Hematological and Clinico-biochemical Characteristics of Leukemia in Fischer 344 Rats

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Seventy-one male and 52 female F 344 rats with leukemia used as controls in the 30-month inhalation studies were characterized by hematological and clinico-biochemical findings. Hematological findings revealed that the leukocyte count, mean corpuscular volume, and mean corpuscular hemoglobin increased in both sexes of leukemic rats showing profound anemia, while the platelet count, erythrocyte count, hematocrit, and hemoglobin concentration decreased. In these rats, the serum levels of low density lipoprotein, free cholesterol, total bilirubin, blood urea nitrogen, and triglyceride and the activities of glutamic oxalacetic trans aminase, glutamic pyruvic transaminase, creatine phosphokinase, alkaline phosphatase, and lactate dehydrogenase increased markedly and the level of high density lipoprotein, the oxygen partial pressure, and the cholinesterase activity decreased. Clinical signs such as decrease in redness of the eyes, decrease in body weight, abdominal distension, staining of the public region, and debility were seen in most leukemic animals. These clinical signs and hematological and clinico-biochemical findings may be helpful in diagnosis of leukemia in long-term experiments. —KEY WORDS: clinical biochemistry, Fischer 344 rats, hematology, leukemia, spontaneous neoplasm

Fischer 344 (F 344) rats have been widely used for toxicological and/or carcinogenic studies since the National Cancer Institute (U. S. A.) laid down guidelines recommending their use for such purposes [3]. Therefore, there are many reports on spontaneous neoplasms in these rats [1, 2, 4, 10–13]. Leukemia of F 344 rats, first reported by Moloney [12] and named large granular lymphocytic leukemia (LGL) or mononuclear cell leukemia, is thought to originate spontaneously in the spleen at high incidence in this strain. The incidence of leukemia in aged F 344 rats is usually noted to be about 20%, and was reported by Maekawa to be 8–28% in males and 10–36% in females [10]. The incidence of leukemia in control animals of this strain in 30-month inhalation studies in our laboratory [6–8, 16, 18], was 24.3% in males and 24.0% in females [19]. However, in spite of the high incidence of spontaneous tumors, there are

few reports concerning the hematological and clinico-biochemical features of these leukemic rats [5, 14, 15].

In 30-month inhalation studies carried out under specific pathogen-free conditions, we obtained data on the blood of 235 males and 234 females of over 78 weeks old of which 71 males and 52 females were diagnosed as having leukemia by histopathological examinations. In this paper, we present the hematological and clinico-biochemical characteristics of leukemia in F 344 rats.

Materials and Methods

Animals, diets, and housing conditions: The specific pathogen-free F 344/Jcl rats used for 30-month inhalation studies on the effects of diesel exhaust were obtained from CLEA Japan, Inc. During the experiment, the rats were housed six to a stainless-steel cage (28 ×

18×40 cm) in inhalation chambers which were maintained in an air-conditioned room (23±2 °C, 55±10% relative humidity), with artificial lighting from 7 AM to 7 PM. The animals were provided with sterilized food (CE-2, CLEA Japan, Inc.) and tap water from an automatic water system *ad libitum*. They were acclimatized to these conditions for a week and used at 5 weeks old. Body weights were recorded periodically throughout the experiment [7].

The environment in the barrier was strictly controlled from the microbiological standpoint to protect the animals from infections and other diseases [6, 17]. Test for air-borne bacteria and 7 kinds of specific pathogens (Sendai virus, *Mycoplasma pulmonis*, Tyzzer's organism, *Corynebacterium kutscheri*, *Salmonella typhimurium*, Mouse hepatitis virus, and Mouse adenovirus) were made every six months.

Hematology and clinical biochemistry : In this 30-month inhalation study both carcinogenicity and chronic toxicity were examined. For examination of chronic toxicity, several male and female rats were sacrificed after 6, 12, 18, and 24 months, respectively, and all rats that survived until the end of the experiment were also examined. Forty-five hematological and clinico-biochemical parameters were examined in all rats. During the experiment, rats that showed clinical abnormalities, such as decrease in redness of the eyes, decrease in body weight, abdominal distension, staining of the pubic region, or debility were killed and promptly examined.

Before sacrifice, the rats were starved overnight, and then anesthetized with ether and blood was drawn from the abdominal aorta into a heparinized syringe. Part of the sample was used for measurement of blood gases and the remainder was centrifuged to separate the plasma. For hematological analyses, part of the blood sample was supplemented with EDTA-2K and stored in a capillary whole blood collector. The rest of the blood sample was centrifuged to separate the serum. Measurements were carried out with a TBA-380 biochemical analyzer, an ELT-8 hematology cell counter, a Corning 158 pH/blood gas analyzer, a Jookoo Na-K analyzer and chloride meter, an Atago refractometer, and a Helena auto-scanner flurvis and quick quant III. The parameters measured were: the activities

of glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), alkaline phosphatase (ALP), amylase (AMY), cholinesterase (ChE), and leucine aminopeptidase (LAP) and blood urea nitrogen (BUN), creatinine (Cr), total bilirubin (TBil), glucose (Glu), triglyceride (TG), total cholesterol (TCHO), free cholesterol (FCHO), low density lipoprotein (LDL), high density lipoprotein (HDL), phospholipid (PL), calcium (Ca), magnesium (Mg), inorganic phosphorus (IP), sodium (Na), potassium (K), chlorine (Cl), total protein (TP), albumin (Alb), α_1 -globulin (α_1 -G), α_2 -globulin (α_2 -G), α_3 -globulin (α_3 -G), β -globulin (β -G), γ -globulin (γ -G), the erythrocyte count (RBC), leukocyte count (WBC), platelet count (PLT), hematocrit (Ht), hemoglobin concentration (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), arterial blood pH (pHa), carbon dioxide partial pressure (PaCO₂), oxygen partial pressure (PaO₂), bicarbonate (HCO₃⁻), the anion gap (A. G.) and body weight at exsanguination (B. W.). The anion gap was calculated as: (sodium + potassium) - (chlorine + bicarbonate). Further, details of measurements are given elsewhere [6, 8].

After autopsy, representative samples were fixed in 10% buffered formalin solution for several days. Several slices were routinely cut from fixed organs and lesions, embedded in paraffin, sectioned at 4 μ m thickness and stained with hematoxylin and eosin. All histopathological examinations were performed by Dr. Yuki Takaki, and Dr. Noriyuki Kuwabara, at the Department of Pathology (I), Juntendo University School of Medicine [19].

Criterion ranges of hematological and clinico-biochemical values : The ranges of many hematological and clinico-biochemical values change markedly with age in rats [8], so it is not possible to judge whether values obtained in aged rats are normal or abnormal from the normal ranges in rats of all ages. Therefore, sera were obtained from leukemic rats of 78 weeks old or more were classified by age into three groups (78~97, 98~117, and 118~136 weeks old). The criterion ranges of parameters were taken as the means $\pm$ two standard deviations of values in the non-

Table 1. Criterional ranges of hematological parameters^a

Parameter	Sex	Age (weeks)		
		78~97	98~117	118~136
WBC	M	2.8±1.8	5.0±4.3	6.5±9.1
(×10 ³ /μℓ)	F	1.4±1.2	2.2±1.4	4.5±11.2
RBC	M	9.5±2.9	9.8±2.9	7.0±5.7
(×10 ⁶ /μℓ)	F	8.3±0.7	8.0±0.9	7.1±3.7
Hb	M	16.5±4.0	16.9±5.4	12.7±8.8
(g/dℓ)	F	15.1±1.0	15.0±1.2	13.0±5.3
Ht	M	63±17	63±18	49±36
(%)	F	57±6	55±4	49±22
MCV	M	65±9	64±9	68±26
(fℓ)	F	70±2	69±3	70±12
MCH	M	18±2	17±1	19±8
(pg)	F	18±1	19±1	19±5
MCHC	M	27±3	27±7	27±4
(%)	F	26±2	27±1	27±4
PLT	M	590±212	680±286	768±741
(×10 ³ /μℓ)	F	617±184	600±79	726±490

^a The ranges shown are the means±two standard deviations for non-leukemic rats: 78~97 weeks old: 47 males and 35 females, 98~117 weeks old: 30 males and 20 females, and 118~136 weeks old: 87 males and 127 females

Table 2. Criterional ranges of clinico-biochemical parameters^a (1)

Parameter	Sex	Age (weeks)		
		78~97	98~117	118~136
pHa	M	7.43±0.07	7.46±0.06	7.43±0.10
	F	7.44±0.05	7.47±0.06	7.44±0.09
PaCO ₂	M	32±6	34±8	34±16
(mmHg)	F	32±7	34±8	37±9
PaO ₂	M	100±19	103±19	97±31
(mmHg)	F	102±19	94±17	97±34
HCO ₃ ⁻	M	21±3	24±4	22±7
(mmol/ℓ)	F	22±4	25±4	24±6
A. G.	M	16±5	16±5	14±12
(mEq/ℓ)	F	16±6	17±6	17±9

^a The ranges shown were calculated as described for Table 1.

leukemic rats (47 males and 35 females of 78~97 weeks old, 30 males and 20 females of 98~117 weeks old, and 87 males and 127 females of 118~136 weeks old).

Results

Survival rates, body weights, and microbiological conditions: The survival rates of both sexes in experimental months 18 and 24 were about 95 and 80%, respectively, and the 50% survival indices of males and females were

similar. Subsequently, the survival rates decreased, being about 30% after 30 months. The body weights increased until 78 weeks in males and 96 weeks in females, and then decreased gradually. Air-borne bacteria in the barrier gave less than three colonies/plate/hour during the test period. Scarcely any air-borne bacteria were detected in the inhalation rooms with inhalation chambers, and serological tests showed that the animals remained pathogen-free throughout the experiment.

Incidences and clinical signs of leukemia:

Table 3. Criterional ranges of clinico-biochemical parameters^a (2)

Parameter	Sex	Age (weeks)		
		78~97	98~117	118~136
GOT	M	142±111	107±92	200±316
(IU/ℓ)	F	167±165	102±100	187±185
GPT	M	54±42	30±28	45±91
(IU/ℓ)	F	69±67	40±38	55±53
LDH	M	334±268	233±186	221±188
(IU/ℓ)	F	294±278	202±130	295±330
CPK	M	58±23	53±32	69±59
(IU/ℓ)	F	50±21	48±15	84±82
ALP	M	168±50	148±61	269±267
(IU/ℓ)	F	127±54	99±60	213±211
LAP	M	26±7	26±5	22±13
(IU/ℓ)	F	28±7	25±4	24±11
ChE	M	1,252±580	2,046±822	1,824±1,821
(IU/ℓ)	F	4,771±1,074	4,309±648	2,894±2,258
AMY	M	1,179±234	1,100±274	1,184±582
(U/dℓ)	F	1,136±334	1,240±346	1,407±1,044

^a The ranges shown were calculated as described for Table 1.

Table 4. Criterional ranges of clinico-biochemical parameters^a (3)

Parameter	Sex	Age (weeks)		
		78~97	98~117	118~136
BUN	M	16±5	16±5	27±21
(mg/dℓ)	F	15±4	13±3	18±16
Cr	M	0.7±0.2	0.7±0.2	0.9±0.6
(mg/dℓ)	F	0.7±0.1	0.7±0.1	0.8±0.2
TBil	M	0.3±0.2	0.3±0.2	0.4±0.3
(mg/dℓ)	F	0.2±0.1	0.2±0.1	0.4±0.3
Glu	M	182±45	168±40	146±94
(mg/dℓ)	F	176±57	176±44	152±79
Ca	M	10±1	11±1	11±3
(mg/dℓ)	F	10±1	11±1	11±2
Mg	M	2.5±0.4	2.4±0.4	3.0±1.1
(mg/dℓ)	F	2.6±0.8	2.4±0.9	2.8±1.2
IP	M	5±2	4±1	5±5
(mg/dℓ)	F	5±2	5±2	5±3
Na	M	144±3	145±3	141±8
(mEq/ℓ)	F	146±6	144±3	141±6
K	M	3.8±0.5	3.9±0.6	4.1±1.0
(mEq/ℓ)	F	3.5±0.5	3.5±0.5	3.6±0.9
Cl	M	111±6	108±4	107±10
(mEq/ℓ)	F	110±6	106±4	105±7

^a The ranges shown were calculated as described for Table 1.

Leukemia was the most frequent malignant tumor, its incidence being 24.3% in males and 24.0% in females of all ages in 30-month inhalation studies and 30.2% in the cases in

males and 22.2% of those in females were diagnosed from blood date. The numbers of leukemic rats diagnosed from blood data in the three age groups were as follows; 78~97

Table 5. Criterional ranges of clinico-biochemical parameters^a (4)

Parameter	Sex	Age (weeks)		
		78~97	98~117	118~136
TG	M	57±36	55±28	201±199
(mg/dℓ)	F	56±29	74±53	228±225
TCHO	M	75±34	88±61	110±108
(mg/dℓ)	F	110±34	135±62	169±141
FCHO	M	15±12	21±19	37±34
(mg/dℓ)	F	26±12	33±24	50±48
LDL	M	27±15	31±16	63±60
(mg/dℓ)	F	22±11	27±18	97±95
HDL	M	68±29	71±51	72±70
(mg/dℓ)	F	109±44	128±52	131±128
PL	M	132±50	164±94	224±215
(mg/dℓ)	F	226±70	296±130	356±266

^a The ranges shown were calculated as described for Table 1.

Table 6. Criterional ranges of clinico-biochemical parameters^a (5)

Parameter	Sex	Age (weeks)		
		78~97	98~117	118~136
TP	M	6.0±0.6	6.1±0.6	5.8±1.4
(g/dℓ)	F	7.0±1.0	7.2±0.8	6.9±2.0
Alb	M	52±11	49±9	39±16
(%)	F	55±6	48±15	42±16
α ₁ -G	M	19±9	19±5	23±14
(%)	F	18±7	22±16	24±15
α ₂ -G	M	3±1	5±2	5±3
(%)	F	3±1	5±3	6±4
α ₃ -G	M	4±2	4±1	4±2
(%)	F	4±1	4±2	4±2
β-G	M	18±5	19±4	20±8
(%)	F	15±3	15±3	16±7
γ-G	M	6±4	8±4	11±7
(%)	F	7±3	8±4	8±5
B. W.	M	212±58	365±48	303±87
(g)	F	224±56	242±42	250±68

^a The ranges shown were calculated as described for Table 1.

weeks old : 6 males and 8 females ; 98~117 weeks old : 17 males and 10 females, and 118~136 weeks old : 48 males and 34 females.

Decrease in redness of the eyes, decrease in body weight, abdominal distension, staining of the pubic region, and debility were observed in 75%, 70%, 66%, 32%, and 62% of 71 males with leukemia and in 65%, 49%, 69%, 18%, and 53% of 52 females with leukemia. The serum was deep yellow in 55% of the males and 41% of the females.

Hematological and clinico-biochemical findings : The criterional ranges of the 45 parameters are shown in Tables 1-6. Fig. 1 show the frequency distributions of LDL values of the males and Hb values of the females with leukemia in three age groups. The proportions of animals deviated from the criterional range of each parameters in these rats are summarized in Fig. 2. Of the males with leukemia increased values were observed for LDL in 77% (Fig. 1), the WBC in 73%, FCHO in 63%, ALP

Fig. 1. Frequency distributions of LDL values of the males (left) and Hb values of the females (right) with leukemia in three age groups $\square$: criterional ranges LDL; 78~97: 27 ± 15 (mg/dl) 98~117: 31 ± 16 (mg/dl) 118~136: 63 ± 60 (mg/dl) Hb; 78~97: 15.1 ± 1.0 (g/dl) 98~117: 15.0 ± 1.2 (g/dl) 118~136: 13.0 ± 5.3 (g/dl)

in 56%, GOT in 56%, TBil in 55%, CPK in 46%, LDH in 48%, the MCV in 44%, BUN in 42%, the MCHC in 41%, and TG in 41%, and decreased values for the Ht in 45%, the RBC in 44%, ChE in 41%, and Hb in 42%. No definite change in LAP was observed.

On the females, increased values were observed for the WBC in 76%, TBil in 71%, LDL in 65%, the MCH in 65%, GOT in 65%, LDH in 61%, CPK in 61%, FCHO in 59%, the MCV in 53%, and ALP in 50%, and decreased values for Hb in 73% (Fig. 1), the RBC in 65%, the Ht in 61%, the PLT in 53%, ChE in 51%, and HDL in 43%. No marked differences were observed in the values for other parameters in leukemic and non-leukemic rats.

Discussion

There are many histological reports on naturally occurring neoplastic and non-neoplastic lesions in F 344 rats, but few on the hematological and clinico-biochemical features of F 344 rats with leukemia. Clinical signs, such as decrease in redness of the eyes, decrease in body weight, abdominal distension, staining of the pubic region, debility, and deep yellow serum were observed in most leukemic animals. These signs may be due to anemia, hypertrophy of the spleen, urobilinogen in the urine, and

bilirubin in the serum, respectively. Splenomegaly or hepatosplenomegaly was also observed in leukemic rats. Enlargement of the lymph nodes was not prominent, although systemic enlargement of the lymph nodes was detected in a few cases. Histologically, infiltration of leukemic cells into the spleen or liver was seen, and some cases also showed cellular infiltration into the lymph nodes, lungs, bone marrow, gastrointestinal tracts, kidneys, adrenal glands, and brain. Infiltration of leukemic cells into the liver was occasionally found, even when splenomegaly was not seen [19].

In both sexes, the hematological and clinico-biochemical characteristics of leukemia were increases in the leukocyte count, total bilirubin, low density lipoprotein, free cholesterol, glutamic oxalacetic transaminase, mean corpuscular hemoglobin, alkaline phosphatase, the mean corpuscular volume, lactate dehydrogenase, creatine phosphokinase, blood urea nitrogen, triglyceride, and glutamic pyruvic transaminase, and decreases in the erythrocyte count, hemoglobin concentration, hematocrit, platelet count, cholinesterase, high density lipoprotein, and oxygen partial pressure. Of the animals sacrificed during the experiment because they showed abnormalities, 70% of the males and 80% of the females were diagnosed

Fig. 2. Proportions of leukemic rats of both sexes with values deviating from the criterional ranges (males: left, females: right) ▨ : increase ▤ : decrease □ : within criterional range ■ : not determined

to have leukemia because of deviations of more than 10 parameters from the criterional ranges. However, the early stage of leukemia could not be diagnosed in this way. Hematological studies revealed that leukemic rats were markedly anemic compared with non-leukemic rats and that anemia correlated well with the clinical sign of decrease in redness of the eyes. Increased serum levels of low

density lipoprotein, free cholesterol, glutamic oxalacetic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase and alkaline phosphatase and reduced levels of high density lipoprotein and cholinesterase indicated both hepatocellular injury and cholestasis [5]. Increased levels of total bilirubin, blood urea nitrogen, and creatine phosphokinase suggested hemolysis, reduction of kidney func-

tion, and injury of the heart, respectively. A reduced oxygen partial pressure might reflect general debilitation.

Stromberg *et al.* [14, 15] reported in depth the hematological and clinico-biochemical deviations from the normal found in the leukemic F 344 rats. These papers, however, did not break down the results into males vs. females or specifically defined age groups.

Most of the rats in this study had several tumors [19], so the results obtained may not exactly reflect the leukemic state. However, in long-term experiments, multiple primary tumors in various organs, such as the pituitary gland, mammary gland, and adrenal gland in individual rats were relatively common. Therefore, in practice, these clinical signs and hematological and clinico-biochemical findings may be helpful in diagnosis of leukemia in long-term experiments.

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白血病 Fischer 344 ラットの血液学的・ 臨床生化学的特徴

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F 344 ラットを用いた長期吸入実験（30ヵ月）において、実験対照群の中で白血病と診断された雄71匹、雌52匹の血液学的・臨床生化学的値を非白血病ラットのそれと比較した。その結果、白血病ラットは非白血病ラットに比べ、赤血球、ヘモグロビン、ヘマトクリット、血小板が減少し重度の貧血を示したが、白血球、平均赤血球容積、平均赤血球色素量は増加した。さらに、血清中の低比重リポタンパク、遊離コレステロール、総ビリルビン、尿素窒素、トリグリセリドおよび GOT, GPT, クレ

アチンホスフォキナーゼ、アルカリ性ホスファターゼ、乳酸脱水素酵素活性などの高値と高比重リポタンパク、酸素分圧、コリンエステラーゼ活性などの低値を示した。また、白血病ラットの臨床観察では、目の赤みの薄れ、体重減少、腹部の膨満、陰部の汚れおよび衰弱などがみられた。これら臨床観察および血液性状の特徴は、長期動物実験におけるラット白血病の診断に有効な判断基準になりうると考えられる。