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Case Report

Spontaneous Malignant T Cell Lymphoma in a Young Male Common Marmoset (*Callithrix jacchus*)

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Abstract: We histopathologically and immunohistochemically investigated a case of malignant lymphoma that spontaneously developed in a male common marmoset at two years of age. Beginning at two years four months of age, the animal had an enlargement of the submandibular and inguinal lymph nodes, small subcutaneous nodules near the right breast and an approximately fivefold increase in peripheral lymphocyte count compared with the previous examination value. The postmortem findings at two years eight months of age showed lymphadenopathy with enlargement of the thymus and spleen. Small- to intermediate-sized neoplastic lymphocytes had diffusely proliferated in the enlarged nodes. The neoplastic cells were pleomorphic and had irregularly shaped nuclei. The nuclear chromatin staining revealed hyperchromatism in the small-sized cells, and the intermediate-sized cells exhibited vesicular staining. An immunohistochemical examination indicated that the neoplastic lymphocytes were positive for CD3 and negative for CD20, thus suggesting that they had originated from T cells. In addition, the proliferation of high endothelial venules and reactive epithelioid histiocytes was observed. Scattered tingible body-laden macrophages were infrequently detected. Neoplastic lymphocytes were also observed in the thymus, spleen, heart, lungs, liver, kidneys, adrenal glands and femoral and sternal bone marrow. This malignant lymphoma in a young male common marmoset was considered to fit the category of "peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)" according to the new WHO system of classification. (DOI: 10.1293/tox.26.301; J Toxicol Pathol 2013; 26: 301–307)

Key words: common marmoset, malignant lymphoma, WHO system of classification, T cell

Spontaneous lymphoma has been reported in nonhuman primates, such as anthropoid apes[1], gibbons[2–4], baboons[5–6], and macaques[7–14]. On the other hand, there have been a few of reports about lymphoma in "new world primates"[15–18].

It is well known that the oncogenesis of malignant lymphoma in humans and nonhuman primates is correlated with infection with retroviruses and herpesviruses. Simian immunodeficiency viruses (SIV) are a group of genetically related viruses belonging to the lentivirus subgroup of retroviruses. The reported incidence of non-Hodgkin's lymphoma (NHL) is between 4% and 15% in rhesus macaques (*Macaca mulatta*) and about 40% in cynomolgus macaques (*Macaca fascicularis*)[19–21]. SIV-infected subjects have a prolonged clinical disease course, and lymphomas are generally detected late. Most of the SIV-associated NHLs in rhesus and cynomolgus macaques are B-cell lymphomas[19, 22]. Simian T-cell leukemia virus (STLV), a type C retrovirus associated with leukemia/lymphoma in old world monkeys, is closely related to human T-cell leukemia virus type 1, the etiologic agent of adult T-cell leukemia/lymphoma (ATLL) in humans. Infection with the virus induced T-cell lymphoma/leukemia in baboons[5], and savanna monkeys (*Cercopithecus aethiops*)[12, 23, 24]. The gammaherpesvirus subfamily contains a number of important human and animal pathogens, and is subdivided into the lymphocryptovirus (γ1 herpesvirus) and rhadinovirus (γ2 herpesvirus) genera[25]. The γ1 herpesvirus genus contains Epstein-Barr virus (EBV) and the nonhuman primate lymphocryptoviruses. Experimental transmission of lymphocryptoviruses and rhadinoviruses to new world monkeys, cottontop tamarins (*Saguinus oedipus*)[26–30] and owl monkeys (*Aotus trivirgatus*)[30–32], resulted in malignant lymphoma.

The common marmoset, one of new world primates, has an average lifespan of nine to 13 years and a maximum life span of 22 years, and is the shortest-lived primate[33]. Due to its small size and its relatively easy adaptation to laboratory conditions, the monkey is increasingly used in many

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Table 1. Hematological Changes in a Male Common Marmoset Monkey

Blood sampling date	Age	WBC					RBC	HGB	HCT	RET	PLT
		Total ($\times10^2$ /μL)	Granulo* ($\times10^2$ /μL)	Lymph ($\times10^2$ /μL)	Mono ($\times10^2$ /μL)	Others ($\times10^2$ /μL)	($\times10^5$ /μL)	(g/dL)	(%)	($\times10^4$ /μL)	($\times10^4$ /μL)
Nov 17, 2009	1 y 9 m	78.3	19.5	53.0	2.5	2.6	667	13.9	44.3	23.04	44.9
Feb 25, 2010	2 y 0 m	90.9	27.9	57.8	1.9	2.6	583	12.3	40.4	20.94	61.4
Jun 22, 2010	2 y 4 m	368.9	33.8	308.2	2.4	12.5	504	11.0	37.9	38.73	30.2
Jul 6, 2010	2 y 5 m	298.2	25.5	254.5	1.5	8.9	498	10.8	37.7	35.62	28.2
Jul 21, 2010	2 y 5 m	319.5	35.4	262.4	1.5	10.9	435	9.3	32.8	28.58	23.9
Sep 17, 2010	2 y 7 m	241.9	26.0	200.9	2.9	4.2	425	10.3	35.8	43.66	17.3
Oct 21, 2010	2 y 8 m	159.8	22.5	131.2	1.5	1.6	480	12.2	40.2	45.14	14.7

* The number of granulocytes represents the total number of neutrophils and eosinophils.

fields of biomedical research, including fundamental biology, pharmacology and toxicology studies[34]. David *et al.* reported a review of necropsy records of 129 marmosets and 52 tamarins. Lymphosarcoma was observed in nine marmosets and one tamarin, suggesting that lymphoma is the most common neoplasm in both marmosets and tamarins[18]. However, the information about clinical, immunological, pathological and biological features of malignant lymphoma in the common marmoset is insufficient.

We had an opportunity to observe a 2-year-old male marmoset with spontaneous malignant lymphoma housed in our animal facility. This case report shows the hematological, histological and immunohistochemical aspects of this case of marmoset lymphoma.

A male common marmoset monkey was obtained from CLEA Japan, Inc. (Kawasaki, Japan) at the age of one year four months and was housed for acclimation in a steel cage (width 390 × depth 550 × height 700 mm; Shin Toyo Seisakusho Ltd., Saitama, Japan) with environmental enrichment, generally a roost, an aerial bar and a table tennis ball. The animal room was maintained at a temperature of 24–30°C with a relative humidity of 30−70%, an air exchange rate of 15 to 17 times/hr, a 12 hour light−dark cycle and free access to a commercial diet (CSM-1M, CLEA Japan, Inc.) and tap water. The marmoset was checked daily by cageside observation and underwent individual detailed clinical observation and body weight measurement weekly. The experiment and care of the marmoset were conducted in accordance with the Guiding Principles for "the Care and Use of Laboratory Animals of Kyowa Hakko Kirin, Co., Ltd.".

Hematological examination of peripheral blood collected from the femoral vein was performed using an automatic hematological analyzer (ADVIA 120: Siemens Medical Solutions Diagnostics). However, this system cannot clearly fractionate neutrophils and eosinophils in marmoset peripheral blood. Therefore, in this study, the number of both cell types was represented as the granulocyte number. In addition, blood smear slides with May-Grünwald Giemsa stain were also prepared at each blood sampling point.

The animal was euthanized by exsanguination under deep anesthesia with isoflurane (Mylan Inc. Canonsburg, USA) to prevent him from suffering and dissected for macroscopic observation. Organs and tissues including the macroscopically abnormal lymph nodes and nodules were fixed in 10% neutral buffered formalin and embedded in paraffin wax. Four to 6 μm thick sections were stained with hematoxylin and eosin (H&E), Giemsa and silver stain (Watanabe's method). Immunohistochemistry (IHC) was performed on paraffin-embedded tissue sections. Briefly, some of the sections were incubated with a primary antibody as a T-cell marker [Rabbit anti-human CD3 polyclonal antibody, DakoCytomation Denmark A/S, Denmark] or B-cell marker [Mouse anti-human CD20 monoclonal antibody, clone no. L26, Dako Denmark A/S, Denmark]. The antigen retrieval method used microwave treatment (500 W, 10 min) in citrate buffer at pH 6.0. Antigen/antibody complexes were visualized with a Dako EnVision+ System-HRP labeled polymer (Dako Denmark A/S, Denmark) and 3, 3-diaminobenzidine as a peroxidase substrate, and then counterstained with hematoxylin.

Enlargement of the submandibular and inguinal lymph nodes on both sides was noted in a male marmoset that was two years and four months old. The submandibular masses increased in size and number over time. Moreover, enlargement of the axillary lymph nodes and small subcutaneous nodules near the right breast were also observed.

In the hematological examination, a remarkable increase in the white blood cell counts, mainly in lymphocytes, was observed after finding the lymph node masses (Table 1). The lymphocyte counts increased about fivefold compared with the previous examination value at two years of age. The high lymphocyte counts continued for two months and then gradually diminished toward the end of the animal's life. The erythroid parameters (red blood cell counts, hemoglobin and hematocrit values) and platelet counts decreased over time. The reticulocyte counts also increased with time. In a morphological examination of smear cells, it was noted that the neoplastic lymphocytes were mainly small to intermediate in size. The small-sized neoplastic cells were slightly larger than the red blood cells and had normal to hyperchromatic nuclei (Fig. 1A). The intermediate-sized cells were about 1.5-fold (within 2-fold) the size of red blood cells, and had rough chromatin and azurophil granules in clear cytoplasm (Fig. 1B). There were only a few large (2-fold or greater in size compared with red blood cells) or irregularly shaped lymphocytes.

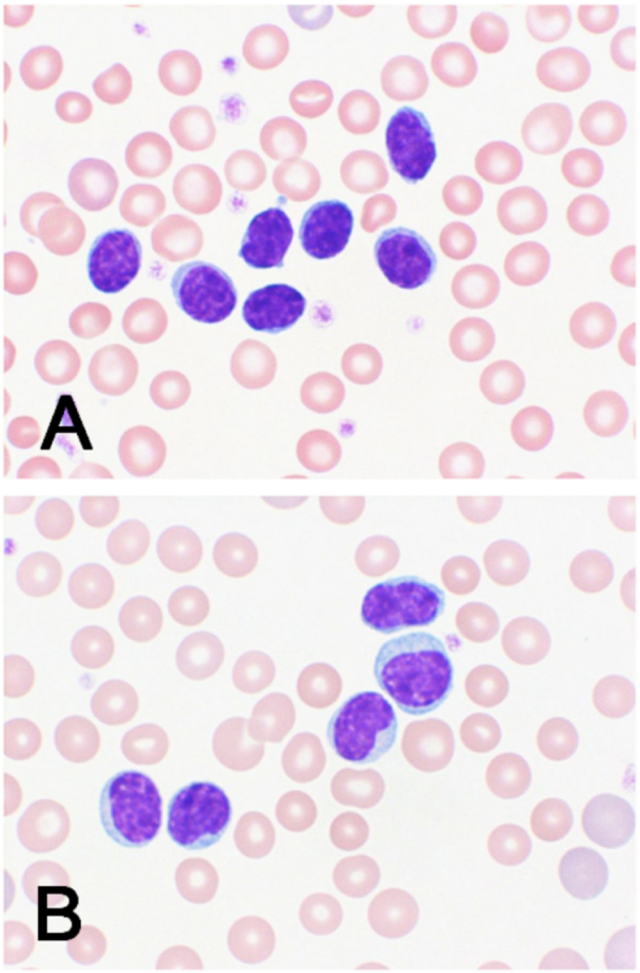

Fig. 1. Photomicrograph of a peripheral blood smear at 2 years 4 months of age. A: Small-sized neoplastic lymphocytes. B: Intermediate-sized neoplastic lymphocytes. May-Grünwald Giemsa stain.

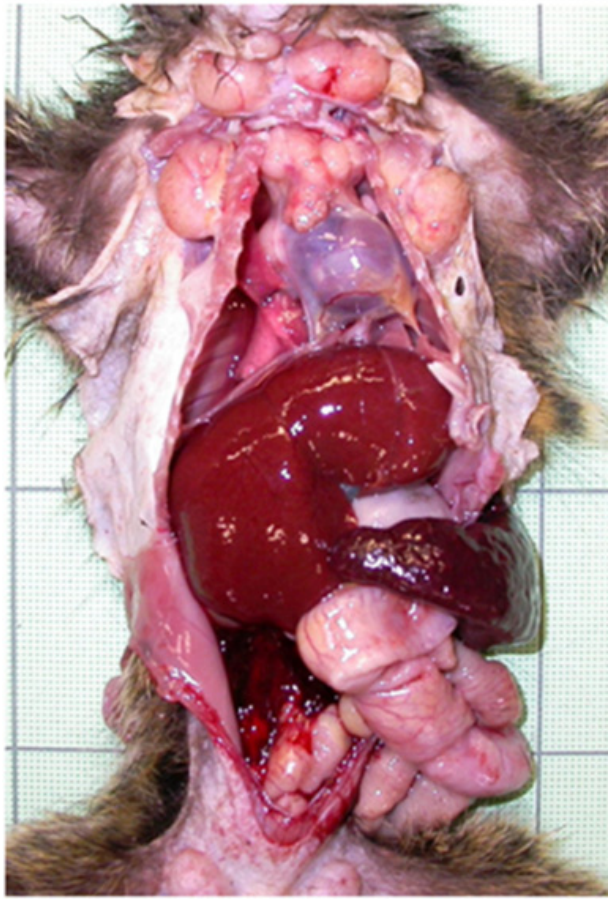

Fig. 2. Postmortem findings of a male common marmoset at 2 year 8 months of age. Multiple lymph nodes and the thymus and spleen were enlarged.

Four months after the detailed examination of the lymphoid mass, the general condition of the animal worsened, and the animal showed low appetite, emesis, diarrhea, lower activity and wasting, and was predicted to have a poor outcome. The animal was euthanized.

The postmortem findings showed a marked diffuse lymphadenopathy. Multiple lymph nodes including the submandibular, axillary and inguinal nodes and the nodes around the heart and thymus were asymmetrically enlarged (Fig. 2). The thymus and spleen were conspicuously enlarged. In the thoracic cavity, about 15 mL of red pleural effusion was retained, and the lungs revealed scattered multiple white spots in the lobules.

In enlarged lymph nodes, neoplastic lymphocytes expanded diffusely, and the sinus was compressed and had obliterated the nodal architecture with the spread of neoplastic cells (Fig. 3A). Most of the neoplastic cells were small- to intermediate-sized atypical lymphocytes with an irregular nuclear shape and one or several small prominent nucleoli (Fig. 3B). The nuclear chromatin staining revealed hyperchromatism in the small-sized cells, and the intermediate-sized cells exhibited vesicular staining. Multiple mitotic figures in the neoplastic cells were also observed. Moreover, an increase in high endothelial venules (HEVs) (Fig. 3C) and reactive epithelioid histiocytes (Fig. 3D) was observed. Multinucleated giant cells were also present. Scattered tingible body-laden macrophages (starry sky pattern) were infrequently detected. Upon immunohistochemical examination, all of the neoplastic lymphocytes were CD3 positive (Fig. 3E) and CD20 negative (Fig. 3F-a). The staining intensity for CD3 revealed the small-sized neoplastic cells to be strongly positive, while the intermediate cells were either weakly or mildly stained. So the neoplastic lymphoid cells were considered to be of T cell origin. Remnants of hypoplastic lymphoid follicles were found, and the constituent cells were revealed to be CD20 positive in affected lymph nodes (Fig. 3F-b).

In the thymus, an abundant cell population consisting of CD3-positive neoplastic lymphocytes arranged in sheets was observed (Fig. 4A). Neoplastic cells obliterated the thymic architecture without cortico-medullary demarcation, and the persistent Hassall's bodies were scattered. In the enlarged spleen, neoplastic lymphocytes had infiltrated the

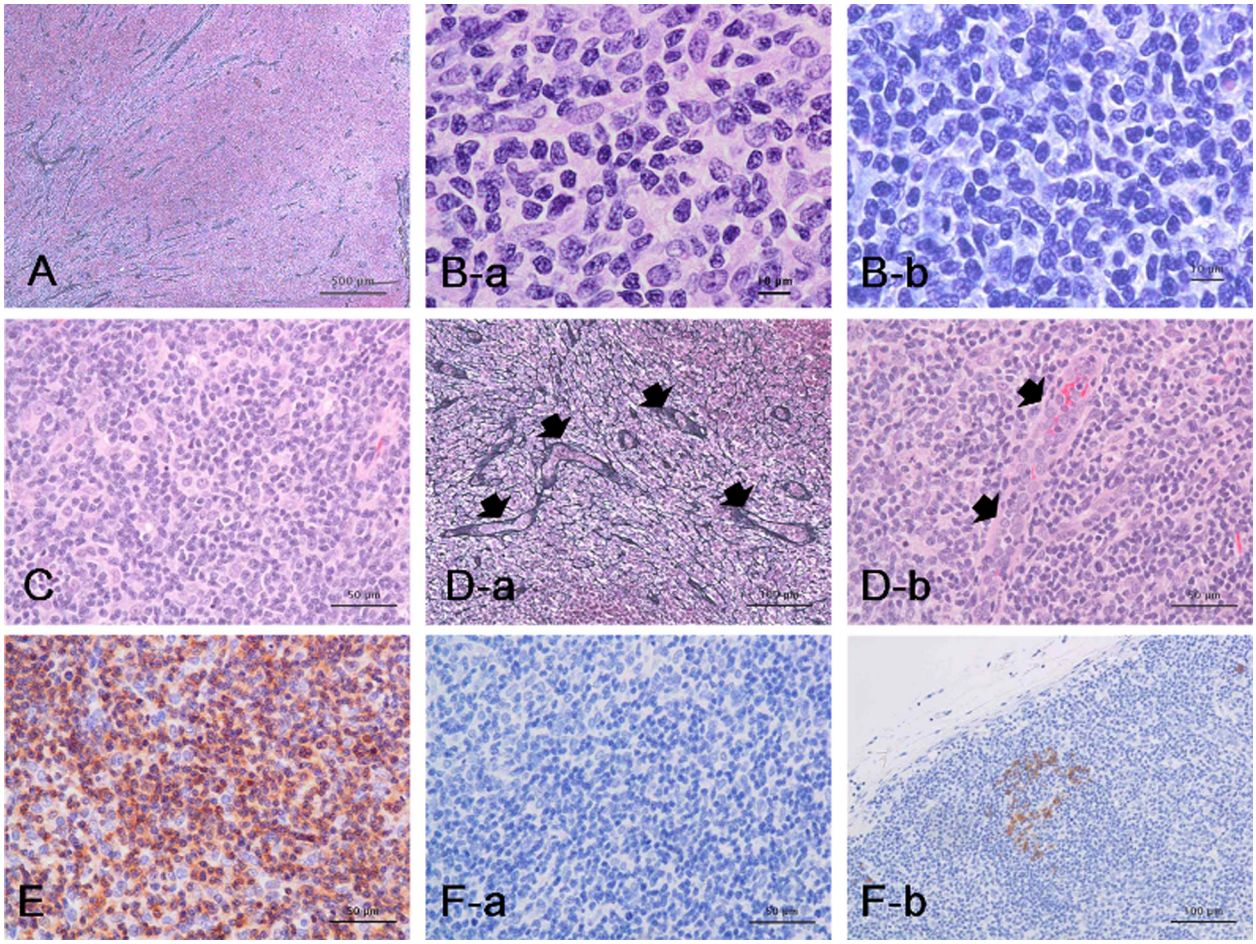

Fig. 3. Photomicrograph of histopathology and immunohistochemistry in enlarged submandibular lymph nodes. A. Obliteration of normal nodal architecture by expanded neoplastic cells. Silver stain. B: The neoplastic cells were pleomorphic and had irregularly shaped nuclei and one or several small prominent nucleoli. a, H&E stain; b, Giemsa stain. C: Increase in reactive epithelioid histiocytes. H&E stain. D: Proliferation of high endothelial venules (arrows). a, silver stain; b, H&E stain. E: The neoplastic cells were revealed to be positive for CD3. CD3 immunohistochemistry. F: The neoplastic cells were revealed to be negative for CD20 (a). The constituent cells of the persistent hypoplastic follicles were revealed to be positive for CD20 (b). CD20 immunohistochemistry.

perivascular lymphoid sheath and marginal zone of the lymphoid follicles (Fig. 4B). In some of the lymphoid follicles, almost all of the constituent cells were replaced with CD3-positive neoplastic cells.

The invasive neoplastic cells were also observed in the lungs, liver, kidneys, adrenal glands and skin. In the lungs, the invasion of neoplastic cells entirely and bilaterally covered the bronchi and alveoli. In the liver, the neoplastic cells had spread periportally, and formed multiple proliferative foci in the sinusoid. In the kidneys, interstitial invasion of neoplastic cells was present. In the adrenal glands, the invasion had occurred in the medulla. In the affected skin, the patches exhibited massive dermal infiltration of neoplastic cells. Some of the neoplastic cells invaded to the epidermis, hair follicles and sweat glands (Fig. 4C). Subepithelial invasion of neoplastic cells was also observed in the tongue. A patchy presence of CD3-positive neoplastic cells was noted in the femoral and sternal bone marrow (Fig. 4D).

The important pathological aspects of this marmoset lymphoma were that 1) there was a diffuse proliferation of small- to intermediate-sized neoplastic lymphocytes, 2) the nuclei were irregularly shaped, 3) nuclear chromatin staining revealed hyperchromatism in the small-sized cells and vesicular staining in the intermediate-sized cells, 4) neoplastic cells were CD3 positive and CD20 negative in the immunohistochemistry, 5) there was proliferation of HEVs, 6) reactive epithelioid histiocytes were present, and 7) a systemic distribution of neoplastic cells was observed including multiple lymph nodes and organs, suggesting the neoplasm was peripheral T-cell lymphoma, which is a general term of nodal and extranodal T-cell lymphoma.

This animal showed leukocytosis, mainly an increase in the lymphocyte counts, with anemia and thrombocytopenia. The increased lymphocyte counts gradually diminished toward the end of its life. On the other hand, there was no change in the granulocyte counts. In the bone marrow,

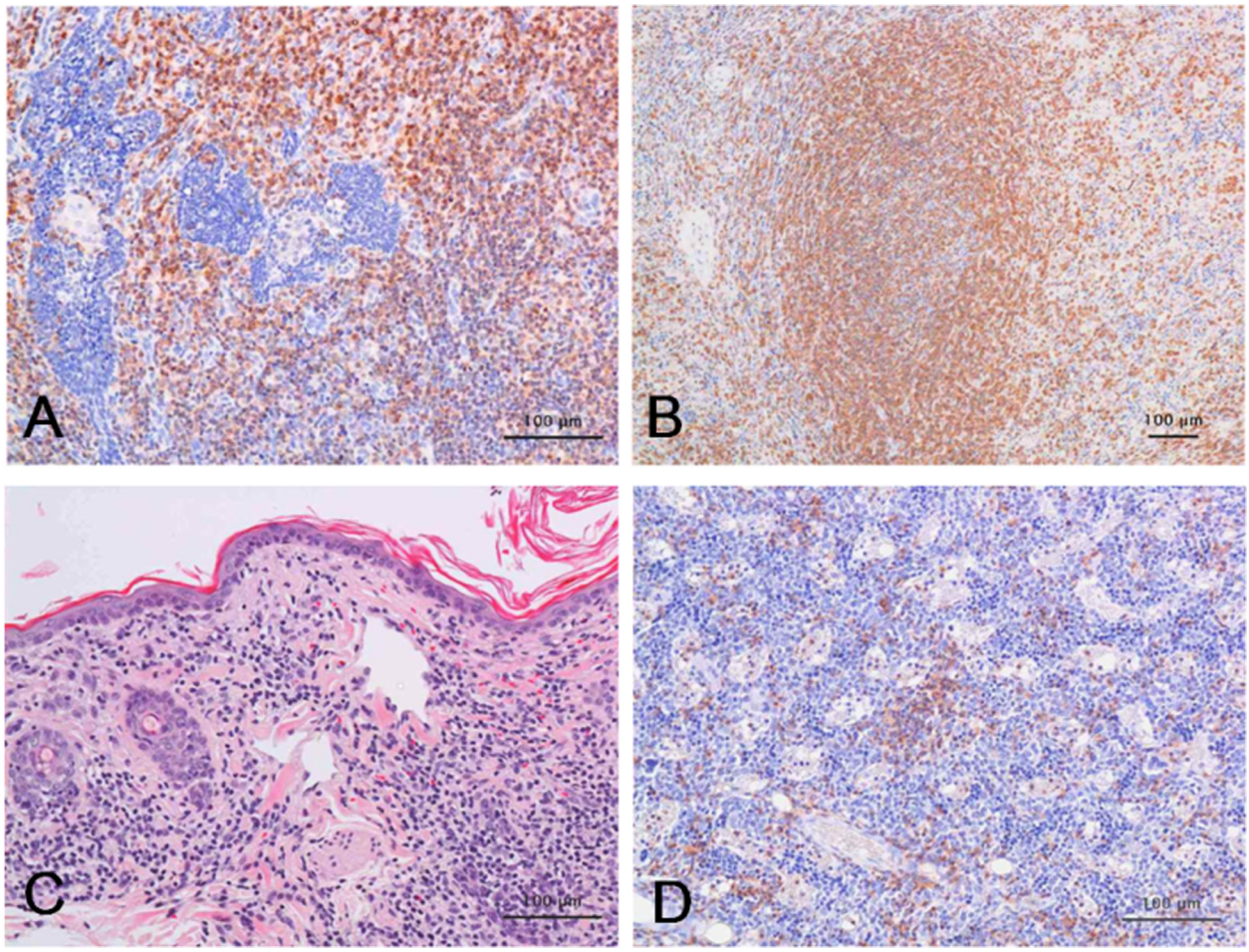

Fig. 4. Photomicrograph of tissues with invasive neoplastic cells. A. Thymus: Obliteration of thymic architecture by invasive CD3-positive neoplastic cells. Persistent Hassall's bodies (arrows) were present. B. Spleen: Infiltration of CD3-positive neoplastic cells into the perivascular lymphoid sheath and marginal zone of the lymphoid follicles. C. Skin: Dermal infiltration of neoplastic cells. Some of the neoplastic cells invaded into the epidermis, hair follicles and sweat glands. D. Femoral bone marrow: A patchy presence of CD3-positive neoplastic cells in marrow. A, B, D: CD3 immunohistochemistry. C: H&E stain.

the neoplastic cells presented multifocally. The invasion of neoplastic cells into the bone marrow might be correlated with the cause of anemia and thrombocytopenia. At the late phase, the animal showed a low appetite and wasting. It is therefore considered that the diminished number of peripheral lymphocytes and thrombocytes in the late phase may have resulted from the worsened general condition of the animal.

In the present case, the normal tissue architecture in some of the lymph nodes and thymus was obliterated by the spread of neoplastic cells. It was difficult to clarify whether the neoplastic cells had originated from the thymus or lymph nodes. Kotani *et al.* reported a case of mixed thymoma in a male cynomolgus monkey that was four years and three months old[35]. The tumor showed two types of proliferation patterns, dense or fascicular proliferation of elongated spindle cells and dense proliferation of thymic cortex-like lymphoid cells, which were CD3 positive and CD20 negative. In the thymus of the present case, only the CD3-positive lymphoid neoplastic cells had spread like a sheet throughout the whole thymus, and there was no observed spindle cell proliferation. Therefore, this case was diagnosed as a lymphoma, not a thymoma.

Simian T-cell lymphomas have been reported in savanna monkeys[16, 24] and baboons[5] in association with STLV, and in tamarins and owl monkeys in association with EBV and *H. saimiri*[30, 31] or *H. ateles*[26]. In the savanna monkey cases, the age at the time of the occurrence of lymphoma ranged from seven to 11 years old. Most of the neoplastic cells were large or very large in size and had vesicular nuclei, which were oval or irregular in shape. In baboons, the age at onset ranged from three to 20 years old, while the STLV-infected baboons with NHL ranged in age from three to 21 years (mean, 13 years)[5]. The morphological characteristics of the dominant neoplastic cells of peripheral T-cell NHL in baboons with STLV-1 infections showed four morphological phenotypes of neoplastic cells: lymphocytic, prolymphocytic-lymphocytic, immunoblastic and large anaplastic[6]. In

lymphocytic and prolymphocytic-lymphocytic lymphomas, high endothelial venules and epithelioid cells were also seen.

In cottontop tamarins, the animals inoculated with EBV died or were moribund by 49 days after EBV inoculation. The tumor tissue contained a nearly homogeneous population of cells. The nucleus of the major neoplastic cells was large and reticular with marginated chromatin and multiple nucleoli. The marmosets inoculated with *H. saimiri* virus died within 48 days. The reticular neoplastic cells had invaded a variety of tissues with leukocytosis [30]. The neoplastic cells in tamarins inoculated with *H. ateles* were of the lymphoblastic type[26].

In a case of spontaneous lymphoma in a cottontop tamarin[15], the neoplastic cells were of a pleomorphic primitive reticular type. The nuclei were oval, but some were very small and others were gigantic. They were indented, elongated or angular in shape. The neoplastic lymphocytes had invaded into the liver, kidneys, adrenals, spleen, lymph nodes, bone marrow and lungs. The pathological features of the present case of lymphoma in a common marmoset are considered to be similar to those of T cell lymphoma in baboons or tamarins. In the present case, verification of the existence of virus infection was not carried out.

The revised World Health Organization (WHO) system of classification of malignant lymphoma includes all relevant diagnostic information: cellular morphology, cell lineage, the topography and general biology of each neoplasm[36, 37]. Recently, the WHO system for classification of human malignant lymphoma has been applied to the classification of canine lymphoma[38, 39].

In a new WHO classification, mature T-cell and natural killer (NK) cell neoplasms are classified into twenty lymphoma types[40]. The disease groups characterized by invasion into various organs or tissues by neoplastic cells are adult T-cell leukemia/lymphoma (ATLL), anaplastic large cell lymphoma (ALCL), angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).

The ATLL neoplastic lymphoid cells are medium-sized to large, often with pronounced nuclear pleomorphism. The nuclear chromatin is coarsely clumped, with distinct, sometimes prominent nuclei. In the peripheral blood smear preparation, the neoplastic cells are medium to large in size, with pleomorphic nuclei and basophilic cytoplasm. Polylobated cells described as "flower cells" are also observed. AITL is characterized by systemic disease, a polymorphous infiltrate involving lymph nodes, with prominent proliferation of HEVs and follicular dendritic cells. The neoplastic cells show a polymorphous population of small to medium sized lymphocytes, usually with clear to pale cytoplasm and distinct cell membranes. ALCL usually consists of large-sized lymphoid neoplastic cells with abundant cytoplasm and pleomorphic nuclei. Several cytomorphological variants have been recognized, including the common, lymphohistiocytic and small cell variants. Most cases of ALCL contain hallmark cells with eccentric, horseshoe- or kidney-shaped nuclei often with an eosinophilic region. The category of PTCL-NOS defined by exclusion encompasses all mature T-cell neoplasms lacking specific features that would allow categorization within any of the better-defined specific subtypes of PTCL described in the WHO classification. In the present case of lymphoma, there were no specific features of ATLL, ALCL and AITL in the histological examination. As a result, this case of lymphoma was considered to fit the category of PTCL-NOS.

We recently experienced the case of a two-year-old male marmoset with spontaneous T-cell lymphoma with systemic invasion of neoplastic cells. The present case was considered to fit the category of "peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS)" according to the new WHO system of classification.

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