role of FeLV. Clinical presentation, suspected pathogenesis, diagnostic testing, and potential treatment options are reviewed.

TERMINOLOGY

Historically, there has been some confusion in the terminology and a lack of consistency in the literature regarding myeloproliferative diseases (Figure 1). An explanation of pertinent vocabulary should facilitate an understanding of this disease. Erythremic myelosis is one of many myeloproliferative disorders. For the purpose of this review, myeloproliferative disorders are defined as neoplastic disorders involving hematopoietic marrow cells. Erythremic myelosis is defined as a proliferative disease of early erythrocyte precursors only. Erythroleukemia is another term that has been used in conjunction with myeloproliferative diseases and in some references has been difficult to differentiate from erythremic myelosis. Erythremic myelosis, however, involves only erythroid cells, whereas erythroleukemia involves both erythroid and myeloid cells. Proliferating erythroid and myeloid neoplastic cells may be seen in erythroleukemia.

The Animal Leukemia Study Group has recently investigated myeloproliferative diseases and has proposed new classification systems. These new reports suggest that erythremic myelosis and erythroleukemia may be different points along a continuum of the same disease complex.

ASSOCIATION WITH FELINE LEUKEMIA VIRUS

Erythremic myelosis is associated with infection by FeLV subgroup C. FeLV, a well-known, transmissible retrovirus responsible for a host of illnesses, includes...
The viral subgroups vary in surface unit proteins (or antigens) on the viral envelope. Viral envelope antigens provide the means for virus attachment and penetration into host cells. Most of the variability in the different subgroup envelopes is from glycoprotein 70 and the p15E proteins. Both of these are derived from an env gene precursor. 

Subgroup A is the infective, horizontally transmissible form of the virus. Subgroups B and C result from viral recombination within individual cats; therefore, neither subgroup B nor C is directly transmissible to other cats. Both forms, by definition, are also always found with subgroup A. Subgroup B, which results from the recombination of subgroup A with endogenous FeLV, is primarily responsible for the development of lymphoma. Subgroup C, which also arises from subgroup A, is the result of viral mutation. This subgroup is responsible for severe anemia and erythremic myelosis.

The cell-surface receptor for FeLV subgroup C was recently identified and cloned. This new discovery may facilitate further understanding of the pathogenesis of FeLV-related diseases.

**PATHOGENESIS**

A maturation arrest of erythrocytes, a component of erythremic myelosis and other diseases, occurs prior to the reticulocyte stage, leading to severe anemia. Figure 2 shows the sequence of normal erythropoiesis. Nucleated erythrocytes are present in the peripheral blood, and there are low-normal to reduced numbers of reticulocytes. The lack of a reticulocyte response with concurrent prolonged anemia is a result of the maturation arrest and is evidence for disease at the bone marrow level.

The pathogenesis of erythremic myelosis has not been completely identified. Most researchers believe that the site of action of the disease in the marrow is at the level of the burst-forming and colony-forming units of the erythroid line (Figure 3).

Direct and indirect mechanisms for erythremic myelosis have been suggested. Onions and colleagues proposed that direct mechanisms might involve direct inhibition of erythropoiesis, potentially via viral effects on early erythroid precursors. This might be related to the viral envelope glycoprotein and its subsequent relation to subgroup specificity. Boyce and colleagues hypothesized another direct mechanism involving viral gene products directly inhibiting erythroid progenitor cells. Boyce and colleagues and others have proposed indirect mechanisms for erythremic myelosis as well. These mechanisms incriminate the accessory cells of
erythropoiesis or the effects of the local environment (i.e., bone marrow) as playing key roles in the pathogenesis. These mechanisms include interaction between FeLV and lymphoreticular cells as well as interaction between FeLV and bone marrow lymphocytes and macrophages. Other possibilities include humoral products from virus-infected cells interfering with erythropoiesis or clonal expansion of a stem cell that has lost the ability to differentiate.\textsuperscript{12,13}

The recent discovery of the receptor for FeLV subgroup C may provide an answer to the pathogenesis question. This receptor has been identified as a $D$-glucarate transporter molecule, which is an organic anion transporter. The link between $D$-glucarate and erythropoiesis is currently unknown, but this receptor molecule is suspected to play a crucial role in normal erythropoiesis.\textsuperscript{11}

**SIGNALMENT AND FELINE LEUKEMIA VIRUS STATUS**

Erythremic myelosis is seen primarily in young cats, usually with some exposure to the outdoors. There has been no breed predilection identified for FeLV or erythremic myelosis. Because this disease is a sequela to FeLV, affected cats are expected to be FeLV positive. The most common screening test for FeLV is an ELISA test on peripheral blood. As with any diagnostic test, the sensitivity and specificity depend on local disease prevalence. The ELISA, immunofluorescent antibody, and polymerase chain reaction (PCR) tests have all been used for leukemia testing. Jackson and colleagues\textsuperscript{14} evaluated ELISA and PCR testing on peripheral blood in populations of cats with high, moderate, and low degrees of suspicion for FeLV-related diseases (e.g., anemia, lymphosarcoma). In this study, cats with a high degree of suspicion for FeLV-related disease were negative for leukemia on ELISA 33% of the time. The rate of detection was the same for the PCR test. It should be noted that none of the cats in this study was diagnosed with erythremic myelosis. In addition, FeLV may be sequestered in certain tissues in the body (e.g., bone marrow) and may not be present in peripheral blood.\textsuperscript{14} I am unaware of any cases of erythremic myelosis that have not concurrently tested positive for FeLV. It is not feasible at this time to test specifically for different viral subgroups of FeLV (i.e., to differentiate subgroup A from B from C). It has been shown that younger cats that are infected with FeLV subgroup C are prone to develop more severe erythremic myelosis.\textsuperscript{12}

**INCIDENCE**

A veterinary medical database\textsuperscript{15} search from 1980 to 1999 revealed that 7253 cats were FeLV positive. During that same time, the number of cases diagnosed with erythremic myelosis was 105, which is an overall 20-year incidence of 1.44%. Interestingly, the number of FeLV-positive cases in 1980 was 539 compared with 22 cases in 1999. Other authors\textsuperscript{16,17} have also noted an apparent decrease in the prevalence of FeLV infection. A similar decreasing trend could not be identified for cases of erythremic myelosis.

**CLINICAL SIGNS**

Most cats with erythremic myelosis present with signs of severe anemia (Box 1). Because of the sedentary nature of some cats, anemia may become profound before owners notice clinical signs, and cats may present with life-threatening anemia. Occasionally, cats present with signs related to other FeLV-associated diseases (e.g., dyspnea caused by a mediastinal mass). In these cases, erythremic myelosis may not be present at the initial presentation but may develop over time. These cats may present again at a later date for signs associated with severe anemia.

**CLINICAL PATHOLOGY FINDINGS**

Most cats with erythremic myelosis present with hematocrits in the 12% to 15% range. The leukocyte series is typically within normal limits. Platelets may be normal or decreased. When cats present with severe anemia, reticulocytes are either in the low-normal range or are not present (Table 1).\textsuperscript{1} FeLV has been associated with other myeloproliferative diseases, which may affect all three bone marrow cell lines to varying degrees.\textsuperscript{3} Thus a complete blood count along with evaluation of a peripheral blood smear for manual cell counts and morphologic determination are indicated.

In some cases, a peripheral blood smear shows a normochromic anemia with anisocytosis. Nucleated erythrocytes, rubricytes, or even more immature rubriblast forms may be seen.\textsuperscript{1} Figure 4 shows a peripheral blood smear from a cat with erythremic myelosis. In Figure 5, a new methylene blue stain highlights the paucity of reticulocytes.

Bone marrow aspiration is further evidence for the disease and is used in conjunction with other clinical

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**Box 1. Clinical Signs Associated with Anemia**

- Collapse
- Cold extremities
- Dyspnea
- Lethargy
- Pale mucous membranes
- Systolic murmur
- Tachypnea
- Weakness
pathologic findings to make the diagnosis. Because of the association between FeLV, anemia, and lymphoma, the differential diagnosis for an FeLV-positive cat with anemia may initially be lymphoma infiltration into the bone marrow. Therefore, if erythremic myelosis is suspected, bone marrow aspiration should be performed (Figure 6). In erythremic myelosis, the erythroid:myeloid ratio is increased, with a predominance of erythrocyte precursors.\textsuperscript{1,2} The erythrocyte precursors from the rubriblast stage are identified by intensely ba-
sophilic cytoplasm and increased nuclear:cytoplasmic ratio, with one to two visible nucleoli. As the erythrocytes mature, nucleoli are usually not identifiable; cytoplasm becomes less basophilic; and cell and nuclear size decrease.18

TREATMENT

There is no cure for erythremic myelosis. The short-term prognosis is guarded, and long-term prognosis is grave. Survival may be somewhat lengthened with aggressive treatment and committed owners. Treatment consists primarily of supportive care for severe anemia. Repeated blood transfusions have been used, with the associated costs and risk.

Immunomodulating agents (e.g., interferon, staphylococcal protein A) have been studied. Engelman and colleagues19 reported a positive response to staphylococcal protein A in cats with FeLV infections. These cats had various hematologic abnormalities that were grouped into a general category of marrow dyscrasias and not diagnosed with erythremic myelosis specifically. Improvements in hematologic parameters were reported, but these results cannot be extended to cases of erythremic myelosis.19

Bone marrow transplants have also been attempted as a treatment for feline retroviral infections. From 1985 to 1992, Colorado State University reported at least 90 transplants, 35 of which were for retroviral infection. The challenge of this procedure has been to prevent newly transplanted marrow cells from becoming infect-


15. Veterinary Medical Database. West Lafayette, IN, Purdue University School of Veterinary Medicine, 2000.


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1. Which of the following is not a diagnostic test of choice for erythremic myelosis?
   a. complete blood count
   b. FeLV testing
   c. blood culture
   d. peripheral blood cytology
   e. bone marrow aspiration

2. At what stage does erythrocyte maturation typically arrest in erythremic myelosis?
   a. metarubricyte
   b. reticulocyte
   c. rubriblast
   d. rubricyte

3. Which of the following has not been proposed as a possible pathogenesis for erythremic myelosis?
   a. direct inhibition of erythropoiesis
   b. viral effects on erythroid precursors
   c. interaction between FeLV and lymphoreticular cells
   d. FeLV-induced myelophtisis
   e. clonal expansion of an abnormal stem cell

4. What is the D-glucarate transporter?
   a. hepatic-induced enzyme
   b. cell-surface receptor for FeLV subgroup C
   c. neurotransmitter
   d. site of FeLV attachment to the erythrocyte
   e. molecule that facilitates the differentiation of the metarubricyte to the reticulocyte

5. Which of the following is not typically used for diagnosing FeLV?
   a. ELISA
   b. immunofluorescent antibody
   c. virus isolation
   d. PCR

6. Which of the following is not a sign of severe anemia?
   a. splenomegaly
   b. pale mucous membranes
   c. dyspnea
   d. systolic murmur
   e. collapse
7. What is the preferred stain for reticulocytes?
   a. hematoxylin-eosin
   b. periodic acid–Schiff
   c. silver stain
   d. new methylene blue
   e. Sudan black B

8. Which of the following is not a criterion of erythrocyte precursors?
   a. intensely basophilic cytoplasm
   b. multinucleated cells
   c. one to two visible nucleoli
   d. increased nuclear:cytoplasmic ratio

9. Which of the following has not been pursued as therapy for erythremic myelosis?
   a. immunotherapy
   b. bone marrow transplant
   c. chemotherapy
   d. blood transfusions
   e. hydroxyurea

10. FeLV subgroup C
    a. is spread by horizontal transmission.
    b. is associated with lymphoma.
    c. is directly contagious.
    d. results from viral mutation.
    e. may be found without other subgroups.