Transplantable Mononuclear Cell Leukemia in F344 Rat with Particular Reference to Nodular Tumor Developing at the Transplant Site

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ABSTRACT. A transplantable mononuclear cell leukemia (MCL) was established from spontaneous MCL in an F344 rat. In this work, we paid special attention to a nodular tumor, named MCL-YSK, developed at the subcutaneous transplant site. MCL-YSK was serially passaged in subcutaneous tissue of syngeneic rats up to the 19th generation. Transplants from MCL-YSK grew into nodules 3 cm in diameter and 11.3 g in weight 9 weeks after subcutaneous implantation. Neoplastic cells forming the nodules had azurophilic cytoplasmic granules, which ultrastructurally appeared to be lysosomes. The cells reacted positively for acid phosphatase and nonspecific esterase, but not for alkaline phosphatase, alpha-1 antitrypsin and lysozyme, nor reacted with anti-rat monocyte/macrophage monoclonal antibody and anti-rat CD-8 monoclonal antibody. They possessed Fc-receptor. Leukemic cells first appeared in the peripheral blood 6 weeks after transplantation when subcutaneous nodules reached an average diameter of one cm. Subsequently, leukemic changes progressed in recipients as MCL-YSK grew larger. The recipients died during the period from 8 to 12 weeks after transplantation, showing anemia, depression, splenomegaly and lymph node enlargement. Diffuse or focal proliferation of sprinkled tumor cells was present in many organs. Hematologic changes suggestive of hemolytic anemia, elevated plasma enzymes and decreased drug-metabolizing enzymes, indicative of hepatic malfunction, were seen in transplant recipients. MCL-YSK was easily transplanted into athymic nude mice. The transplanted mice showed leukemic changes similar to those observed in rats with transplanted MCL-YSK.—KEY WORDS: F344 rat, leukemia, nodular tumor, transplantation.


Mononuclear cell leukemia (MCL), also known as Fischer rat leukemia, monocytic leukemia or large granular lymphocyte leukemia, has been reported to occur in 10 to 35% of aged F344 rats [13, 20, 21]. The leukemia is characterized by circulation of variable numbers of unusual mononuclear cells with azurophilic cytoplasmic granules. Main clinical signs of tumor-bearing rats include anemia, emaciation, icterus and palpably enlarged spleen, resulting in death at the average age of 24 months [10, 13, 20, 21, 23]. Leukemic cells morphologically resemble large granular lymphocytes (LGLs) of animals and humans [3, 6, 17, 20, 26], which have phenotypic and functional properties of both T cells and myelomonocytic cells, as well as cytotoxic activity [3, 17]. Neoplastic LGLs in F344 rats have been shown to be heterogeneous in their surface antigens [26], and their origin and lineage remain to be determined [3, 11].

MCL has been transplanted into syngeneic rats either by intraperitoneal, subcutaneous or intravenous inoculation of cells or by implantation of tissue fragments from leukemic rats [11, 16, 19, 24–26]. Recently, we established a transplantable tumor by subcutaneous implantation of rats with a piece of the enlarged spleen from a female F344 rat with spontaneous MCL. The transplant recipients developed nodular tumor at the implantation site, accompanied by the appearance of neoplastic cells in the peripheral blood. The subcutaneous tumor was serially passaged by subcutaneous implantation of rats, and designated MCL-YSK. Tumors developed in subcutaneous tissue provided a good opportunity for exploring syndromes associated with tumor progression, because tumor development could easily be followed from an early stage by external observations.

In the present studies, morphologic characteristics of neoplastic cells and clinicopathologic influence of MCL-YSK transplants on syngeneic rats and athymic nude mice were investigated. Because, there has been little attention focused upon the tumors developed at the implantation site, although such tumorous growths have been mentioned in F344 rats with transplanted MCL [25, 26].

MATERIALS AND METHODS

Animals and environment: Specific-pathogen-free male and female F344/DuCrj rats, either purchased
from Charles River Japan, Inc. (CRJ) or bred in the authors’ laboratory, were used. For heterotransplantation, athymic Crj: CD-1 (ICR)-nu/nu female nude mice were obtained from CRJ. The animals were housed in barrier rooms controlled at 23±2°C, and 50±20% relative humidity.

**Transplantation in syngeneic rats:** A 20-month-old female F344 rat subjecting to a life-span study became anemic and depressed and had the palpably enlarged spleen. Therefore, the rat was euthanized and autopsied. A small piece of her spleen was implanted into subcutaneous tissue of two syngeneic female rats. Nodular tumors developed at the transplant sites were minced into small pieces, < 2 mm in diameter, with scissors and then transplanted subcutaneously in the mid line of the interscapular region through a trochar with a diameter of 2 mm. The major (a) and minor axes (b) of tumors were measured in mm once weekly with calipers, and tumor volume was estimated by the following formula: \( a \times b^2 / 2 \). The tumor was serially transplanted using two to four male and female F344 rats, 10 to 20 weeks old, in each generation at 6- to 8-week intervals.

**Influence of MCL-YSK transplants on syngeneic rats or nude mice:** A total of 42 6-week-old male rats were used. Of these animals, 24 rats were allocated to the transplanted group and the remainder to the non-transplanted control group. Rats of the transplanted group were subcutaneously implanted with a piece of tumor from the 3rd generation of serial subcutaneous passage. At 2, 6 and 9 weeks after transplantation, 6 rats of each group were examined hematologically and blood biochemically, and a portion of their livers was used for measurement of drug-metabolizing enzyme activity. The remaining 6 rats of the transplanted group were observed until death. During the observation period, body-weight, daily food-intake and tumor growth were measured once weekly.

Nine 6-week-old female nude mice implanted subcutaneously with a piece of tumor from the 9th generation were observed for 8 weeks after transplantation. At the end of the observation period, their hemograms were compared with those of 6 age- and sex-matched control mice.

**Hematology:** Blood samples were obtained from the abdominal aorta of animals anesthetized with a mixture of alcohol, ether and chloroform. Red blood cell count (RBC), hemoglobin concentration (Hb), hematocrit value (Ht), white blood cell count (WBC), and platelet count (Pl) were determined in blood treated with ethylenediaminetetraacetic acid-2 potassium salt by a Microcell Counter (CC-180A, Toa Co., Ltd., Japan). Differential leukocyte counts were calculated by observing 200 WBC on May-Grünwald-Giemsa stained smears. Reticulocytes (Rl) were counted on blood smears stained with new methylene blue according to the Brecher method.

**Blood biochemistry:** Plasma was separated from heparinized blood and tested for following items using a Clinaalyzer (JCA-VX 1000, JEOLE Co., Ltd., Tokyo, Japan): glucose (Glu), total protein (TP), triglyceride (TGL), non-esterified fatty acid (NEFA), total bilirubin (T. Bil), glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactic acid dehydrogenase (LDH), creatine phosphokinase (CPK), calcium (Ca) and inorganic phosphate (IP). Potassium (K) and sodium (Na) were measured by a flame photometer (205D, Hitachi Co., Ltd., Tokyo, Japan).

**Drug-metabolizing enzyme activity:** Liver blocks were homogenized in 1.15% KCl and centrifuged at 10,000 × g for 15 min. Aminopyrine N-demethylase (AMD) and aniline hydroxylase (ANH) activities were determined as described previously [9, 14]. The protein measurement was done by the method described by Lowry et al. [12].

**Cytological markers:** Immunorosette formations for Fc- and C3-receptors were assayed using single cells prepared from MCL-YSK at passage 17 by the conventional methods [28].

**Light microscopy:** All animals which were euthanized or found dead during the experiments were autopsied completely. All organs and subcutaneous tumors were fixed in 10% neutral buffered formalin. They were embedded in paraffin, sectioned, and stained with hematoxylin and eosin (HE). Selected sections from the tumors were also stained with periodic acid-Schiff (PAS) with and without diastase digestion, Watanabe’s silver impregnation for reticulin, and azan-Mallory. Stamped samples from subcutaneous tumors were stained with May-Grünwald-Giemsa.

For the indirect immunoperoxidase method, paraffin-embedded sections from MCL-YSK at passage 3 were reacted with anti-rat monocyte/macrophage monoclonal antibody (MAB1435: Chemicon Internal Inc., CA) or anti-rat CD-8 monoclonal antibody (CD-8: Holland Biotechnology Inc., the Netherlands), and peroxidase-conjugated affinipurpure goat anti-mouse IgG, Fc fragment antibody (J-
son Immunoresearch Laboratory (JIL, PA) as secondary antibody; rabbit polyclonal antibodies against alpha-1 antitrypsin and lysozyme (Cambridge Research Laboratory, MA) were also applied to the sections, subsequently using peroxidase conjugated affinity goat anti-rabbit IgG (JIL) as secondary antibody. In these immunoperoxidase stainings, diaminobenzidine tetrahydrochloride was used as a substrate.

For enzymehistochemistry, frozen sections from fresh specimens of MCL-YSK at passages 3 and 17 were stained by the Gomori's method for acid phosphatase (ACP) (pH 5.0), by the alpha-naphthyl acetate method for nonspecific esterase (NSE) (pH 7.4), and by the naphthol AS method for alkaline phosphatase (ALP) (pH 9.0) as described [28].

Electron microscopy: Small blocks of subcutaneous tumors at passage 17 were fixed in 2.5% buffered glutaraldehyde for 2 hr and postfixed in 1% buffered osmium tetroxide for 1 hr. The blocks were embedded in epoxy resin. Thin sections were stained with uranyl acetate and lead citrate, and examined in a JEM-100B electron microscope at 80 kV.

Statistical analysis: Hematologic, blood biochemical and drug-metabolizing enzyme activity values were compared between the control and transplanted groups using the Student's t test.

RESULTS

Natural leukemia: Splenohepatomegaly was a striking gross finding in the rat with natural leukemia. Examination of peripheral blood smears revealed large numbers of mononuclear cells. The cells were 15–20 μm in diameter, and had a round, reniform nucleus and abundant cytoplasm localized to one side of the cell. The cytoplasm contained various numbers of azurophilic granules (Fig. 2). Leukemic cells diffusely infiltrated in many organs.

Serial transplantation of MCL-YSK in syngeneic rats: Two female rats, which had been implanted with a piece of the spleen from the rat with natural leukemia, became anemic and had palpable splenomegaly at postimplantation (PI)-week 8. A nodule measuring 0.7 cm in diameter was located at the implantation site of either rat when autopsied at PI-week 10. Many organs were severely infiltrated by leukemic cells. A portion of the subcutaneous nodule was implanted into subcutaneous tissue of 2nd generation rats. Thereafter, tumors developing in subcutaneous tissue were serially passaged in syngeneic rats until the 19th generation during a 2.2-year period. The tumor was successfully transplanted in both sexes at a 100%-positive rate in each generation. There was no marked difference in tumor growth between different passage levels from the 2nd generation onwards. The growth curve of MCL-YSK determined at the 3rd generation is shown in Fig. 1. Tumors could be palpated at PI-week 2, and progressively grew into nodules, 1 cm in diameter and 2.2 g in weight on the average at PI-week 6. At PI-week 9, they reached an average diameter of 3 cm, and weight of 11.3 g.

Characteristics of tumor cells constituting MCL-YSK: The subcutaneous tumors were well delineated and uniformly white in color (Fig. 3). The tumors consisted of mononuclear round and oval
cells arranged in a compact sheet (Fig. 4). Mitotic figures were frequently seen. Scant collagenic fibers were present among neoplastic cells, but no reticulin fibers were observed around the cells. These histologic findings were common to all nodules in different passages. Cells with azurophilic cytoplasmic granules were consistently seen on impression smears prepared from subcutaneous nodules. The cells reacted moderately to strongly for NSE (Fig. 5) and ACP, but not for ALP, alpha-1 antitrypsin and lysozyme, nor with MAB1435 (Fig. 6) and CD-8 (Fig. 7). They contained PAS-positive, diastase digestible material in their cytoplasm.

Ultrastructurally, neoplastic cells had an irregularly shaped, indented nucleus with clumped chromatin and a single nucleolus. The cytoplasm contained numerous free ribosomes or polysomes, a small number of mitochondria and scant rough-surfaced endoplasmic reticulum (Fig. 8). In most of neoplastic cells, there were variable numbers of electron-dense granules with lysosomal structures in association with the Golgi apparatus. β glycogen particles were scattered throughout the cytoplasm.

Fifteen % of neoplastic cells expressed rosette formation for Fe-receptor, whereas no positive rosette formation was seen for C3-receptor.

Influence of MCL-YSK transplants on syngeneic rats and athymic nude mice: No leukemic changes were detected in transplanted rats when killed at PI-week 2, despite the development of palpable tumor at the implantation site. Leukemic cells first appeared in the peripheral blood of one out of 6 rats and 4 out of 6 rats when killed at PI-week 6 and 9, respectively. In these animals, ratios of leukemic cells to the total leukocyte count ranged from 29 to 80%.

Transplant recipients developed clinicopathologic abnormalities in advanced stages of tumor growth, and died between PI-week 8 and 12. One to two weeks prior to death they revealed depression,
Fig. 6. A section of MCL-YSK showing neoplastic cells which react negatively to anti-rat monocyte/macrophage monoclonal antibody (MAB1435). Infiltrating macrophages give a positive reaction (arrow) to MAB1435. Indirect immunoperoxidase method, counterstained with hematoxylin, ×250.

Fig. 7. A section of MCL-YSK showing neoplastic cells which react negatively for anti-rat CD-8 monoclonal antibody (CD-8). One infiltrating T lymphocyte positive to CD-8 is present (arrow). Indirect immunoperoxidase method, counterstained with hematoxylin, ×450.

Fig. 8. Electron micrograph of neoplastic cells constituting MCL-YSK. The cells have irregularly shaped indented nuclei, numerous free ribosomes and varying numbers of characteristic small granules in their cytoplasm. ×4,000.

anemia, dyspnea and palpably enlarged spleen. Simultaneously, they showed a decrease in body weight and food consumption.

Hematologic findings are shown in Table 1. Values of RBC, Hb, Ht and Pl in the transplanted group were significantly lower at PI-week 9 than those in the control. The numbers of WBC and Rt in the transplanted group showed a tendency to increase at PI-week 6 and 9. Anisocytosis, polychromatocytosis and poikilocytosis were often seen in rats with hematologic abnormalities.

Blood biochemically, plasma levels of Glu and TP of the transplanted group were significantly decreased at PI-week 9, contrarily, those of NEFA, TGL, T. Bil, GOT, GPT, LDH, CPK, Ca, IP, Na and K in the transplanted group showed a significant elevation or a tendency to increase at PI-week 6 or 9 (Table 2). In rats killed at PI-week 9, AMD tended to decrease and ANH was significantly lower compared with controls (Table 3).

A splenohepatomegaly was a consistent finding in transplanted rats with advanced leukemic changes. Marked enlargement was observed in the axillary (Fig. 3), mesenteric and bronchial lymph nodes. Neoplastic cells infiltrated to varying extents into many organs or tissues from rats killed at PI-week 6 and 9, or died during the course of observation. Hepatocellular degeneration and necrosis, fatty change of adrenal cortical cells, and petechiae in the lungs and brain were frequent findings in dead animals. Erythroagocytosis by neoplastic cells was often observed in the liver and spleen.

All nude mice, which were implanted with a piece of MCL-YSK, developed nodular growth at the subcutaneous transplant site (Fig. 1). Tumors reached an average diameter of 1.2 cm and weight of
Table 1. Hematologic findings in the control and MCL-YSK-transplanted rats

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>No.</th>
<th>RBC* (10^6/mm^3)</th>
<th>Hb (g/dl)</th>
<th>Ht(%)</th>
<th>WBC(10^3/mm^3)</th>
<th>Pt(10^3/mm^3)</th>
<th>Rt(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Control</td>
<td>6</td>
<td>919±323</td>
<td>15.7±0.5</td>
<td>45.0±1.4</td>
<td>61±15</td>
<td>68.6±2.9</td>
<td>15±5</td>
</tr>
<tr>
<td>Transplanted</td>
<td>6</td>
<td>836±188</td>
<td>14.4±3.0</td>
<td>42.0±6.5</td>
<td>191±343</td>
<td>51.7±22.4</td>
<td>42±48</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Control</td>
<td>6</td>
<td>1000±20</td>
<td>15.4±0.3</td>
<td>45.5±1.3</td>
<td>52±7</td>
<td>64.6±10.2</td>
<td>18±4</td>
</tr>
<tr>
<td>Transplanted</td>
<td>6</td>
<td>684±266*</td>
<td>11.8±3.0*</td>
<td>37.2±7.3*</td>
<td>439±430</td>
<td>30.8±22.8**</td>
<td>125±140</td>
<td></td>
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</table>

a) See abbreviations in “Materials and Methods”.
b) Mean±standard deviation.
Significant difference from control, *, P<0.05; **, P<0.01.

Table 2. Blood biochemical findings in the control and MCL-YSK-transplanted rats

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>No.</th>
<th>Glu* (mg/dl)</th>
<th>TP (g/dl)</th>
<th>NEFA (μEq/l)</th>
<th>TGL (mg/dl)</th>
<th>T.Bil (mg/dl)</th>
<th>GOT (IU/l)</th>
<th>GPT (IU/l)</th>
<th>LDH (IU/l)</th>
<th>CPK (IU/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Control</td>
<td>6</td>
<td>197±128</td>
<td>6.36±0.13</td>
<td>584±63</td>
<td>67.1±14.3</td>
<td>0.05±0.01</td>
<td>71.7±8.1</td>
<td>38.5±3.2</td>
<td>107±31</td>
<td>147±27</td>
</tr>
<tr>
<td>Transplanted</td>
<td>6</td>
<td>183±48</td>
<td>6.48±0.14</td>
<td>687±74*</td>
<td>88.2±18.8</td>
<td>0.10±0.07</td>
<td>185.2±241</td>
<td>88.0±98.6</td>
<td>1030±1945</td>
<td>227±138</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Control</td>
<td>6</td>
<td>213±33</td>
<td>6.57±0.19</td>
<td>603±61</td>
<td>97.0±15.6</td>
<td>0.14±0.04</td>
<td>69.2±10.3</td>
<td>45.3±7.2</td>
<td>114±56</td>
<td>114±21</td>
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<tr>
<td>Transplanted</td>
<td>6</td>
<td>152±57*</td>
<td>6.15±0.20**</td>
<td>918±111***</td>
<td>186.0±113.0</td>
<td>0.34±0.15</td>
<td>225.2±183.0</td>
<td>116.7±103.4</td>
<td>1238±1081*</td>
<td>234±108*</td>
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a) See abbreviations in “Materials and Methods”.
b) Mean±standard deviation.
Significant difference from control, *, P<0.05; **, P<0.01; *** P<0.001.

Table 3. Liver drug-metabolizing enzyme activity in the control and MCL-YSK-transplanted rats

<table>
<thead>
<tr>
<th>Week</th>
<th>Group</th>
<th>No.</th>
<th>AMD* (nmol/mg protein/min)</th>
<th>ANH (nmol/mg protein/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Control</td>
<td>6</td>
<td>1.91±0.108*</td>
<td>0.181±0.031</td>
</tr>
<tr>
<td>Transplanted</td>
<td>6</td>
<td>2.11±0.408</td>
<td>0.187±0.035</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Control</td>
<td>6</td>
<td>1.89±0.189</td>
<td>0.145±0.022</td>
</tr>
<tr>
<td>Transplanted</td>
<td>6</td>
<td>1.492±0.417</td>
<td>0.099±0.034</td>
<td></td>
</tr>
</tbody>
</table>

a) See abbreviations in “Materials and Methods”.
b) Mean±standard deviation.
Significant difference from control, *, P<0.05.

2.9 g at PI-week 8. Ratios of leukemic cells to the total leukocyte count in the peripheral blood ranged from 2 to 13%. Hemogram from the transplanted mice revealed a tendency to decrease in RBC, Hb and Ht, a significant decrease in Pt and a significant increase in WBC, compared with those of controls. Neoplastic cells were spread and proliferated in a variety of organs examined.

DISCUSSION

In the present study we established a transplantable nodular tumor (MCL-YSK) from spontaneous MCL in an F344 rat. When tumor tissues were implanted into syngeneic rats or athymic nude mice, transplants progressively grew into large, palpable nodules at the subcutaneous transplant site and
subsequently leukemia developed in transplant recipients. Neoplastic cells forming MCL-YSK had azurophilic cytoplasmic granules and reacted positively for NSE and ACP but not for ALP. Fifteen % of the cells possessed Fc-fragment of IgG. These cytological characteristics agreed with those of peripheral leukemic cells previously reported on spontaneous MCL, although expression of ACP and NSE has been mentioned to be variable [10, 20, 23, 26].

LGLs are defined as a population of mononuclear cells with azurophilic cytoplasmic granules, and characterized ultrastructurally by the abundant cytoplasm, irregular cell surfaces, indented nuclei, and unit membrane-bound lysosome-like granules [3, 6, 20]. Neoplastic cells of MCL-YSK appeared similar in many aspects to LGLs described in spontaneous MCL of F344 rats [20, 26], with the exception that β-glycogen particles, apparently corresponding to PAS-positive, diastase-digestible material seen in stained preparations, were present in MCL-YSK cells. Whether LGLs are derived from T cells or from myelomonocytic lineage still remains unclear [3, 11]. Positive reactions for lysosomal enzymes such as ACP and NSE suggest that MCL-YSK cells may be derived from the mononuclear phagocyte system. However, such monocytic markers as demonstrable by stainings for alpha-1 antitrypsin, lysozyme and MAB1435 were negative. MCL-YSK cells failed to react with CD-8, whereas neoplastic LGLs in F344 rats have been reported to give a positive reaction to CD-8 (OX-8 antibody) specific for cytotoxic/suppressor T lymphocytes [11, 16, 26].

The heterogeneity in immunophenotype and cytotoxic activity has been reported in neoplastic LGLs of F344 rats [26]. Enzymehistochemical staining patterns have also been described to be variable among cases of leukemia or lymphocytosis of LGLs in humans [1–3, 8, 15], rats [20, 26], dogs [27], cat [4], and horse [5]; LGLs in human and feline cases reacted strongly for ACP but were negative in dog cases; a positive reaction for NSE was observed in human and dog cases but not in feline and horse cases; ALP activity was not reported in rat cases, whereas it was detected in one of dog cases. Additional histochemical and functional studies are needed to clarify the origin of neoplastic cells of MCL-YSK, although LGL tumors in F344 rats have been reported to represent a heterogeneous group of leukemias [26].

It is obvious from the present observations that MCL-YSK caused leukemia in transplant recipients due to neoplastic cells spread from tumorous growth at the implantation site. Hematologic, blood biochemical and pathologic abnormalities observed in MCL-YSK-transplanted rats were similar generally to those described in rats with spontaneous MCL or in rats with experimentally induced MCL [10, 16, 21–24, 26]. Standard deviations were rather highly fluctuated in rats with MCL-YSK, probably depending on the degree of tumor cell growth. An increase in the number of circulating leukemic cells caused a decrease in RBC, Ht, Hb and Pl, an increase in Rt, and morphologic alteration of erythrocytes, suggesting hemolytic anemia, as postulated by previous workers [10, 21, 23]. A decrease in Glu and TP, and an increase in NEFA, TGL, Ca, IP, Na and K may be associated with hepatic and renal failures due to neoplastic cell infiltration or with electrolyte-imbalance possibly resulting from hemolytic anemia. A marked increase in liver-related enzymes such as GOT, GPT, LDH and CPK as well as a decrease in AMD and ANH suggest hepatic malfunction in rats with MCL-YSK. Recently, Harada et al. reported the presence of difference in development of altered hepatocellular foci between spontaneous MCL-a affected and non-affected F344 rats [7]. A hepatic malfunction as suggested by the present study may have resulted from hepatic damage.

Hyperbilirubinemia was a consistent finding in rats with advanced spontaneous MCL and related with clinical jaundice [10, 22]. However, plasma level of total bilirubin (0.24±0.15 mg/dl) in rats with MCL-YSK, that were killed at PI-week 9, was much lower than that of rats with spontaneous MCL (more than 1.16 mg/dl [22]), and icterus was not observed even in dead animals bearing MCL-YSK. Myelofibrosis and medullary osteosclerosis or reduced bone formation accompanied with a decrease in serum Ca and IP, which have been observed in rats with spontaneous MCL [21] or in rats injected intraperitoneally with neoplastic LGLs [18], were not seen in rats with MCL-YSK. The pathogenesis of these MCL-associated disorders remains unanswered.

Athymic nude mice with transplanted MCL-YSK manifested hematologic and pathologic conditions similar to those observed in syngeneic rats with MCL-YSK. However, the degree of these abnormal findings in the mice was appreciably lower than in rats, apparently relating to the difference in the
observation period and heterotransplantation. This may be the first attempt at transplantation of MCL into nude mice.

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REFERENCES


