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Case Report

Spontaneous globule leukocyte tumor accompanied by inflammatory cells in a Wistar Hannover rat

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Abstract: We encountered hematolymphoid neoplastic lesions in the form of many nodules in the spleen and liver in a 110-week-old male Wistar Hannover rat (Crl:WI (Han)). The lesions contained atypical proliferative cells, eosinophils, lymphocytes, and macrophages. The proliferative cells comprised various atypical cell types with or without cytoplasmic eosinophilic granules. The granules were positively stained using periodic acid-Schiff and elastase stains, were bluish purple using phosphotungstic acid and hematoxylin, and showed no metachromasia using toluidine blue. In immunohistochemical staining, the proliferative cells with or without granules were positive for granzyme B, rat mast cell protease II, and Ki67. Electron microscopic examination revealed that single to multiple high-density granules of variable size were covered by a membrane. These findings led to a diagnosis of globule leukocyte tumor. The accompaniment of this tumor by inflammatory cells is likely evoked by mast cell-like active mediators contained in the granules of the globule leukocytes. (DOI: 10.1293/tox.2018-0068; J Toxicol Pathol 2019; 32: 189–195)

Key words: globule leukocyte, tumor, Wistar Hannover, rat, spleen, liver

Hematolymphoid tumors are commonly encountered in rat carcinogenicity studies. In particular, large granular lymphocyte (LGL) leukemia is the most prevalent tumor in Fischer (F344) rats[1, 2]. Despite its name, the proliferative cells of LGL leukemia are neither large nor granular in hematoxylin and eosin (HE)-stained sections. In SD and Wistar Hannover rats, in contrast, LGL leukemia is extremely rare, while malignant lymphoma, myeloid leukemia, and histiocytic sarcoma are sometimes observed[1].

We recently encountered hematolymphoid neoplastic lesions in the form of numerous small to large nodules in the spleen, in both the red pulp and white pulp, and in Glisson's sheath of the liver in a Wistar Hannover rat. Many of the neoplastic cells contained distinct eosinophilic granules or droplets, which were identified as mast cells; plasma cells (Motto cells)[3]; abnormal granulocytes that are seen in Chediak Higashi syndrome[4]; phagocytic macrophages; or globule leukocytes[5–10]. Various histochemical and immunohistochemical stains and electron microscopic examination revealed that this neoplasm was a globule leukocyte tumor. While eosinophilic granulated round cell tumors[11] and an eosinophilic granulated cell tumor[12] with similar granules were previously reported in rats, the origin of these granulated cells was not clear. To our knowledge, no report has yet described a diagnosis of globule leukocyte tumor in rats.

Globule leukocytes are observed in the interepithelium of the gastrointestinal mucosa in rodents and increased by administration of chemicals such as iron lactate[8] and polyethylene glycol[10].

In this study, we investigated the histological features of a globule leukocyte tumor in a WH rat and examined its origin based on the results of various histochemical and immunohistochemical stains.

The present case was a 110-week-old male Wistar Hannover rat (Crl:WI (Han)) that was being examined in a carcinogenicity background data-collecting study. The animal arrived at 4 weeks old and was used for study from 6 weeks old. Rats were individually housed in hanging-type stainless steel wire mesh cages (195 mm [w] × 325 mm [d] × 180 mm [h]; Tokiwa Kagaku Kikai Co., Ltd., Tokyo, Japan) in an animal room maintained at 22 ± 3°C, with relative humidity of 50 ± 20%, 6–20 air changes/h, and a 12-h light/dark cycle. A diet of pelleted food (radiation sterilized CR-LPF, Oriental Yeast Co., Ltd., Tokyo, Japan) and tap water supplied automatically were provided ad libitum. The animals were cared for in accordance with the principles outlined in the guides for the care and use of laboratory animals prepared by the Japanese Association for Laboratory Animal Science and our institution.

The rat did not show any abnormalities in clinical

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signs, hematological, and serum biochemical analyses. The animal was euthanized by exsanguination under pentobarbital anesthesia and necropsied. After the necropsy, all of its tissues were fixed in phosphate-buffered 10% formalin solution, embedded in paraffin, and serially sectioned at 4 μm. The sections were stained with hematoxylin and eosin, and additionally, spleen and liver sections were stained with phosphotungstic acid and hematoxylin (PTAH), esterase, periodic acid-Schiff (PAS), Masson's trichrome (MT), toluidine blue (TB), Berlin blue (BB), Giemsa, and Luna stains. Procedures for immunohistochemistry, including the primary antibodies, dilution, and antigen retrieval procedures are summarized in Table 1. Spleen and liver sections were immunohistochemically reacted for Ki67, granzyme B, rat mast cell protease II (RMCP II), CD68, Iba1, κ light chain, CD3, and CD20 using an LSAB kit (Dako Japan Co., Ltd., Kyoto, Japan)[13]. Sections were lightly counterstained with hematoxylin. Additionally, as a positive control for globule leukocytes, PTAH, esterase, granzyme B, and RMCP II staining were also performed on the stomach section from this animal. Small pieces of the formalin-fixed spleen tissue were also processed for ultrastructural examination. The tissue pieces were cut into 1- to 2-mm^3 cubes and washed in 0.1 M phosphate-buffered saline (PBS, pH 7.4) for 30 min, postfixed in 1% osmium tetroxide, and embedded in epoxy resin. Ultrathin sections were mounted onto copper grids, stained with uranyl acetate and lead citrate, and examined using an H-7600 transmission electron microscope (Hitachi High-Tech Fielding Corporation, Tokyo, Japan).

Macroscopically, three protrusions were observed on the surface of the spleen (5–8 mm in diameter). On the cut surface, multiple pale white- or yellow-colored nodules were noted. No macroscopic abnormalities were observed in other organs or tissues.

Microscopically, numerous pale foci of variable size comprising proliferative cells were observed in the splenic parenchyma, causing the entire spleen to become expanded and rounded (Fig. 1). The foci of proliferative cells were observed in the white pulp, marginal zone, and red pulp and were not enclosed by a capsule but instead were spread invasively and did not apply any prominent pressure against the surrounding parenchyma. Similar multiple proliferative foci were noted in Glisson's sheath including the surrounding parenchyma in the liver (Fig. 2). The cells of the foci were relatively large and round, oval, or polygonal in shape with or without eosinophilic granules and were accompanied by a varying number of inflammatory cells such as eosinophils, lymphocytes, and pigmented macrophages. While the inflammatory cells in the foci of the spleen comprised mainly eosinophils and pigmented macrophages (Fig. 3), in Glisson's sheath of the liver, they primarily comprised lymphocytes (Fig. 4). The proliferative cells had medium to large, round to oval, or bean-shaped nuclei with single or double clear nucleoli. They contained dense cytoplasmic granules that were eosinophilic and ranged from fine to large granules or droplets, some of which were larger in diameter than red blood cells (Fig. 5). The nuclei of cells with abundant granules were eccentrically located due to their presence in the cytoplasm, and these cells had low nucleus/cytoplasm (N/C) ratios. Some proliferative cells were atypical, exhibiting a hypogranulated or non-granulated cytoplasm. These atypical cells had large nuclei and nucleoli, non- or bi-lobed nuclei, centric nuclei, a high N/C ratio, a ganglion-like shape and/or basophilic cytoplasm (Fig. 6). Atypical cells without granules were interspersed with the granulated cells in the proliferative foci. Atypical cells without granules were noted at 15–25% of the total tumor cells. The atypical and pleomorphic features of the nuclei of proliferative cells with or without granules did not resemble those of intraepithelial globule leukocytes in the glandular stomach, because normal intraepithelial globule leukocytes did not show atypical or pleomorphic features, which were uniform, typically small and dark, with no nucleoli.

The results of histochemical staining of the proliferative cells and other various cells in the tumor are shown in Table 2. The cytoplasmic granules were positive for PTAH (dark-blue staining) (Fig. 7A), PAS, MT (red staining) (Fig. 7B), and esterase (Fig. 7C) and negative for Berlin blue, TB indicating no metachromasia (Fig. 7D), and Giemsa. The cytoplasm of atypical cells was stained dark blue using PTAH and Giemsa (Fig. 7E).

The results of immunohistochemical staining are presented in Table 2. Cytoplasms with granules were positive for granzyme B (Fig. 7F) and RMCP II (Fig. 7G). Hypogranulated atypical cells were also positive for these antibodies. In atypical cells without granules, it was difficult to conclude whether staining was positive or negative because we could not distinguish between the positively stained cy-

Table 1. Procedure and Primary Antibodies Used in Immunohistochemical Analysis

Antibody	Supplier	Host	Clone	Dilution	Antigen retrieval	Positive control
Granzyme B	Spring Bioscience	Rabbit	Polyclonal	×100	pH 6.0, 98°C, 10 min	Globule leukocyte
Rat Mast Cell Protease II	Nichirei	Rabbit	Polyclonal	×500		Globule leukocyte Mast cell
Ki67	Abcam	Rabbit	Polyclonal	×1,600	pH 6.0, 121°C, 20 min	Intestine
CD68	Abcam	Mouse	Monoclonal	×800	pH 6.0, 121°C, 5 min	Macrophage
Iba1	Wako	Rabbit	Polyclonal	×500	pH 6.0, 62–65°C, overnight	Macrophage
κ light chain	Abcam	Rabbit	Polyclonal	×100	pH 6.0, 121°C, 10 min	Plasma cell
CD3	Abcam	Rabbit	Polyclonal	×50	pH 6.0, 120°C, 20 min	T lymphocyte
CD20	Santa Cruz	Goat	Polyclonal	×200	DW, MW, 30 min	B lymphocyte

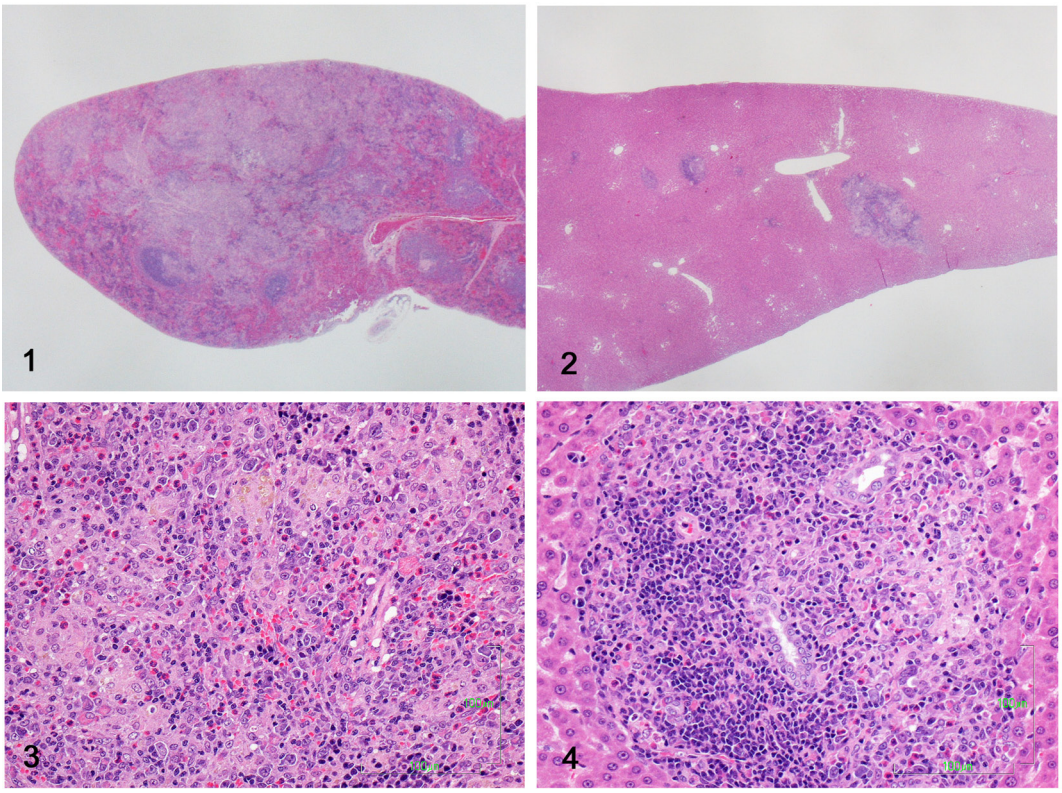

Fig. 1. Low magnification of the microscopic features of nodules in the spleen. Large pale proliferative foci were observed in the splenic parenchyma. The spleen was expanded and rounded by the proliferative foci. HE stain. ×2.5.

Fig. 2. Low magnification of the microscopic features of the liver. Multiple foci of proliferative cells were observed in Glisson's sheath including the surrounding parenchyma. HE stain. ×2.5.

Fig. 3. A focus of proliferative cells in the spleen. Neoplastic cells with or without eosinophilic granules were accompanied by eosinophils, macrophages, and a small number of lymphocytes. HE stain.

Fig. 4. A focus of proliferative cells in the liver. Proliferative cells similar to those in the spleen were observed in the liver. Lymphocytic inflammation was prominent in Glisson's sheath. HE stain.

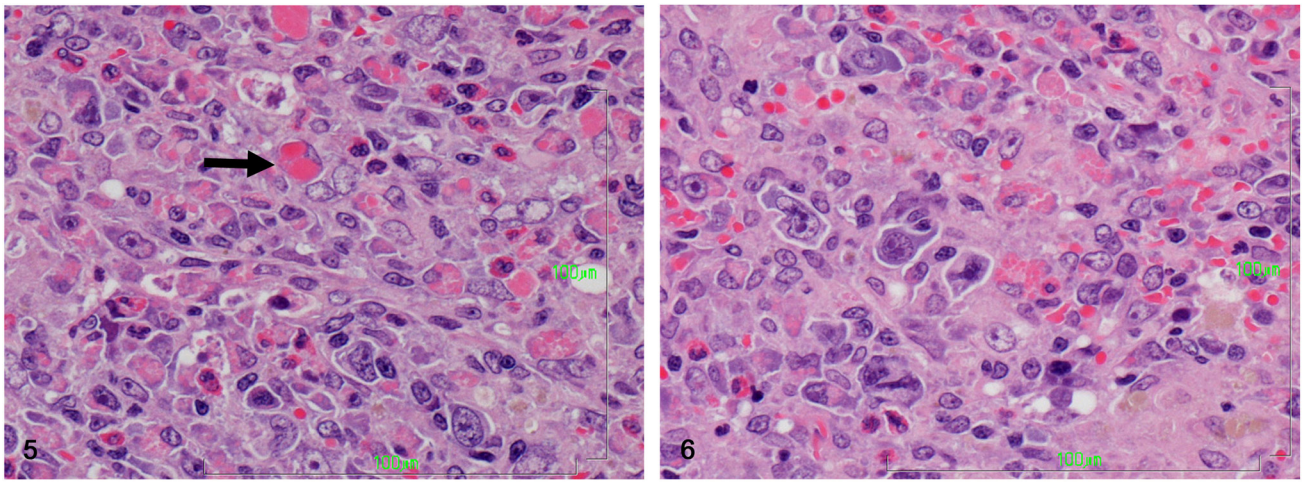

Fig. 5. Granulated cells scattered throughout a proliferative focus in the spleen. Cytoplasmic granules were dense, eosinophilic fine granules or large droplets. Some large droplets (arrow) were noted in the cytoplasm. HE stain.

Fig. 6. Atypical cells interspersed with proliferative cells in the spleen. Atypical cells had a hypogranulated or non-granulated cytoplasm; large nuclei, bean-shaped nuclei, or bi-nuclei; large and multiple nucleoli; and basophilic cytoplasm. HE stain.

Table 2. Histochemical and Immunohistochemical Stains

	Various cells comprising the tumor				
	Proliferative cell with granules	Atypical cell without granules	Eosinophil	Macrophage including pigment	Lymphocyte
PTAH	+ Dark blue	+ Dark blue	−	−	−
Esterase	+	−	−	−	−
PAS	+/week	−	−	−	−
MT	Red	−	Red	−	−
TB	−	−	−	−	−
Giemsa	−	Dark blue	−	−	−
BB	−	−	−	+	−
Luna	−	−	+	−	−
Granzyme B	+	− or +	−	−	−
RMCP II	+	− or +	−	−	−
Ki67	−	+	−	−	−
CD68	−	−	−	+	−
Iba1	−	−	−	+	−
κ light chain	−	−	−	−	+ (Plasma cell)
CD3	−	−	−	−	+
CD20	−	−	−	−	+

PTAH, phosphotungstic acid and hematoxylin; PAS, periodic acid-Schiff; MT, Masson's trichrome; TB, toluidine blue; BB, Berlin blue; RMCP II, rat mast cell protease II.

toplasm of atypical cells with few granules and no granules in the immunostained specimens. Atypical cells without granules were positive for Ki67 (Fig. 7H), while cells with granules were negative for Ki67. All proliferative cells were negative for CD68 (Fig. 7I), Iba1, κ light chain, CD3, and CD20. Infiltrated eosinophils were positive for Luna stain; lymphocytes were positive for CD3 or CD20, with some also being positive for the κ light chain; and pigmented macrophages were positive for BB stain, CD68 (Fig. 7I), and Iba1. Hematopoietic cells in the spleen were positive for esterase and/or Ki67. In comparison, intraepithelial globule leukocytes of the glandular stomach were positive for PTAH, esterase (Fig. 7J), granzyme B (Fig. 7K), and RMCP II (Fig. 7L).

Electron microscopic examination revealed many granule-containing cells with large nucleoli (Fig. 8A). The granules varied in number and size and were homogenously electron dense and surrounded by a membrane (Fig. 8C). Some granules contained needle- or tubule-like structures (Fig. 8A and B). Rough endoplasmic reticulum was relatively abundant in cytoplasms without granules (Fig. 8A and C).

There were no histological changes in other lymph-hematopoietic organs, such as the bone marrow and lymph nodes, and the gastrointestinal tract.

Based on the results of microscopic and electron microscopic examination, the proliferative cells were positive for PTAH, elastase, granzyme B, and RMCP II, which was similar to globule leukocytes in the stomach, prompting the conclusion that these proliferative cells were globule leukocytes. At first, we also considered mast cells, plasma cells (Motto cells), abnormal granulocytes that are seen in Chediak Higashi syndrome, and phagocytic macrophages as possibilities for the origin of the tumor and confirmed various histochemical and immunohistochemical stains. The possibility of plasma cells was rejected based on the negative reaction for κ light chain. Abnormal granulocytes that are seen in Chediak Higashi syndrome show similar staining to these tumor cells; however, the possibility of abnormal granulocytes was denied based on the positive reactions for granzyme B and RMCP II. The possibility of macrophages was rejected based on the negative reaction for CD68. Mast cells show similar staining for esterase, granzyme B, and RMCP II to these tumor cells; however, the possibility of mast cells was rejected based on these being no metachromasia for TB stain.

Given that this lesion contained prominent inflammatory cells, it was necessary to determine whether it was a neoplastic or nonneoplastic lesion. The growth pattern of the tumor cells was nodular in the spleen, where it did not discriminate between white pulp and red pulp, and also in and around Glisson's sheath of the liver. We speculate that this tumor primarily occurred in the spleen. Among hematolymphoid tumors in rats, LGL leukemia exhibits diffusely scattered proliferation without nodules in the red pulp of the spleen and the sinusoid of the liver, while a nodular growth pattern is rare. Malignant lymphoma is characterized by proliferation mainly in the white pulp of the spleen and in Glisson's sheath including the surrounding tissue in the liver. Myeloid leukemia is characterized by proliferation mainly in the red pulp of the spleen and in Glisson's sheath including the surrounding tissue in the liver. Histiocytic sarcoma exhibits characteristic nodular growth in the spleen and/or liver. While the proliferative pattern of the tumor in the present case did not resemble that of lymphocytic or myeloid leukemia in the spleen, it did resemble that of leukemia in the liver. Its morphological features, such as its nodular

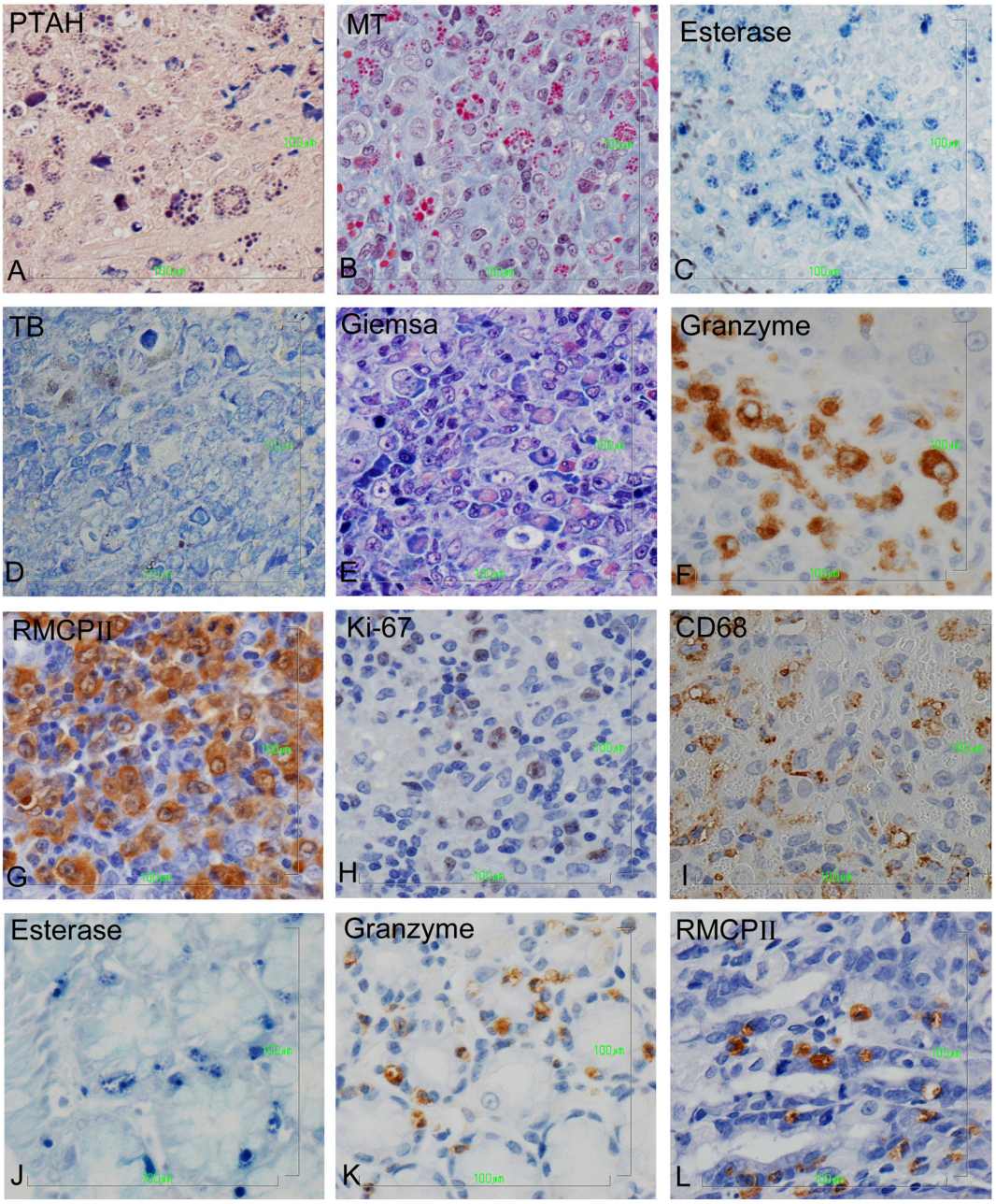

Fig. 7. Histochemical staining and immunohistochemical staining of proliferative cells. (A) Phosphotungstic acid and hematoxylin stain, spleen. Granules were positively (dark blue) stained. (B) Masson's trichrome stain, spleen. Granules were stained red. (C) Esterase stain, spleen. Granules were positively (blue) stained. (D) Toluidine blue stain, spleen. Granules did not show metachromasia. (E) Giemsa stain, spleen. Granules did not show metachromasia, while the cytoplasm was stained dark blue. (F) Granzyme B immunostaining, spleen. The cytoplasm with granules was positively stained. (G) Rat mast cell protease II immunostaining, liver. Cytoplasm with granules was positively stained. (H) Ki67 immunostaining, spleen. Nuclei of atypical cells were positively stained. (I) CD68 immunostaining, spleen. Granules and cytoplasm of the tumor cells were not stained, while macrophages were positively stained. (J) Esterase stain, stomach. Globule leukocytes were positively stained. (K) Granzyme B immunostaining, stomach. Globule leukocytes were positively stained. (L) Rat mast cell protease II immunostaining, stomach. Globule leukocytes were positively stained.

proliferation, distribution in the liver, growth in multiple organs, morphology of atypical cells, and positive reaction for Ki67, suggest a neoplastic lesion.

Some granules of the tumor cells contained needle- or tubule-like structures in the electron microscopic examination. The ultrastructural features of granules resembled eosinophilic granulated cells comprising a tumor in a Fischer rat in a previous report of Miyajima et al.[12]. They reported that the granules partially showed a filament-like structure. In feline globule leukocyte tumor[14] or rat mast cell tumor[15], however, granules contained nonstructural and homogenous materials. It was also reported that the characteristic feature

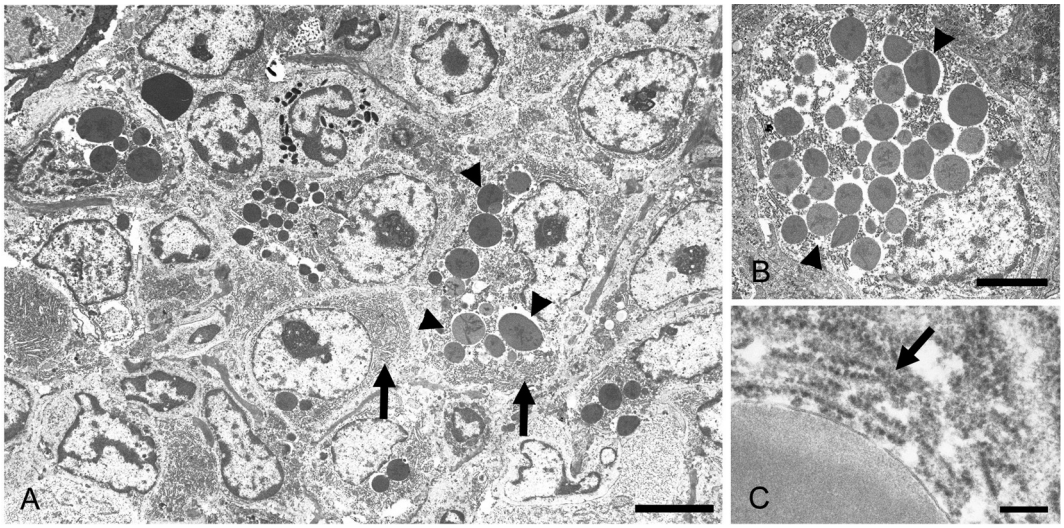

Fig. 8. Electron microscopic features. Cells with large nucleoli had varying numbers and sizes of granules (A). Some granules contained needle- or tubular-like structures (arrowheads) (A, B). Cytoplasm without granules contained abundant rough endoplasmic reticulum (arrows) (A, C), and granules were surrounded by a membrane (C). Scale bar (A) 50 µm, (B) 25 µm, (C) 200 nm.

of normal intestinal globule leukocytes in adult rats was the presence of paracrystalline inclusions in the granules[16]. Based on their electron microscopic features, it is suggested that the tumor cells resemble those of rat globule leukocytes.

Globule leukocytes of the interepithelium of the gastrointestinal mucosa in rodents are positive for esterase[5, 6], mast cell protease[5, 8–10], granzyme B[9], and c-kid[9]. Mast cells are also positive for esterase[5], mast cell protease[5, 9, 15], granzyme B[9], and c-kid[9, 15, 17]. Granzyme B is a cytotoxic lymphocyte-associated protease in cytotoxic T cells or natural killer (NK) cells, although previous reports suggest that mast cells produce and release granzyme B upon activation[18, 19]. The resemblance of globule leukocytes, according to their positive immunohistochemical reactions to mast cells, suggests a similar function and common precursor in rats[8–10]. Interestingly, this tumor also contained Ki67-positive atypical cells without granules, which may represent juvenile cells along the globule leukocyte and mast cell lineage.

This tumor also exhibited inflammatory cell infiltration in the neoplastic foci or nodules. Polymorphic features accompanied by lymphocytes and eosinophils have been observed in mastocytosis and mast cell sarcoma[17, 20]. The granules of mast cells are known to contain chemotactic mediators that facilitate eosinophilic infiltration or other inflammatory changes and play a central role in type 1 hypersensitivity[8]. The accompaniment of this tumor by inflammatory cells may be evoked by mast cell-like active mediators contained in the granules of the globule leukocytes.

Globule leukocyte tumors have been reported in cats[14, 21–24]. Most feline globule leukocyte tumors have been observed in the intestine, and reports suggest that feline globule leukocytes are a type of intraepithelial large granular lymphocyte lymphoma that originates from cytotoxic T cells or NK cells based on their immunoreactivity for perforin, a pore-forming protein unique to cytotoxic lymphocytes[23, 24]. It is unclear whether the origin of globule leukocyte tumors in the intestine of cats and intraepithelial globule leukocytes in rodents are one and the same due to the use of different antibodies in immunohistochemical staining among studies in each animal species. It is possible that despite showing similar morphology, globule leukocytes have a different function and origin in different animal species.

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References

1. Frith CH, Ward JM, and Chandra M. The morphology, immunohistochemistry, and incidence of hematopoietic neoplasms in mice and rats. Toxicol Pathol. 21: 206–218. 1993. [Medline] [CrossRef]
2. Ward JM, and Reynolds CW. Large granular lymphocyte leukemia. A heterogeneous lymphocytic leukemia in F344 rats. Am J Pathol. 111: 1–10. 1983. [Medline]
3. Sano T, Takai Y, Anayama H, Watanabe T, and Fukuda R. Accumulation of Mott cells in the spleen in a CB6F1-Tg rasH2 mouse. J Toxicol Pathol. 29: 265–268. 2016. [Medline] [CrossRef]
4. Ozaki K, Maeda H, Nishikawa T, Nishimura M, and Narama I. Chediak-Higashi syndrome in rats: light and electron

microscopical characterization of abnormal granules in beige rats. J Comp Pathol. 110: 369–379. 1994. [Medline] [CrossRef]
5. Huntley JF, McGorum B, Newlands GFJ, and Miller HRP. Granulated intraepithelial lymphocytes: their relationship to mucosal mast cells and globule leucocytes in the rat. Immunology. 53: 525–535. 1984. [Medline]
6. Frederix M, and Baert J. Naphthol-AS-D-chloroacetate esterase activity in globule leucocytes in the tracheal epithelium of rats. Acta Anat (Basel). 125: 93–95. 1986. [Medline] [CrossRef]
7. Kobayashi K, and Kawai Y. Globule leukocytes in transitional cell hyperplasia and carcinomas of aged mice. Exp Anim. 44: 329–331. 1995. [Medline] [CrossRef]
8. Narama I, Ozaki K, Matsushima S, and Matsuura T. Eosinophilic gastroenterocolitis in iron lactate-overloaded rats. Toxicol Pathol. 27: 318–324. 1999. [Medline] [CrossRef]
9. Vogel P, Janke L, Gravano DM, Lu M, Sawant DV, Bush D, Shuyu E, Vignali DAA, Pillai A, and Rehg JE. Globule leukocytes and other mast cells in the mouse intestine. Vet Pathol. 55: 76–97. 2018. [Medline] [CrossRef]
10. Ueda Y, Tsuboi M, Ota Y, Makita M, Aoshima T, Nakajima M, and Narama I. Gastric mucosal changes induced by polyethylene glycol 400 administered by gavage in rats. J Toxicol Sci. 36: 811–815. 2011. [Medline] [CrossRef]
11. Nagatani M, Nakamura A, Yamaguchi Y, Aikawa T, and Tamura K. Spontaneous eosinophilic granulated round cell tumors in rats. Vet Pathol. 38: 317–324. 2001. [Medline] [CrossRef]
12. Miyajima R, Hosoi M, Yamamoto S, Mikami S, Yamakawa S, Iwata H, and Enomoto M. Eosinophilic granulated cells comprising a tumor in a Fischer rat. Toxicol Pathol. 27: 233–236. 1999. [Medline] [CrossRef]
13. Furukawa S, Nagaike M, and Ozaki K. Databases for technical aspects of immunohistochemistry. J Toxicol Pathol. 30: 79–107. 2017. [Medline] [CrossRef]
14. Honor DJ, De Nicola DB, Turek JJ, Render JA, and Serra DA. A neoplasm of globule leukocytes in a cat. Vet Pathol. 23: 287–292. 1986. [Medline] [CrossRef]
15. Terayama Y, Matsuura T, and Ozaki K. Malignant mast cell tumor of the thymus in an Royal College of Surgeons (RCS) rat. J Toxicol Pathol. 30: 63–67. 2017. [Medline] [CrossRef]
16. Ikeda Y, and Yamashina S. Developmental changes in intestinal globule leukocytes of normal rats. Cell Tissue Res. 273: 447–455. 1993. [Medline] [CrossRef]
17. Monnier J, Georgin-Lavialle S, Canioni D, Lhermitte L, Soussan M, Arock M, Bruneau J, Dubreuil P, Bodemer C, Chandesris M-O, Lortholary O, Hermine O, and Damaj G. Mast cell sarcoma: new cases and literature review. Oncotarget. 7: 66299–66309. 2016. [Medline] [CrossRef]
18. Strik MCM, de Koning PJ, Kleijmeer MJ, Bladergroen BA, Wolbink AM, Griffith JM, Wouters D, Fukuoka Y, Schwartz LB, Hack CE, van Ham SM, and Kummer JA. Human mast cells produce and release the cytotoxic lymphocyte associated protease granzyme B upon activation. Mol Immunol. 44: 3462–3472. 2007. [Medline] [CrossRef]
19. Pardo J, Wallich R, Ebnet K, Iden S, Zentgraf H, Martin P, Ekiciler A, Prins A, Müllbacher A, Huber M, and Simon MM. Granzyme B is expressed in mouse mast cells in vivo and in vitro and causes delayed cell death independent of perforin. Cell Death Differ. 14: 1768–1779. 2007. [Medline] [CrossRef]
20. Baselmans AHC, Kuijpers MH, and van Dijk JE. Brief communication, Histopathology of a spontaneously developing mast cell sarcoma in a Wistar rat. Toxicol Pathol. 24: 365–369. 1996. [Medline] [CrossRef]
21. Kariya K, Konno A, Ishida T, Washizu T, and Tomoda I. Globule leukocyte neoplasm in a cat. Nippon Juigaku Zasshi. 52: 403–405. 1990. [Medline] [CrossRef]
22. McEntee MF, Horton S, Blue J, and Meuten DJ. Granulated round cell tumor of cats. Vet Pathol. 30: 195–203. 1993. [Medline] [CrossRef]
23. Kariya K, Konno A, and Ishida T. Perforin-like immunoreactivity in four cases of lymphoma of large granular lymphocytes in the cat. Vet Pathol. 34: 156–159. 1997. [Medline] [CrossRef]
24. Sato H, Fujino Y, Chino J, Takahashi M, Fukushima K, Goto-Koshino Y, Uchida K, Ohno K, and Tsujimoto H. Prognostic analyses on anatomical and morphological classification of feline lymphoma. J Vet Med Sci. 76: 807–811. 2014. [Medline] [CrossRef]