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Dysmyelopoiesis in a cat with immune-mediated hemolytic anemia

Do-Hyeon Yu, Jong-Hyun Lee, Ji-Seon Yoon, Ying-Hua Li, Mi-Jin Lee, Jinho Park*

College of Veterinary Medicine & Bio-Safety Institute, Chonbuk National University, Jeonju 561-756, Korea
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Abstract : A 3-year-old spayed female Persian feline with non regenerative anemia showed persistent autoagglutination in EDTA anticoagulated blood. Primary immune-mediated hemolytic anemia (IMHA) was suspected and the underlying causes for IMHA were excluded by radiologic, sonographic, serologic and molecular studies. Cytologic examination of the bone marrow revealed that dysmyelopoiesis and dysplastic changes were prominent in the erythroid cells. These changes included asynchronous maturation of the nucleus and cytoplasm, binucleation, trinucleation, fragmented or lobulated nuclei and multilineages. Mild dysgranulopoiesis and dysmegakaryocytopoiesis were also detected including pseudo Pelger-Huet anomalies, giant band neutrophils, asynchronous maturation of the nucleus and cytoplasm in granulopoiesis and large hypolobulated forms as well as dwarf megakaryocytes in megakaryocytopoiesis. Myelodysplastic syndrome and congenital dysmyelopoiesis was ruled out by the low number of blast cells. Finally, secondary dysmyelopoiesis associated with IMHA was diagnosed and immunosuppressive treatment was successfully responsive.

Keywords : autoagglutination, dysmyelopoiesis, immune-mediated hemolytic anemia, myelodysplastic syndrome

Dysmyelopoiesis is a hematologic disorder characterized by the presence of dysplastic conditions in one or more hematologic cell lines of the blood or bone marrow [7] and it is a relatively common finding in dogs [9]. Cats are considered to have dysmyelopoiesis if they meet the criteria that include finding > 10% dysplastic cells in 1 or more hematologic cell lines in the bone marrow showing concurrent cytopenias in the blood [8]. In general, three types of dysmyelopoiesis have been described in dogs, cats and humans; myelodysplastic syndromes (MDSs), secondary dysmyelopoiesis and congenital dysmyelopoiesis. MDSs are clonal proliferative disorders that result from mutations in hematopoietic stem cells [6] whereas secondary dysmyelopoiesis is frequently associated with disease conditions including IMHA or immune-mediated thrombocytopenia (45%), lymphosarcoma (25%) and myelofibrosis (15%) [2, 4, 9]. Differentiating cats with MDSs from cats with immune-mediated hemolytic anemia (IMHA) was difficult because changes were similar in both conditions characterized by severe nonregenerative anemia, autoagglutination, and metarubricytosis [8].

Recently, several factors were proposed to differentiate theses condition: high numbers (>5 %) of bone marrow myeloblasts or rubriblasts in animals supports a diagnosis of MDSs while a response to immunosuppressive treatments includes cats with immune-mediated secondary dysmyelopoiesis [8, 9]. This distinction is also clinically useful in differentiating dysmyelopoiesis and predicting prognosis in cats.

In the case study reported here, dysplastic changes in bone marrow aspirates from a cat with IMHA are described.

A 3-year-old spayed female Persian feline, 2 months previously diagnosed with idiopathic hepatic lipidosis by liver aspirates, presented at Chonbuk Animal Medical Center, Chonbuk National University, with splenomegaly and persistent mild anemia over a month. The hepatic lipidosis was almost corrected by nutritional and metabolic support. The serum total bilirubin (T-Bil) and liver enzyme levels were decreased compared to 2 months previously. However, normochromic normocytic nonregenerative anemia was found along with adequate WBC count and differential percentages of WBCs (Table 1). On a blood smear, persistent erythrocyte agglutination and metarubricytosis were remarkably found

*Corresponding author: Jinho Park
College of Veterinary Medicine, Chonbuk National University, Jeounju 561-756, Korea
[Tel: +82-63-270-2557, Fax: +82-63-270-3780, E-mail: jpark@chonbuk.ac.kr]

Table 1. Results of hematological examination of a cat with dysmyelopoiesis

Item	Days before 56	36	29	14	9	IMHA 0	after 9	14	55	Reference range
WBC (× 10^3/μl)	6.3	5.4	8.8	3.9	4.2	6.2	5.3	3.8	3.5	5.5 ~ 19.5
RBC (× 10^6/μl)	8.13	6.10	6.09	5.59	4.80	3.47	5.98	7.66	2.91	5.80 ~ 10.70
HB (g/dl)	10.6	8.2	8.5	7.9	5.7	4.9	8.6	11.0	4.5	9 ~ 15
HCT (%)	34.2	26.1	27.5	24.9	21.4	15.5	32.2	35.5	14.2	30 ~ 47
PLT (× 10^3/μl)	380	576	274	449	387	219	622	402	114	300 ~ 800
MCV (fl)	42	43	45	45	45	45	54	46	49	41 ~ 51
MCH (pg)	13.0	13.4	13.9	14.1	11.9	14.1	14.3	14.4	15.5	13 ~ 18
Aggr Reti* (× 10^3/μl)	–	–	n.d†	n.d†	–	13.8	328.9	–	–	0 ~ 282
ALP (U/l)	116	71	66	51	–	35	–	–	34	16 ~ 71
GOT (AST) (U/l)	195	68	53	59	–	34	47	27	18	12 ~ 65
GPT (ALT) (U/l)	309	299	134	225	–	117	438	216	53	22 ~ 109
BUN (mg/dl)	14.6	11.2	8.2	12.0	–	22.1	17.0	18.0	26.2	17.2 ~ 31.1
Glucose (mg/dl)	130	234	145	90	–	181	145	76	160	63 ~ 139
Phosphorus (mg/dl)	4.6	6.2	4.6	5.0	–	8.4	–	–	5.8	2.7 ~ 8.1
Albumin (g/dl)	3.6	3.5	2.9	2.8	–	3.4	3.1	–	2.6	2.5 ~ 3.6
Creatinine (mg/dl)	0.4	0.4	0.4	0.3	–	0.4	–	–	0.4	0.7 ~ 2.4
T-Bil (mg/dl)	10.5	5.4	0.8	0.8	–	1.3	0.6	–	1.3	0 ~ 0.2
T-Protein (g/dl)	9.8	9.2	8.7	9.0	–	11.5	8.1	–	10.1	6.3 ~ 8.9
Globulin (g/dl)	6.2	5.7	5.8	6.2	–	8.1	–	–	7.5	3.5 ~ 5.9
Sodium (mEq/l)	151	155	155	159	–	-	–	–	–	145 ~ 158
Potassium (mEq/l)	3.7	3.7	5.0	3.7	–	-	–	–	–	3.6 ~ 4.8
Chloride (mEq/l)	115	122	126	125	–	-	–	–	–	105 ~ 120

*Aggr Reti: aggregate reticulocytes; †n.d: not detected.

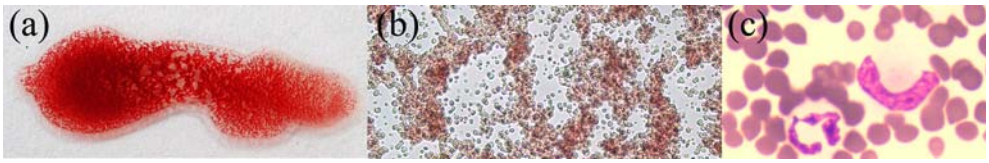

Fig. 1. Photographs of peripheral blood. macroscopic (a) and microscopic (b) identification of autoagglutination in EDTA anticoagulated blood, (c) a dysplastic giant neutrophil (right) Diff-Quik stain.

(Fig. 1). The results of serum biochemical analysis and urinalysis revealed hyperglobulinemia characterized by a polyclonal gammopathy on an electrophoretic trace (data not shown), bilirubinuria (> 4 +), urobilinogenuria (3+) and hematuria (1 +). Primary IMHA was diagnosed based on persistent erythrocyte agglutination but spherocytosis could not be identified because normal feline red blood cells are much smaller than canine RBCs and do not have a central pallor.

Because secondary dysmyelopoiesis could be associated, evaluation of bone marrow aspirate including a 500-cell differential count was performed. Marrow cellularity was normocellular with a normal myeloid : erythroid ratio (1.83 : 1) and the numbers of rubriblasts and myeloblasts were also normal (< 5%). There were no observable evidences of necrosis or fibrosis. However, dysplastic changes were noted mainly in the erythroid series (20%) and also in the granulopoietic and megakaryocytopoietic cell lines. Features of dyserythropoiesis included asynchronous maturation of the nucleus and cytoplasm, binucleation, trinucleation, fragmented or lobulated nuclei and multilineages. A subjective increase in mitotic and erythrophagocytic changes was also observed. In addition, a small amount of dysgranu-

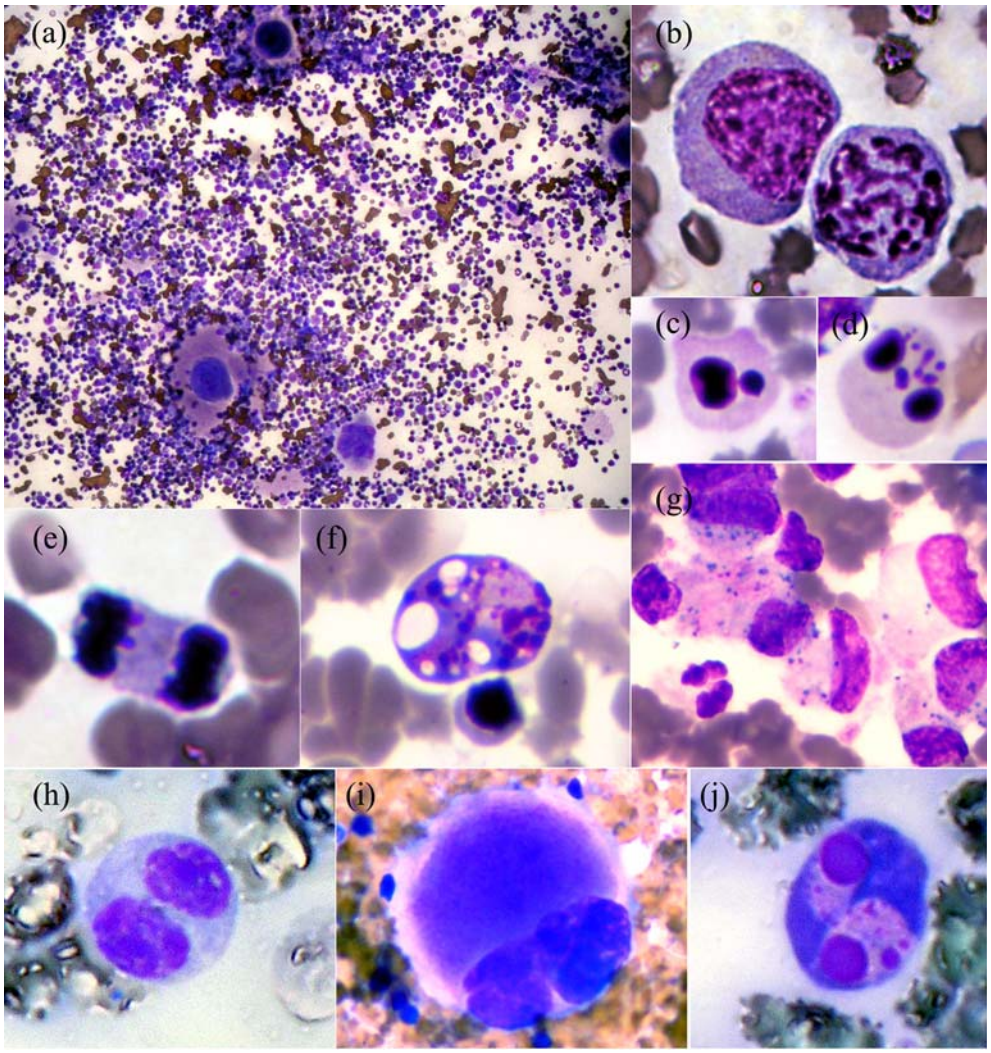

Fig. 2. Photographs of the bone marrow aspirate (Diff-Quik stain). (a) Low magnification (× 40) of the marrow smear with megakaryocytes, (b) a rubricyte with dispersed nuclei (right), (c) a lobulated polychromatophilic metarubricyte, (d) a dysplastic rubricyte with multi-nuclei, (e) erythroid mitosis, (f) increased erythrophagocytosis (upper) and metarubricyte (lower), (g) stainable iron, (h) a pseudo Pelger-Huet dysplastic change, (i) a hypolobulated basophilic megakaryocyte, (j) dysplastic change featuring two cells lineage.

lopoiesis and dysmegakaryocytopoiesis was also found including pseudo Pelger-Huet anomalies, giant band neutrophils, asynchronous maturation of the nucleus and cytoplasm in granulopoiesis and large hypolobulated forms as well as dwarf megakaryocytes in megakaryocytopoiesis (Fig. 2).

Because low percentages of rubriblasts and myeloblasts were observed, secondary dysmyelopoiesis was diagnosed and it was considered to be associated with IMHA. Underlying causes of IMHA had been excluded by diagnostic imaging, serologic tests for FIV antibodies, FeLV antigen (SNAP FIV/FeLV Combo Plus Test; IDEXX Laboratories, USA), FIP 7b protein (Antech diagnostics, USA) and PCR assays for FeLV, FIV [1] and for feline hemoplasmas [11] (data not shown). Oral administration of prednisolone was started (2 mg/kg, q 12 h) to suppress the patient's immune status.

On the basis of the results of the blood analysis, prednisolone treatment improved of the hematologic disorder when assessed on 9 and 14 days after the

initial diagnosis (Table 1).

After 2 months of the initial diagnosis, however, pancytopenia and autoagglutination occurred while tapering the prednisolone dosage. The patient suddenly expired on her way to hospital. The client did not accept post-mortem examination.

Primary or idiopathic (auto-) IMHA, the most common cause of hemolysis in dogs, has rarely been documented in cats [5, 10] and could be associated with secondary dysmyelopoiesis.

In the present study, a subjective increase in the mitotic and erythrophagocytic changes was observed on bone marrow aspirate examination. It could be associated with immune-mediated hemolytic anemia. Stainable iron which cannot normally be detected in aspirates of bone marrow from healthy cats was also detected in small amounts in the bone marrow. This suggests that destruction of erythroid cells from an immune mediated disorder had taken place.

A persistent autoagglutination and mild increase in the total bilirubin concentration provides further support for a concurrent IMHA. It is therefore concluded that, this immune-mediated disorder had caused secondary dysmyelopoiesis.

Because immune system attack may induce features of dysplasia in hematopoietic precursor cells, immune-mediated hematologic conditions have been associated with myelodysplastic features in bone marrow [4]. These dysplastic changes in the bone marrow were not sufficiently different to differentiate MDS from secondary dysmyelopoiesis [8]. In this case, however, the number of myeloblasts and rubriblasts were < 5% of the bone marrow aspirates and dysplastic changes were predominant (> 10%), which suggests secondary dysmyelopoiesis occurred due to primary IMHA. Furthermore, this dysmyelopoiesis was reversible with immunosuppressive treatment. The response to immunosuppressive treatment and the low number of blast cells supported the diagnosis of secondary dysmyelopoiesis.

In the end, autoagglutination had recurred and pancytopenia was identified after tapering the dosage of prednisolone. Concomitant involvement of erythroid and megakaryocytic cell lines might be associated with this stage of the disease. The low platelets might also indicate systemic thrombosis or disseminated intravascular coagulation. In a previous study, relapses occurred in 31% of 16 cats with primary IMHA [3]. Therefore, aggressive and long-term immunosuppressive therapy by corticosteroids alone or in combination with other immunosuppressive drugs should have been carried out, and serial cytological evaluation of bone marrow aspirates was needed regarding immune disorders of blood progenitors. Human polyclonal immunoglobulin might also have had a beneficial effect for such an immune mediated hematologic disorder in a cat [12] although data on the use and safety of this product are lacking.

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