# Acute monoblastic leukemia in a feline leukemia virus-negative cat

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**ABSTRACT.** A 12-year-old female domestic short-haired cat was presented due to weight loss, anorexia, and tachypnea. Complete blood count revealed severe anemia, leukocytosis with massive undifferentiated blast cells, and thrombocytopenia. Bone marrow aspiration showed acute myeloid leukemia, subclassified as monoblastic leukemia (M5a) based on the outcomes of the cytochemistry examinations. The SNAP feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) test using whole blood was negative. In addition, FeLV/FIV proviral polymerase chain reaction test using bone marrow aspirate was also negative. Although the cat was treated with doxorubicin, cytosine arabinoside, and prednisolone, anemia did not improve without blood transfusion. The owner declined further treatment after 2 months, and the cat died a few days later.

**KEY WORDS:** acute monoblastic leukemia, cat, feline leukemia virus

Acute myeloid leukemia (AML) is a neoplastic disease of the bone marrow, which is associated with clonal disorders of hematopoietic stem cells [18]. The feline leukemia virus (FeLV) infection is the most common infectious disease in cats and is directly associated with tumorigenesis of hematopoietic tumors [5]. Leukemia has demonstrated a strong association with FeLV infections and 60–80% of cases of feline myeloid leukemia have been positive for the FeLV antigen [2]. AML in cats is rare with poor prognosis. AML and myelodysplastic syndrome are classified into subtypes based on the origin and degree of differentiation of the blast cells by the animal leukemia study group [9]. Acute myeloblastic leukemia without (M1) or with (M2) maturation and erythroleukemia (M6) are considered to be the most common variants of myeloid neoplasia in cats. However, acute monocytic leukemia (M5) is less common in cats, with an incidence of less than 5.0% [8]. Here, we present a case of acute monoblastic leukemia (M5a) in a FeLV-negative cat.

A 12-year-old female, domestic, short-haired cat was presented to a primary care veterinarian with a 2-week history of weight loss, anorexia, and tachypnea. The cat was referred immediately to the Veterinary Medical Center, Obihiro University of Agriculture and Veterinary Medicine (VMC-OUAVM) to treat the severe anemia and marked leukocytosis. At the time of presentation to VMC-OUAVM, the cat was lethargic with a body condition score of 2/9 and weight of 2.5 kg. Physical examination revealed that all lymph nodes were normal in size, along with the presence of a pale mucous membrane and splenomegaly. The heart rate was 180 beats per minute, with normal heart sounds, and the rectal temperature was 37.2°C. The cat had 5% dehydration status by palpation.

A blood sample was processed for complete blood count (Celltac α, Nihon Kohden, Tokyo, Japan) and serum biochemical analysis (TBA-120 FR, Canon Medical Systems, Ohtahara, Japan). Hematological findings indicated marked leukocytosis (137,200 cells/$\mu l$), severe thrombocytopenia (25,000 cells/$\mu l$), and severe nonregenerative anemia ($1.23 \times 10^6$ cells/$\mu l$, aggregate reticulocytes 4,920 cells/$\mu l$). Giemsa-stained peripheral blood smears indicated the presence of 73.5% blast cells (Table 1). The peripheral blood smears stained with Wright-Giemsa demonstrated several large immature mononuclear cells with round, lobed, or horse-shoe shaped nuclei, and basophilic cytoplasm, along with a small number of large-sized, dysplastic eosinophils and monocyte-like cells (Fig. 1). Serum biochemical analysis revealed high alanine aminotransferase (217 IU/$l$; reference range, 12–130 IU/$l$), high lactate dehydrogenase (2,312 IU/$l$; reference range, 0–798 IU/$l$), and high blood urea nitrogen (35 mg/d$l$; reference limits, 14–28 mg/d$l$).
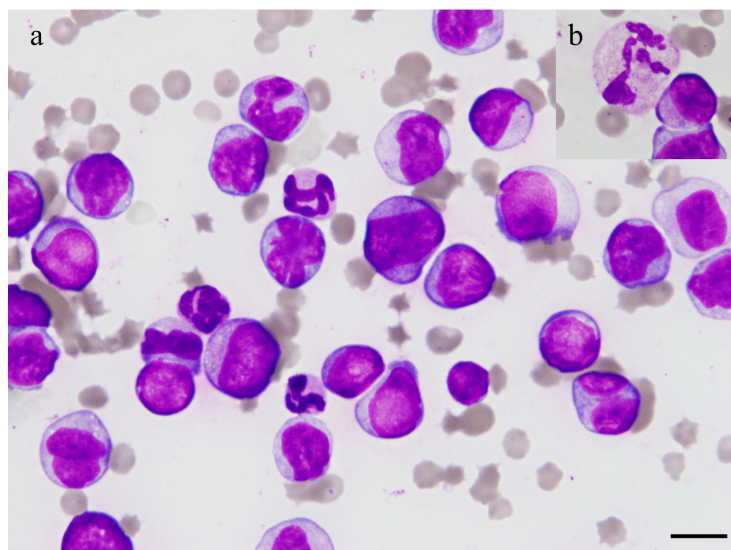
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**Fig. 1.** Peripheral blood smear (Wright-Giemsa stain, ×100 objective). (a) Several large immature mononuclear cells and monocyte-like cells are visible. (b) Few large-size, dysplastic eosinophils are also visible (bar=10 $\mu$m).

**Table 1.** Hematology and chemistry of the case

| Test | Results | Range | Reference |
|---|---|---|---|
| WBC (×10³/$\mu l$) | 137.2 | 5.4–15.4 | |
| Neutrophils | 13.7 | 2.3–9.8 | |
| Lymphocytes | 4.1 | 0.9–5.5 | |
| Eosinophils | 4.8 | 0–1.8 | |
| Monocytes | 13.7 | 0–0.8 | |
| Blast cells | 100.8 | N/A | [7] |
| RBC (×10⁶/$\mu l$) | 1.23 | 7.4–10.4 | |
| Hb (g/d$l$) | 5.8 | 11–16 | |
| PCV (%) | 9.0 | 34–51 | |
| MCV (f$l$) | 73.2 | 42–52 | |
| MCHC (g/d$l$) | 64.4 | 30–33 | |
| Platelets (×10⁴/$\mu l$) | 2.5 | 16–50 | |
| TP (g/d$l$) | 6.7 | 5.7–8.9 | |
| ALB (g/d$l$) | 2.7 | 2.3–3.9 | |
| ALT (IU/$l$) | 217 | 12–130 | |
| AST (IU/$l$) | 80 | 0–48 | |
| ALP (IU/$l$) | 66 | 14–111 | |
| T.BIL (mg/d$l$) | 0.3 | 0–0.9 | Our |
| LDH (IU/$l$) | 2,312 | 0–798 | laboratory |
| T.CHOL (mg/d$l$) | 69 | 65–225 | |
| BUN (mg/d$l$) | 35 | 16–36 | |
| Cre (mg/d$l$) | 0.7 | 0.8–2.4 | |
| Ca (mg/d$l$) | 9.4 | 7.8–11.3 | |
| P (mg/d$l$) | 5.9 | 3.1–7.5 | |

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PCV, packed cell volume; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; TP, total protein; ALB, albumin, ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; T.BIL, total bilirubin; LDH, lactate dehydrogenase; T.CHOL, total cholesterol, BUN, blood urea nitrogen; Cre, creatinine; Ca, calcium; P, phosphorus; N/A, not applicable.

The cat tested negative for the FeLV antigen and for antibodies to FIV (Snap FIV/FeLV, IDEXX Laboratories, Westbrook, ME, USA). Clonality testing for antigen rearrangements in T and B cell receptors was performed using the genomic DNA extracted from peripheral blood samples; this was adopted from Kiupel *et al* [10]. The amplicons were analyzed by microcapillary electrophoresis on the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA), and the results were negative (Fig. 2). Thoracic and abdominal radiography and abdominal ultrasonographic examination did not reveal any abnormalities except mild splenomegaly.

Bone marrow aspiration was performed under general anesthesia on day 2 after blood transfusion to identify the etiologies of the hematological abnormalities. The bone marrow smears were stained with Wright-Giemsa, and more than 500 cells were counted. The marrow was hyperplastic, and the myeloid to erythroid (M:E) ratio was 2.25:1 (Table 2). The majority of blast cells had a round to oval nucleus with a fine chromatin structure and large, distinct nucleoli, along with a moderately to lightly basophilic cytoplasm with high nuclear/cytoplasmic ratio. Furthermore, there was a small number of large-sized, dysplastic eosinophils (Fig. 3). The percentage of blast cells constituted up to 86.4% of all nucleated cells (ANCs) and 91.3% of all non–erythroid cells (NECs). The characteristics specific to these blast cells were clarified via myeloperoxidase (MPO) staining and double esterase staining for alpha-naphthol butyrate esterase (α-NBE; nonspecific esterase) and naphthol AS-D chloroacetate-esterase (NSADCA) (Obihiro Clinical Laboratory, Obihiro, Hokkaido, Japan). MPO staining outcomes indicated negative results for several blast cells, and the positivity rate was 9.3% of all NECs. However, most blast cells presented with positive results for α-NBE staining but negative for NSADCA, and these reactions were inhibited by sodium fluoride (NaF). Therefore, these results suggested that the blast cells were monoblasts, and their proportion was more than 80% of blast cells. Additionally, bone marrow samples were fixed in 15% neutral-buffered formalin, processed routinely, and sectioned at 4 $\mu$m. Sections were stained with hematoxylin and eosin (HE), and immunohistochemistry was performed. Anti-human CD3 (F7.2.38, DAKO Cytomation, Carpinteria, CA, USA), anti-human CD20 (RB-9013-P0, Thermo Fisher Scientific, Inc., Waltham, MA, USA) and anti-human Human Leukocyte Antigen–DR isotype (HLA-DR; TAL.1B5, DAKO Cytomation) were used for the identification of the respective cells in the bone marrow. Antigen retrieval involved microwave oven at 97°C for 15 min with pH 6.0 citrate buffer. Sections were then treated with 3% hydrogen peroxide-methanol at room temperature for 5 min and incubated in 10% skimmed milk phosphate buffered saline with 0.1% Tween 20 at 37°C for 40 min to avoid non-specific reactions. The Envision+ single regent mouse or rabbit polymers (DAKO Cytomation) were used as the secondary antibody, and signals were detected with 0.05% 3,3′-diaminobenzidine (DAB) (Dojindo, Tokyo, Japan). Less
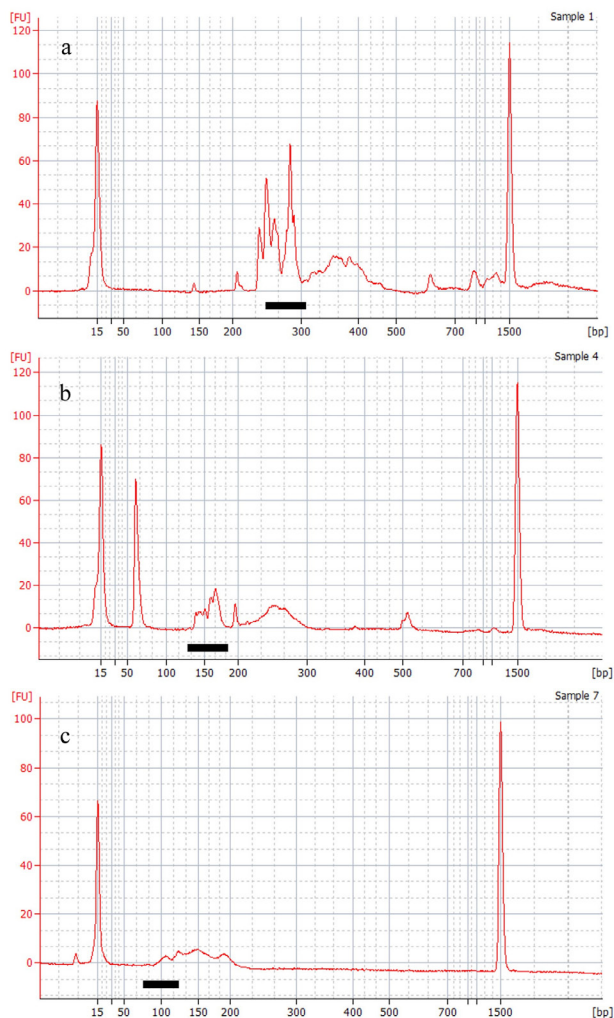
**Fig. 2.**

**Table 2.** Myelogram of the case

|  | Results | Range[a] |
|---|---|---|
| Myeloid cells |  |  |
| Myeloblast | 0.6% | 0–0.4 |
| Promyelocyte | 0.2% | 0–3.0 |
| Myelocyte | 0.0% | 0.6–8.0 |
| Metamyelocyte | 0.6% | 4.4–13.2 |
| Band neutrophil | 0.8% | 12.8–16.6 |
| Segment neutrophil | 1.4% | 6.5–22.0 |
| Eosinophilic myelocyte | 0.4% | 0.8–3.2* |
| Eosinophilic metamyelocyte | 0.6% | - |
| Eosinophilic band | 0.6% | - |
| Eosinophilic segment | 2.0% | - |
| Monocyte | 1.0% | 0.2–1.6 |
| Erythroid cells |  |  |
| Rubriblast | 0.8% | 0–0.8 |
| Prorubricyte | 1.2% | 0–1.6 |
| Rubricyte | 0.6% | 10.2–29.4 |
| Metarubricyte | 0.6% | 1.0–10.4 |
| Others |  |  |
| Megakaryopoietic cell | 0.0% | N/A |
| Lymphocyte | 2.2% | 11.6–21.6 |
| Blast cell | 86.4% | N/A |
| M/E ratio | 2.25 | 1.21–2.16 |

*Reference range of total eosinophilic cells. a) Cited from [6]. N/A, not applicable.

**Fig. 2.** Results of analysis using Bioanalyzer 2100 in the patient. (a) Immunoglobulin heavy chain variable region (FR2). (b) Immunoglobulin heavy chain variable region (FR3). (c) T cell receptor gamma region. Peaks at 15 bp and 1,500 bp represent lower and upper markers. Positive and negative controls were also applied (data not shown). Bar indicates each target range.
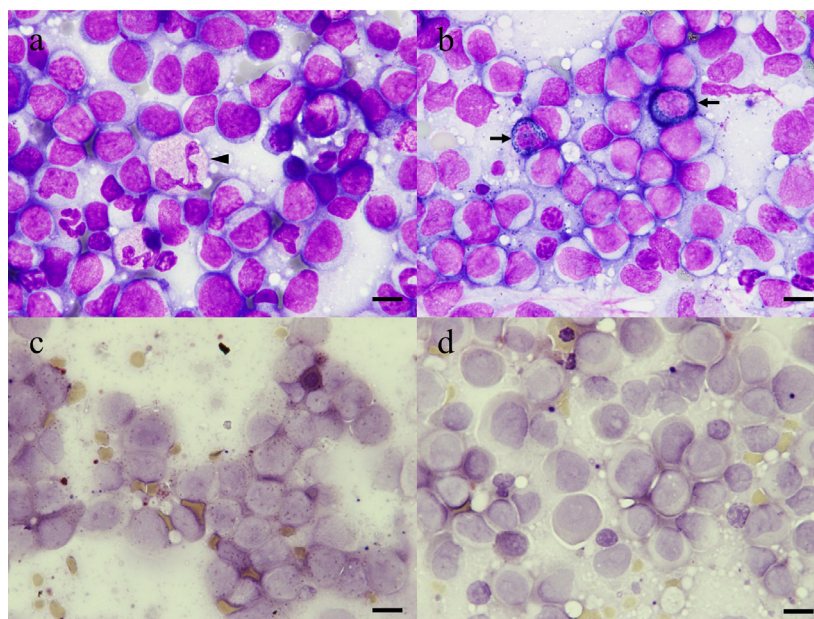


**Fig. 3.** Bone marrow aspiration smear. (a) Wright-Giemsa stain. Blast cells have a round to oval nucleus and moderately to lightly baso-philic cytoplasm with high nuclear/cytoplasmic ratio. Large-size, dysplastic eosinophils are also visible (allowhead). (b) Peroxidase stain. A small number of myeloid cells have dark blue granules in their cytoplasm (allows). (c) Alpha-naphthol butyrate esterase (α-NBE) stain. Almost monocytic cells have brown granules in their cytoplasm. (d) α-NBE staining is inhibited by sodium fluoride (bar=10 $\mu$m).

than 3% of the cells in the bone marrow expressed either CD3 or CD20; however, nearly the entire population of non-erythroid cells expressed HLA-DR, suggesting the presence of a monocytic lineage (Fig. 4). FeLV/FIV proviral polymerase chain reaction test (IDEXX) was performed using the bone marrow aspirate to confirm the FeLV/FIV negative status of the cat. Considering these findings, the cat was diagnosed with FeLV-negative acute monoblastic leukemia (M5a).

The cat was treated by multi-drug chemotherapy including cytarabine (300–400 mg/m$^2$, constant rate infusion for 4 hr; Nippon Shinyaku, Kyoto, Japan), doxorubicin (1 mg/kg, IV; Aspen Japan, Tokyo, Japan), and prednisolone (2 mg/kg, PO, q24hr; Teva Takeda Pharma, Osaka, Japan) based on a modified protocol for canine AML [21]. Although the number of blast cells in the peripheral blood decreased after multi-drug treatment, thrombocytopenia and anemia did not improve. No major gastrointestinal toxicities, as described [20], were observed, and the cat was healthy and ate well after whole blood transfusion. At VMC-OUAVM, blood transfusion is operated according to previously proposed guidelines [11, 14]. Whole-blood products were obtained from five healthy donors breeding in the laboratory animal building. Crossmatch was performed prior to every blood transfusion, and the subject required eight blood transfusions (Fig. 5). After week 9, treatment was stopped on the owner's request. The cat died a few days later. Unfortunately, a necropsy was not performed.
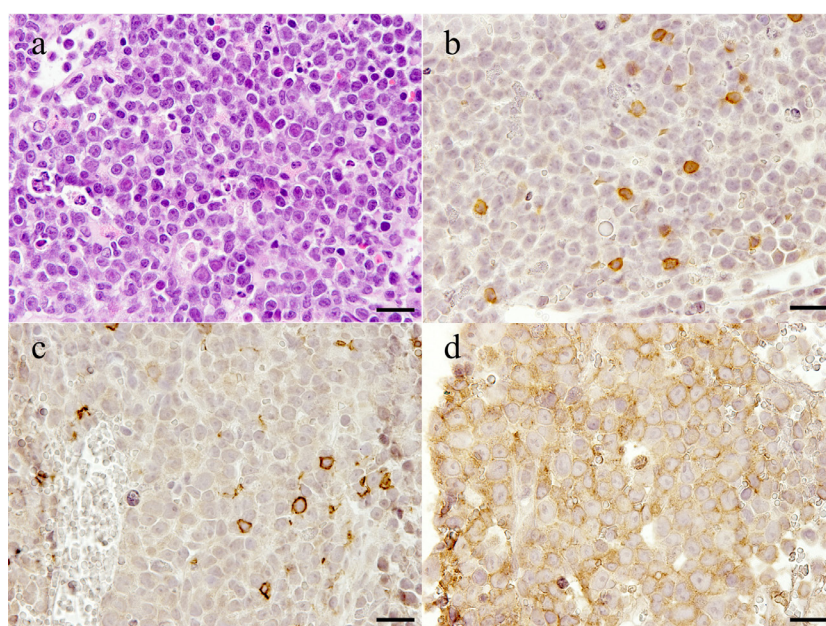


**Fig. 4.** Bone marrow core histopathology of the case. (a) Hematoxylin and eosin stain. Stained with antibodies versus CD3 (b), CD20 (c), and HLA-DR (d). Less than 3% of the cells in the bone marrow are expressed as either CD3 or CD20. In contrast, nearly the entire population of non-erythroid cells expressed HLA-DR (bar=20 $\mu$m).
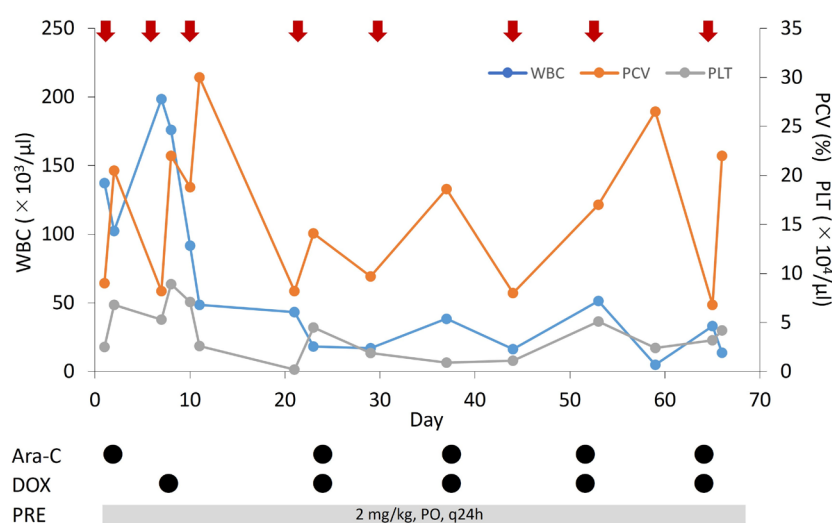


**Fig. 5.** Changes in white blood cells (WBC), packed-cell volume (PCV), and platelets (PLT) during the course of chemotherapy of the cat. Ara-C, cytarabine; DOX, doxorubicin. Red arrow indicates blood transfusion.

AML in cats is a rare disorder, and its diagnosis and subclassification are based on the characteristics of blast cells in the peripheral blood and bone marrow [9]. Presence of >30% blast cells in ANCs in the bone marrow is defined as acute leukemia. Acute monocytic leukemia (M5) is a subtype of AML with two distinct morphological subcategories, M5a and M5b. M5a is diagnosed based on the following conditions: 1) 80% of leukemic cells are morphologically of monocytic lineage, including monoblasts, promonocytes, and monocytes; 2) a minor granulocytic component may be present (<20% of NEC); 3) in M5a, the percentage of monoblasts and promonocytes is ≥80% of NECs; 4) in M5b, proportion of monoblasts and promonocytes is 20 to 79% of NECs and maturation to monocytes is prominent; 5) usually, the leukemic population shows intense nonspecific esterase activity, inhibited by NaF [9]. In our case, the proportion of blast cells was 91.3% of NECs, and morphological, cytochemical, and immunohistopathological findings suggested that the blast cells were monoblasts. According these findings, the cat was diagnosed with acute monoblastic leukemia (M5a).

In this case, numerous blast cells were found in the peripheral blood smear. The results of cytochemical and immunohistopathological staining of peripheral blood were also similar to bone marrow findings. While bone marrow aspirate examination is always essential for confirmation of diagnosis, blood smear might be helpful for the diagnosis or classification of leukemia in cases such as this.

Interestingly, a small number of large-sized, dysplastic eosinophils was observed in both peripheral blood and bone marrow samples. Dysplastic changes of the hematopoietic cells are characteristic of myelodysplastic syndrome [16]. In humans, such abnormal eosinophils are part of the leukemic cell population in acute myelomonocytic leukemia with abnormal eosinophils (AML-M4Eo) [4]. It is therefore required to characterize the dysplastic eosinophils in feline AML.

It is a well-known fact that FeLV infections are associated with myeloid neoplasia in cats [2, 5]. Few cases of M5 have been reported in association with FeLV [13, 15]. However, the cat in this report was negative for FeLV antigens in the peripheral blood and also negative for FeLV provirus in the bone marrow. Since AML without FeLV status is a rare condition, clinical pathological findings or prognosis of the status is not well recognized. Further studies would be required to clarify whether these are different for AML patients based on the presence or absence of an underlying FeLV infection.

Chemotherapeutic agents such as cytosine arabinoside, doxorubicin, cyclophosphamide, prednisone, and vincristine have been unsuccessfully used both independently and in combination in a few cases of acute myeloid neoplasia in cats, with the total survival duration ranging from 3 to 8 weeks [1, 12]. In this case, a combination of cytosine arabinoside and doxorubicin was used as the chemotherapeutic agent. Therefore, the total number of blast cells decreased and the cat's health subsequently improved. However, severe anemia and thrombocytopenia were not recovered, and the owner denied further treatment. In human medicine, there are many different treatment approaches to acute leukemia [3]. The backbone of therapy is a combination of cytarabine- and anthracycline-based regimens with allogeneic stem cell transplantation. The prognosis, however, remains still poor [3]. In veterinary medicine, the use of bone marrow transplantation is limited. Further studies are required to develop an effective therapeutic regimen for acute monocytic leukemia in cats. In addition, many possible complications occur in patients with leukemia. Coagulopathy is one of the important complications to develop in patients with acute myeloid leukemia [19]. Bleeding at the site of blood sampling and cachexia were seen in this case, however, coagulation test was not performed. Assessment of complications is important to manage the patients with leukemia.

In this case, there were no clonal rearrangements in the B or T cell receptors in the peripheral blood of the cat. Additionally, the possibility of an acute leukemia of a lymphoid origin was also eliminated considering the outcomes of the cytochemical and immunohistochemical staining. Recently, clonal rearrangements in B or T cell receptors were found in 64% of dogs with AML. The report showed that the clonality testing should not be used as a tool to distinguish between acute leukemia of myeloid or lymphoid origin [17]. The importance of clonality testing for feline AML has not been considered or sufficiently investigated until now.

Therefore, we described a rare case of acute monoblastic leukemia (M5a) in a FeLV-negative cat. Although a combined administration of cytosine arabinoside and doxorubicin was effective, severe anemia and thrombocytopenia were not ameliorated. Blood transfusion can still be regarded as a crucial treatment approach for myeloid neoplasia in cats.

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