NOTE *Clinical Pathology*

Hypereosinophilic Syndrome in Two Cats

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ABSTRACT. Two cats showing chronic vomiting, diarrhea and weight loss were found to have leukocytosis with marked eosinophilia. Both cats were diagnosed with hypereosinophilic syndrome by the findings of increased eosinophils and their precursors in the bone marrow, eosinophilic infiltration into multiple organs, and exclusion of other causes for eosinophilia. Although cytoreductive chemotherapy with hydroxycarbamide and prednisolone was performed, these two cats died 48 days and 91 days after the initial presentation.
KEY WORDS: eosinophilia, feline, gastrointestinal symptoms, hydroxycarbamide.

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Hypereosinophilic syndrome (HES) is a rare systemic disorder in cats and is characterized by sustained eosinophilia due to overproduction of eosinophils in the bone marrow, infiltration of eosinophils into multiple tissues and subsequent organ damage [5, 6, 8–11, 18, 19]. Since feline HES was first reported in 1981 [5], more than 10 cases with the disease have been reported [6, 8–11, 18, 19]. HES can be diagnosed based on eosinophilia in the peripheral circulation and bone marrow, organ infiltration with eosinophils, and the absence of other recognizable causes for the eosinophilia [1, 19]. Other causes of eosinophilia in cats include flea allergy, parasitism, bronchial asthma, eosinophilic granuloma complex, eosinophilic enteritis, mast cell tumor, and lymphoma [1, 19]. Treatment moderities for feline HES have been discussed.

In this study, we report two cats with HES and discuss on the disease classification and treatment choice. These two cases received cytoreductive chemotherapy with hydroxycarbamide (Hydrea; Bristol-Myers, New York, NY, U.S.A.) and prednisolone; however, died 48 and 91 days after the initial presentation.

Case No. 1; A 9-year-old neutered male mixed-breed cat was referred to the Veterinary Medical Center of the University of Tokyo (UT-VMC) with a 1-month history of vomiting, diarrhea, and weight loss. On physical examination, the cat was moderately dehydrated and thin (BW 3.15 kg).

A complete blood cell count (CBC) indicated nonregenerative anemia and leukocytosis with marked eosinophilia (Table 1). The serum chemical profile revealed no abnormality except for a decreased albumin level (Table 1). On the peripheral blood smear, increase of relatively large mature eosinophils was noted (Fig. 1A). Feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibody (FIV-FeLV Snap Combo Test for FeLV p27 antigen and specific antibodies to FIV; IDEXX, Westbrook, ME, U.S.A.) were negative. Fecal floating examination was negative for intestinal parasite; however, a large number of eosinophils were found in the fecal smear stained with Wright-Giemsa solution. Abdominal ultrasonography revealed mildly thickened intestinal walls. Histopathological findings of the endoscopic biopsy revealed eosinophilic infiltration in the submucosa of the stomach and duodenum. The bone marrow cytology showed normocellularity with a myeloid/erythroid (M/E) ratio of 1.36 and increased eosinophilic precursors (Table 1 and Fig. 1B).

The cat was hospitalized and treated with prednisolone (1–1.7 mg/kg, q12h), ampicillin (20 mg/kg, q12h), and famotidine (0.5 mg/kg, q12h) in conjunction with electrolyte fluid therapy. In addition, the cat received whole blood transfusions (20–40 m*l*) five times because of the progressive anemia (Fig. 2A). However, eosinophilia and diarrhea did not improve. Exploratory laparotomy performed on Day 36 revealed ascites, enlarged mesenteric lymph nodes and thickened intestinal walls. Histopathological examinations of the biopsied specimens revealed eosinophilic infiltration in the spleen and lymph nodes. Therefore, the cat was diagnosed as having HES, and hydroxycarbamide (20–30 mg/kg, q24h) was administered from Day 39. After Day 45, coagulation panel tests revealed prolonged activated partial thromboplastin time, elevation of fibrin/fibrinogen degradation products and thrombocytopenia. These findings indicated a development of disseminated intravascular coagulation (DIC) due to the organ damage. Although blood transfusion and an intravenous infusion with low-molecular-weight heparin (100 U/kg/day) were carried out, the cat showed profound anemia and marked icterus, and then died on Day 48.

Autopsy revealed icterus, celiac lymphadenopathy, ascites, and marked thickening of the intestinal walls. Histopathologic examination revealed infiltration of mature

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Table 1. Hematologic values and serum chemical profiles at the first admission and myelograms by bone marrow cytology

	Case 1	Case 2
RBC ($\times 10^6$/m*l*)	6.00	5.36
Hemoglobin (g/d*l*)	8.4	11.1
PCV (%)	25	33
WBC (/μl)	33,300	53,600
Neutrophils, band (/μl)	0	0
Neutrophils, segmented (/μl)	18,700	10,700
Eosinophils (/μl)	12,300	39,200
Lymphocytes (/μl)	1,300	3,200
Monocytes (/μl)	1,000	500
Basophilis (/μl)	0	0
Platelets ($\times 10^3$/μl)	561	374
BUN (mg/dl)	22.9	23.1
CRE (mg/d*l*)	1	1.6
ALP (U/*l*)	36	43
ALT (U/*l*)	42	64
ALB (g/d*l*)	2.4	2.2
Proerythroblasts	0.7%	0.0%
Basophilic erythroblasts	4.6%	0.4%
Polychromatic erythoblasts	20.7%	4.2%
Orthochromatic erythoblasts	14.6%	17.6%
Myeloblasts	0.6%	4.0%
Promyelocytes	1.3%	2.8%
Neutrophilic myelocytes	3.0%	0.0%
Neutrophilic metamyelocytes	6.1%	0.4%
Neutrophils, band	14.6%	6.9%
Neutrophils, segmented	7.2%	8.9%
Eosinophilic myelocytes	7.6%	9.5%
Eosinophilic metamyelocytes	5.9%	9.3%
Eosinophils, band	5.6%	16.2%
Eosinophils, segmented	3.7%	18.8%
Monocytes	0.9%	0.0%
Lymphocytes	0.6%	0.6%
Plasma cells	1.7%	0.0%
Megakaryocytes	0.6%	1.0%
Myeloid/Erythroid ratio	1.36	3.46

eosinophils into the spleen, celiac lymph nodes, adrenal medulla, and the submucosa of the jejunum, ileum (Fig. 1C, D), colon, and bladder. In addition, intravascular microthrombi were observed in the spleen, pancreas, adrenal gland, and renal glomerulus.

Case No.2; A 9-year-old spayed female American domestic shorthair cat was referred to UT-VMC with a 3-month history of coughing and vomiting, 1-month history of anorexia, and weight loss. On physical examination, the cat was moderately thin (BW 4.0 kg), but no other abnormality was noted.

CBC indicated leukocytosis with remarkable eosinophilia (Table 1). The serum chemical profile was within the normal range (Table 1). Many mature eosinophils were detected on the peripheral blood smear (Fig. 1E). FeLV antigen and FIV antibody tests and heartworm antigen test (Snap Canine Heartworm PF; IDEXX) were negative. Fecal flotation was negative for intestinal parasites. Thoracic radiography revealed diffuse bronchial patterns in the lung fields. In a cytologic evaluation of tracheal exudates, a large number of eosinophilis admixed with neutrophils and tracheal epithelial cells were found. In endoscopic examination, thickened fragile duodenal mucosa was observed. Histopathological examination of the biopsied tissues revealed lymphocytic, plasmacytic and eosinophilc infiltration in the submucosa of the duodenum. Bone marrow aspiration biopsy showed hypercellularity, a high M/E ratio (3.46), and increased eosinophilic precursors (Table 1 and Fig. 1F). Based on these findings, the cat was diagnosed as having HES.

Although prednisolone (2–3 mg/kg, q12h) was administered to the cat for 42 days, intermittent vomiting persisted intermittently (Fig. 2B). Treatment with hydroxycarbamide (15 mg/kg, q24h) was started from Day 43. The cat showed hematochezia and severe anemia on Day 67, thereby, hydroxycarbamide medication was withdrawn. The cat was treated with prednisolone, intermittent blood transfusions, and interferon α (10,000 U/kg, on Days 75 and 77) in conjunction with electrolyte fluid therapy. On Day 77, an abdominal radiography indicated the presence of pneumoperitoneum probably due to the gastrointestinal perforation. Exploratory celiotomy performed on Day 78 showed multiple ulcerative perforations in the fundus of the stomach and concurrent suppurative peritonitis. Partial gastrectomy with a resection of the ulcerated area was performed. Histopathological examination of the resected stomach indicated infiltration of eosinophils in the mucosa and submucosa as well as fibrosis in the submucosa and serosa (Fig. 1G, H). These findings supported the diagnosis of HES in this case. After the surgery, the cat showed deterioration, and then died on Day 91. Autopsy could not be performed.

Remarkable eosinophilia, as seen in the cats reported here, is characteristically observed in eosinophilic proliferative disorders such as HES and chronic eosinophilic leukemia (CEL) [4, 6, 14]. Both diseases have a similar clinical presentation in cats that often reflects gastrointestinal involvement (anorexia, weight loss, vomiting, and diarrhea) [4, 6, 14, 19]. Feline CEL has been distinguished from HES in the points of the presence of blasts in the peripheral blood, morphological abnormalities and immaturity with abnormal granulation in the eosinophilic lineage, high M/E ratio in the bone marrow, and marked anemia [4, 6, 14]. Nevertheless, the clinical course of both diseases is similar, and death occurs mainly from infiltration into multiple organs (gastrointestinal tract, spleen, liver, lymph nodes, heart and lungs) [4, 6, 14, 19]. Organ damage and dysfunction can be caused by a release of cytotoxic substances from eosinophils such as eosinophil cationic protein, major basic protein, eosinphil-derived neurotoxin, oxydating molecules including eosinophil peroxidase and free oxygen radicals, and enzymes including elastase and collagenase [12, 13].

Currently, in human medicine, HES is regarded as a group of disorders that are characterized by marked eosinophilia in the peripheral blood, tissues, or both, often without other identifiable causes [7, 13]. CEL is regarded as a subtype of myeloproliferative variant of HES with an occurrence of a stem cell mutation leading to clonal expansion of

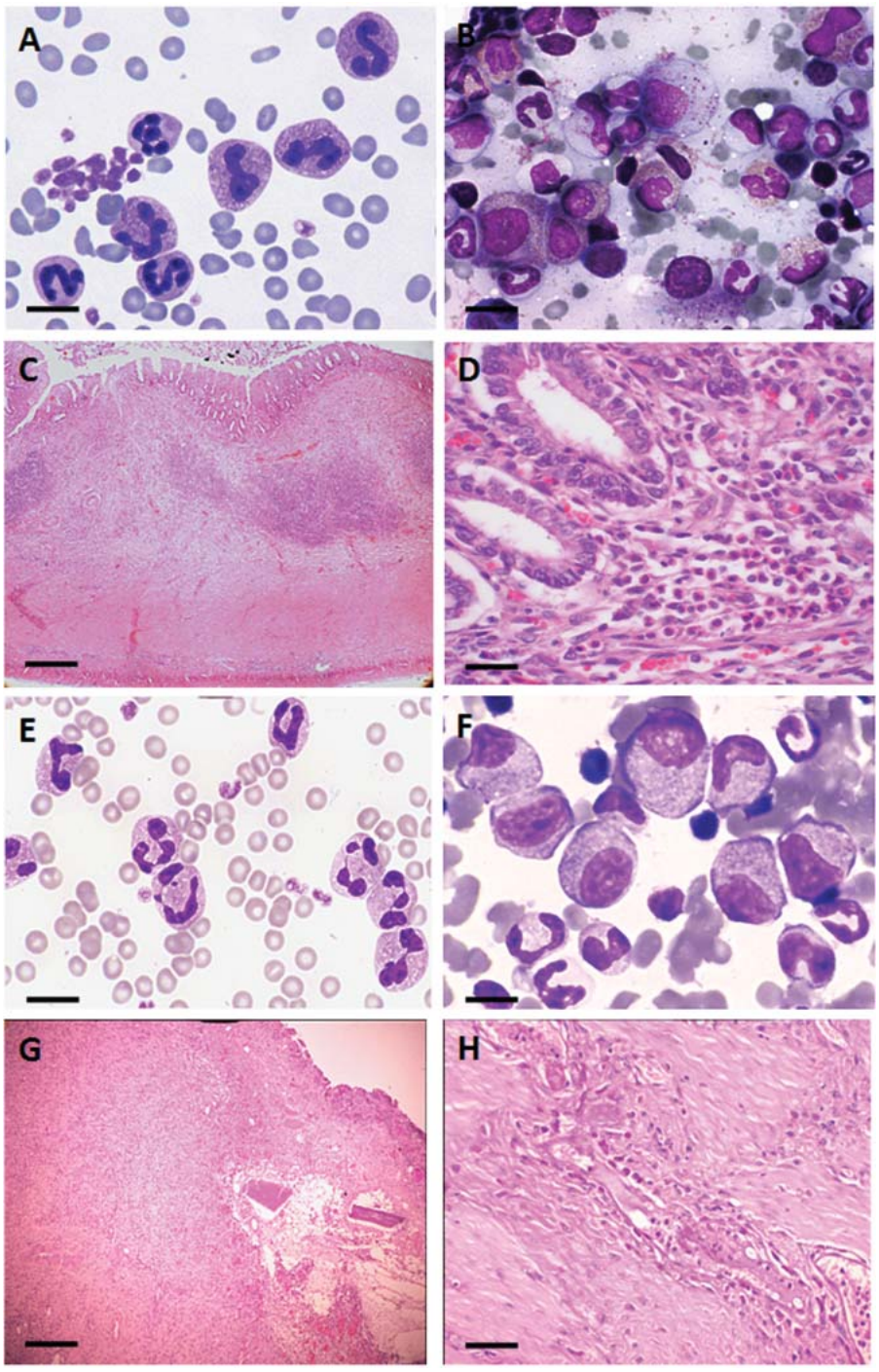

Fig. 1. Cytological findings of the peripheral blood and bone marrow smear and histopathological findings of gastrointestinal tract in Cases 1 and 2 . Case 1: Increase of large-sized eosinophils in the peripheral blood (A) and eosinophilic precursors in the bone marrow (B) are observed. Atrophy of the villus and thickening of tunicae muscularis of the ileum (C), and eosinophilic infiltration into the submucosa of ileum (D). Case 2: Increase of mature eosinophils in the peripheral blood (A) and eosinophilic precursors in the bone marrow (B) are observed. Fibrosis in the submucosa and serosa of the stomach (G), and eosinophilic infiltration into mucosa and submucosa of the stomach (H) are observed. A, B, E and F: Wright-Giemsa stain. C, D, G and H: hematoxylin-eosin stain. Bar=10 μm (A, B, E and F), 500 μm (C, G), 25 μm (D), 50 μm (H).

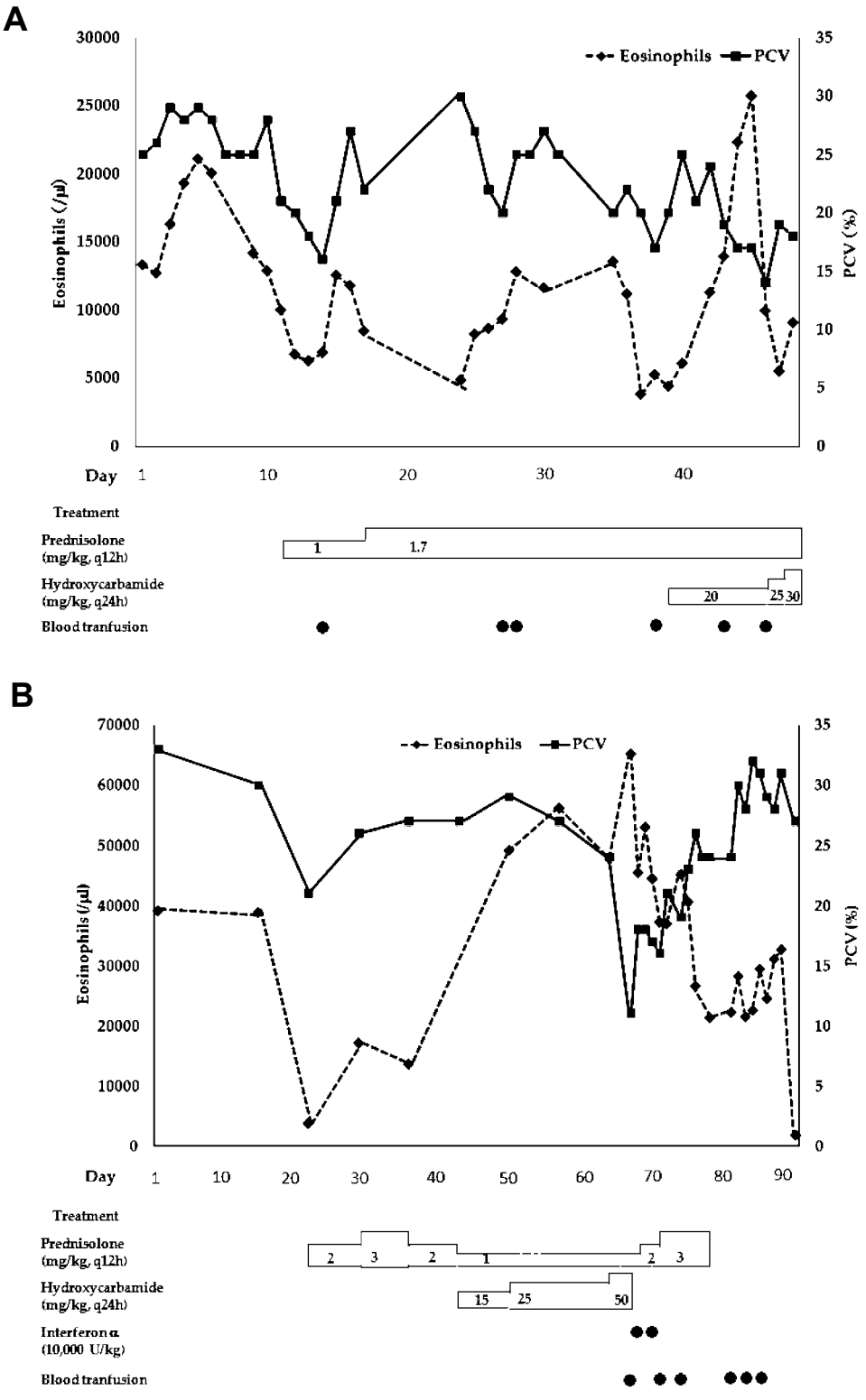

Fig. 2. Changes of the peripheral blood eosinophil count and PCV during the treatment in Cases 1 (A) and 2 (B).

eosinophils [7, 13]. It is very difficult to make an accurate diagnosis as HES or CEL in the two cats in this study as well as previously reported feline cases [3–6, 8–11, 14–19]. For the differential diagnosis between HES and CEL, clonality analysis of the proliferating eosinophilic cells is needed by the cytogenetic analysis. Because the 2 cats reported in this study showed marked eosinophilia in the peripheral blood, bone marrow, and other tissues without other identifiable causes, they could be diagnose with HES according to the criteria in human medicine [7, 13]. Since the clonality of the eosinophilic cells in the present cases could not be clarified, they were preferably categorized into a brooder diagnosis of HES.

As the therapy for feline HES and CEL, immunosuppressive doses of corticosteroids have been used; however, responses to the therapy were uniformly poor [4, 14, 19]. There has been only one reported feline case in which the blood eosinophil count could be controlled for more than 28 months by medication with prednisolone and hydroxycarbamide [9]. In humans with HES, treatment with interferon-α achieved a successful outcome [13]. In the present cases, both cats were treated with prednisolone and hydroxycarbamide. Case 2 was treated with interferon-α in a short term. However, these therapies were unsuccessful in achieving remission of eosinophilia in the 2 cases.

Recent advances in molecular biology and immunology have led to the recognition of myeloproliferative variant of HES in humans. A part of the disorder is characterized by possessing a fusion gene, *FIP1L1-PDGFRA* [2]. For a *FIP1L1-PDGFRA*-positive patient, treatment with a tyrosine kinase inhibitor such as imatinib has become a first-line therapy [2, 13]. Since molecular basis for the development of feline HES has not been revealed, further case accumulation and investigation on its pathogenesis are required.

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