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## A CASE OF MEGALOBLASTIC ANEMIA IN THE GIBBON (HYLOBATES FOOLOCK)

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An adult female gibbon kept in a zoo for six years was affected with a disease showing diarrhea and anemia. Blood examinations revealed that she was diseased by the macrocytic megaloblastic anemia associated with a marked left shift in neutrophils. Nuclei of the neutrophils were large and bizarre, and Döhle bodies and toxic granules were observed in the cytoplasm. By the treatment with vitamin B<sub>12</sub> injection for two days, the megaloblasts in peripheral blood disappeared and instead normoblasts increased.

Autopsy findings showed no significant gross changes, however histopathologically, focal edematous induration in the liver and subacute catarrhal enterocolitis were markedly noticed.

### INTRODUCTION

It has been thought that megaloblastic anemia is due to deficiencies of either vitamin B<sub>12</sub> or folic acid, or both of them, and macrocytic hyperchromic anemia, leukopenia and megaloblastosis are the hematological characteristics of the disease<sup>1,4,13</sup>.

In the human medicine, macrocytic megaloblastic anemia had been well known as pernicious anemia for long time. However, at the present time, only the type of megaloblastic anemia caused by deficiency of stomach factor is called pernicious anemia or Addison's anemia and it is distinguished from other symptomatic megaloblastic anemia<sup>13</sup>. In the veterinary medicine, true pernicious anemia has not been demonstrated and only a few cases of other types of the disease are reported<sup>6,7,8,12</sup>. In this paper, a case of megaloblastic anemia in the gibbon was described.

### OBSERVATIONS

#### 1 Clinical findings

On May 2, 1970, an adult female gibbon kept in open cage on the Japan Monkey Centre for six years was brought to the clinic of the centre with the history of diarrhea for more than a week. She was in a condition of general weakness, anorexia and weight

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loss; the mucous membrane of her eyelids was pale and body temperature was 40.9°C. By the administration of antibiotics and glucose solution she became afebrile, but the mucous membrane was still very pale. On May 10, blood examinations were carried out; a number of megaloblastic cells were present on the blood film. Therefore, 10  $\mu$ g of cyanocobalamine per day were injected subcutaneously for four days, the megaloblastic cells had disappeared and normoblasts increased in number thereafter. But her general condition became worse and she died on May 15.

## 2 Hematological findings

Results of the hematological examinations were listed in the table 1. The first blood examination was carried out on May 10. In the blood films stained by Giemsa stain, neutrophils decreased in number and showed the marked shift to the left with attendant Döhle bodies and toxic granules. The other feature seen in neutrophils was a large bizarre nucleus. Erythrocytes were stained deeply and anisocytosis with occasional macrocytosis

TABLE 1 *Results of Blood Examinations*

DATE	RBC	HCT.	WBC	DIFFERENTIAL COUNT OF LEUKOCYTES							NUCLEATED RED CELLS (PER 200 LEUKOCYTES)
				Bas.	Eos.	Met.	St.	Seg.	Ly.	Mon.	
10/v	mill. 3.30	% 23	8,600	% 0	% 0	% 0.5	% 4.5	% 10.0	% 76.5	% 8.5	104
12/v	3.09	25	9,400	0	0	0	6.0	64.0	24.5	5.5	120

and poikilocytosis were present. One hundred and four nucleated red cells were seen per 200 leukocytes; many were similar to the megaloblast. On the basis of their nuclear structure and size, those cells were classified into three types. The results are summarized in the table 2. In others, mitotic figures were sometimes seen in the nucleated red cells. The differential count of the cells is shown in the table 3.

The second blood examination was carried out on May 12, after injection of cyanocobalamin for two days. In blood films the neutrophils increased in number. The neutrophils with the bizarre nuclei disappeared mostly and instead the cells with normal nuclei in shape and size increased. However, appearance of Döhle bodies and toxic granules were more remarkable.

One hundred and twenty nucleated red cells were seen per 200 leukocytes, many were orthochromic normoblasts with pyknotic nuclei and some were polychromic macro-erythroblasts with large round or oval darker stained nuclei. The differential count of those cells is shown in table 3.

## 3 Gross and microscopic lesions

**Gross lesions** The surface of the liver was smooth and slightly yellowish. Some white miliary foci were present. The other organs showed no significant gross lesions.

**Microscopic lesions: Liver** The blood content of the liver was greatly increased and the veins and the sinusoids showed distinct dilatation. The Disse's spaces were also dilated and the endothelial cells showed phagocytosis (hemosiderosis). Dissociation of the

TABLE 2 *Morphology of the Nucleated Red Cells on May 10\**

TYPE	SIZE		SHAPE OF NUCLEUS	STRUCTURE OF NUCLEAR CHROMATIN	CYTOPLASM
	Range	Average			
I	11~19 $\mu$	15 $\mu$	Round, oval, kidney-shaped, eccentric	Fine punctate masses (mesh-like)	Abundant, Polychromatophilic (rarely Basophilic)
II	10~15	12	Round or oval	Coarser than those of the type I	Abundant, Polychromatophilic or Orthochromic
III	9~15	11.8	Round, sometimes separate	Varies from a coarse network to a dense mass	Abundant, Orthochromic

\* Two hundred nucleated red cells were studied in the blood smear stained with Giemsa stain

TABLE 3 *Change of Nucleated Red Cells with V. B<sub>12</sub> therapy\**

DATE	SIZE (average)	CYTOPLASM			TYPE OF CELLS				
		Basophilic	Polychromic	Orthochromic	I	II	III	Mitosis	Normoblast
10/v	12.5 $\mu$	1.0%	51.5%	47.5%	11.0%	21.5%	66.5%	1.0%	0%
12/v	9.4	0	18.0	82.0	0	0	4.0	0	86.0

\* Two hundred nucleated red cells were studied in the blood smear stained with Giemsa stain.

liver cell cords was markedly noticed. The regressive processes were rather varying, the lobuli within certain parts of the liver showed almost entirely hydropic degeneration, while in the other parts slight granular degeneration had occurred. Pigmentation in the parenchymal cells was frequently seen throughout the liver lobuli. In the periportal area, the connective tissues showed marked edematous appearance. In these areas, infiltration of lymphocytic elements and proliferation of histiocytes and pigmentphages could be seen. Especially sero-fibrinous exudation was marked. Proliferation of the bile-ducts was seen. Those periportal lesions often extended widely to the adjacent tissues.

**Spleen** The splenic pulp was rich in blood and the follicles were markedly atrophic. The walls of the central arteries and their branches were generally edematous. Sometimes fibrinoid or hyalinous deposits were found in the walls of these blood vessels and the reticular tissues. Hematopoiesis and hemosiderosis were frequently seen in the red pulp.

**Kidneys** Slight congestion and focal hemorrhages were seen in the cortex. Sero-fibrinous exudate was often contained in the Bowman's capsules. Some of the glomeruli showed fibrinoid necrosis. In some parts of the renal tubules dilation was marked and hyaline casts were contained. Hemosiderosis was also found in the tubular epithelial cells. Granular and vacuolar degenerations of the tubular epithelial cells were commonly found.

**Heart** The myocardial fibers showed diffuse granular degeneration. Some part showed vacuolar degeneration.

**Lungs** The lungs showed slight catarrhal bronchitis with congestion.

**Tongue** The ulcer was covered with fibrinous exudate and was accompanied by cellular reaction.

**Stomach** The mucous membrane was atrophic and edematous. Submucosal edema was markedly noticed.

**Intestines** The intestines showed subacute catarrhal enteritis. (Epithelial cells were desquamated and lamina propria was infiltrated by inflammatory cells, such as polymorphous leukocytes, plasma cells, lymphocytes, macrophages and eosinophils. Submucosa was edematous.)

**Lymph node (mesenterici)** Lymphadenitis catarrhalis. (The sinus showed blood resorption and distended with a large number of lymphoid cells and activated reticulum cells. The follicles showed hyperplasia and the walls of the blood vessels were edematous.)

The bone marrow, the spinal cord and the brains could not be examined.

## DISCUSSION

There have been a few reports of megaloblastic anemia in animals<sup>7,8,12</sup>. In those reports, almost of them were related to the anemia produced experimentally by the feeding of a special diet. SCHALM reported a case of megaloblastic anemia which occurred naturally in the dog. However, erythrocyte morphology in that case indicated a normocytic normochromic anemia, so he thought that the anemia was not ascribed to the lack of vitamins or iron but rather to the toxic depression of erythropoiesis.

WILLS & STEWART reported that they produced a megaloblastic macrocytic anemia in rhesus monkeys by deficient diet. SUNDBERG et al. succeeded to produce the anemia in monkeys by feeding milk diets, low in folic acid, and deficient in ascorbic acid.

In the present case, clinical signs of general weakness, diarrhea and pale mucous membranes, and macrocytic megaloblastic anemia with neutropenia were the characteristic findings. These clinical and hematological findings are entirely like that seen in the megaloblastic anemia of man<sup>13</sup>). The megaloblastic cells with nuclear chromatin of mesh-like structure and with abundant cytoplasm are also similar to the megaloblasts observed by DOWNEY, SUNDBERG et al. and WINTROBE.

By the treatment with cyanocobalamine, the megaloblastic cells disappeared in a few days and instead normoblasts appeared on the blood films. These findings suggest that the anemia observed in the present case might be produced by the deficiency of vitamin B<sub>12</sub>.

Another hematological interesting finding is the neutrophils with large and bizarre nuclei. These cells seem comparable to the prematurely segmented neutrophils seen in megaloblastic anemia in man and in the monkeys to be described by Sundberg et al.

The presence of DÖHLE bodies and toxic granules in the cytoplasm of the neutrophils of this case is not common in the findings of the human megaloblastic anemia. However, Sundberg et al. described that they found DÖHLE bodies in the neutrophils of some monkeys with megaloblastic anemia and the DÖHLE bodies were most prominent in the monkeys which received vitamin B<sub>12</sub> therapy.

In general, the histopathological changes of pernicious anemia in human are found chiefly in the bone marrow, the central nervous system and alimentary tracts. Especially, severe atrophy of the mucosal membrane was found in the stomach<sup>1,3,13</sup>). In the present case though the bone marrow and the central nervous system were not examined, the atrophy of the mucosal membrane of the stomach was found. However, the most striking histopathological findings of this case were the edematous induration in the liver and subacute catarrhal enteritis. These findings were uncommon in pernicious anemia in human.

On the other hand, it is known that the megaloblastic anemia in human occurs also in malabsorption syndrom and liver cirrhosis<sup>5,9,13</sup>).

UKYO described that the disturbance of vitamin B<sub>12</sub> metabolism was observed in the patients of liver cirrhosis. From the above findings, it may be considered that the present case is not pernicious anemia but rather the megaloblastic anemia which is due to the disturbance of vitamin B<sub>12</sub> metabolism in the liver

or the disturbance of its absorption from the intestines, or both of them.

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## EXPLANATION OF PLATE

### PLATE

- Fig. 1 A nucleated red cell of type I; mesh-like chromatin and abundant cytoplasm characteristic  
Giemsa stain × 1,000
- Fig. 2 A nucleated red cell of type I with kidney-shaped nucleus  
Giemsa stain × 1,000
- Fig. 3 A nucleated red cell of type II; coarser chromatin and smaller nucleus than those of type I  
Giemsa stain × 1,000
- Fig. 4 A nucleated red cell of type III; like a normoblast, but more abundant cytoplasm  
Giemsa stain × 1,000
- Fig. 5 A nucleated red cell with eccentric nucleus in the peripheral blood on May 10  
Giemsa stain × 1,000
- Fig. 6 A large bizarre neutrophil with toxic granules, Döhle bodies and vacuoles in the cytoplasm  
Giemsa stain × 1,000
- Fig. 7 A neutrophil and a nucleated red cell before vitamin B<sub>12</sub> treatment  
Giemsa stain × 1,000
- Fig. 8 A neutrophil and a nucleated red cell after vitamin B<sub>12</sub> treatment  
Giemsa stain × 1,000
- Fig. 9 Hydropic and granular degeneration of the liver parenchymal cells  
H. E. × 400
- Fig. 10 Focal edematous induration in the periportal area of the liver  
Sero-fibrinous exudation was conspicuous and fibroblastic elements showed proliferation.  
H. E. × 100
- Fig. 11 Subacute catarrhal enteritis  
H. E. × 100



