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Case Report

Spontaneously Occurring Intracranial Lipomatous Hamartoma in a Young BALB/c Mouse and a Literature Review

Tomo Sasaki[1,2], Katsuhiko Yoshizawa[1], Yuichi Kinoshita[1,3], Hisanori Miki[1], Ayako Kimura[1], Takashi Yuri[1], Norihisa Uehara[1], and Airo Tsubura[1]

[1] Department of Pathology II, Kansai Medical University, Moriguchi, Osaka 570-8506, Japan
[2] Department of Toxicological Research, Research Laboratories, Maruho Co., Ltd., Kyoto, Kyoto 600-8815, Japan
[3] Division of Cytopathology, Kansai Medical University Takii Hospital, Moriguchi, Osaka 570-8507, Japan

Abstract: An intracranial lipomatous hamartoma was found in the third ventricle of a 7-week-old female BALB/cAnNCrlCrlj mouse. The nodule was composed of mature white adipose cells, which contained one large fat droplet, and there was no evidence of cytological atypia. The brain parenchyma at the retrosplenial granular cortex and the hippocampus in the cerebrum were slightly compressed, and the choroid plexus was dislocated downward. Scattered capillary vessels penetrated the nodule from the surrounding tissue. Based on these findings, the lesion was diagnosed as a lipomatous hamartoma that occurred from the roof of the third ventricle. This extremely rare tumor-like nodule represents an overgrowth of the mature adipocyte population as a malformation rather than a true neoplasm. (DOI: 10.1293/tox.25.179; J Toxicol Pathol 2012; 25: 179–182)

Key words : brain, cerebrum, lipoma, lipomatous hamartoma, mice, third ventricle

Spontaneous primary tumors and tumor-like lesions of the rodent central nervous system (CNS) are not well defined. In the mouse CNS, tumor-like lesions, such as lipomatous hamartoma and epidermoid cysts, are rarely encountered[1]. Intracranial lipomatous hamartoma is a benign lesion characterized by the accumulation of mature adipose tissue within the ventricles or midline of the brain[2,3]. Intracranial lipomatous hamartoma never shows evidence of invasion or any other indication of malignancy[4]. Therefore, it is considered to be a malformation and not a true neoplasm. Although intracranial lipomatous hamartoma is thought to be related to a neural tube closure defect during embryogenesis[4] and may be associated with dysgenesis of the corpus callosum and lateral displacement of the adjacent blood vessels[5], the histogenesis remains uncertain. In the present report, we describe the histopathological features of a lipomatous hamartoma in a young BALB/c mouse.

The lipomatous hamartoma occurred in a 7-week-old female BALB/cAnNCrlCrlj mouse that was purchased from Charles River Laboratories Japan, Inc. (Atsugi, Japan) and used in an acute chemical toxicity study. The mice used in the study were housed in plastic cages with paper-chip bedding (Paper Clean, SLC, Hamamatsu, Japan) in an air-conditioned room at 22 ± 2°C and 60 ± 10% relative humidity with a 12-h light/dark cycle and fed a commercial diet (CMF 30 Gy; Oriental Yeast, Chiba, Japan) and tap water *ad libitum*. All procedures were in accordance with the guidelines for animal experimentation at Kansai Medical University.

The mouse was anesthetized with isoflurane (Forane®; Abbott Japan, Tokyo, Japan) and sacrificed by abdominal aortic transection. A complete necropsy was conducted. No abnormalities were observed when the mouse was alive or during the necropsy. The brain and other organs were fixed overnight in 10% neutral buffered formalin. Coronal sections of the cerebrum and cerebellum were embedded in paraffin, sectioned and stained with hematoxylin and eosin (HE). Sequential sections were immunohistochemically stained for 1 h at room temperature with anti-proliferating cell nuclear antigen (PCNA) antibody (monoclonal, clone PC10, 1:100 dilution; Leica Biosystems, Newcastle upon Tyne, UK), anti-glial fibrillary acidic protein (GFAP) antibodies (polyclonal, 1:500 dilution; Dako, Carpinteria, CA, USA) or anti-alpha-smooth muscle actin (α-SMA) antibody (monoclonal, clone 1A4, 1:500 dilution; Dako). Antigen retrieval was necessary for PCNA and GFAP visualization and was conducted by pressure-cooker heating (Pascal, Dako). The antigen-antibody complexes were identified using a streptavidin-biotin (LSAB) staining kit (Dako) according to the manufacturer's instructions. The reaction products were visualized with 3-3'-diaminobenzidine tetrahydrochloride.

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Mailing address: Katsuhiko Yoshizawa, Department of Pathology II, Kansai Medical University, 10-15 Fumizono, Moriguchi, Osaka 570-8506, Japan
TEL: 81-6-6993-9432 FAX: 81-6-6992-5023
E-mail: yoshizak@takii.kmu.ac.jp

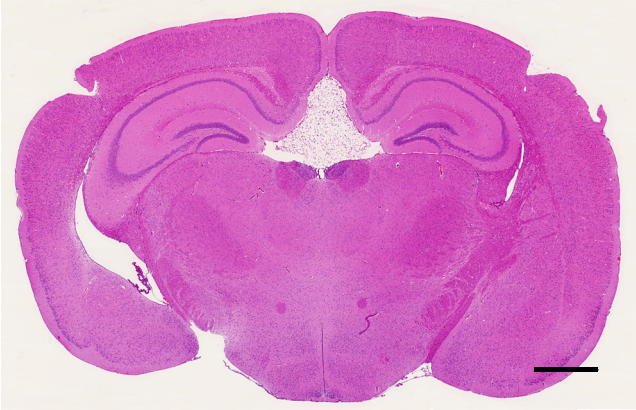

Fig. 1. Lipomatous hamartoma in the third ventricle of the cerebrum. HE stain, bar = 1 mm.

Histopathological findings were reviewed by a toxicologic pathologist certified by the Japanese Society of Toxicologic Pathology and the International Academy of Toxicologic Pathology (K.Y.), according to the previously defined histopathological terminology and diagnostic criteria[3,5].

Histopathologically, a well-demarcated nodule was observed in the third ventricle (Fig. 1). It was composed of well-differentiated adipocytes resembling those seen in adipose tissue, and each adipocyte contained one large fat droplet (Fig. 2a). Cytological atypia was not observed. PCNA signals were not seen in any nuclei of the cells in the nodule (Fig. 2b), suggesting a low level of proliferation. The brain parenchyma at the retrosplenial granular cortex and the hippocampus in the cerebrum were slightly compressed; however, no degenerative changes were seen in the adjacent tissues (Fig. 2c). GFAP-positive glial cells did not proliferate within the nodule or the surrounding parenchyma (Fig. 2d). Scattered capillary vessels penetrated the nodule from the surrounding tissue (Fig. 2e) and were visualized by α-SMA immunohistochemistry (data not shown). The choroid plexus, which is usually located in the roof of the third ventricle, was displaced downward due to compression by the nodule (Fig. 2f). A detailed pathological examination of the organs and tissues revealed no additional lesions in the brain and no distant metastases (data not shown). None of the other study animals had brain abnormalities; therefore, this lesion was believed to be spontaneously occurring and unrelated to chemical exposure.

The lesion was a well-demarcated nodule located in the ventricle and composed of multiple clusters of mature white adipose cells, which are characteristics of a benign lipomatous lesion. The cells had a low level of proliferative activity, as no PCNA signals were seen in the nodule. The characteristics of the lipomatous lesion were not suggestive of a choristoma, which is an overgrowth of heterotopic normal mature resting adipocytes. Rather, the lesion contained an overgrowth of the mature adipocyte population that normally occurs at the site of origin; therefore, it was diagnosed as a lipomatous hamartoma that developed from the roof of the third ventricle. This lipomatous lesion appears to have occurred in the interstitium of the choroid plexus of the third ventricle, and the choroid plexus was displaced downward by the adipose tissues. Capillary vessels in the nodule appeared to be nutrient vessels from the surrounding tissue; hence, our case should be distinguished from an angiolipoma, which includes numerous small vessels. Other elements, such as neural tissues, bone and cartilage, were not present[4,6,7].

The terms "lipoma," "lipomatous hamartoma" and "choristoma" have been used for lesions similar to our case, and these lesions have been reported in several kinds of laboratory animals and humans. Lipomas of the CNS have been observed in the pig, horse, cow, dog, rabbit and fox[8]. In humans, lipomas or lipomatous hamartomas are also rare disorders in the CNS[6,9,10]. The recent World Health Organization (WHO) classification of tumors of the CNS[11] still contains the term "lipoma" for humans. Lipomas are classified as mesenchymal, non-meningothelial tumors and described as "benign lesions that microscopically resemble normal adipose tissue." Additionally, lipomatous hamartomas is used as a synonym of lipomas in the AFIP Atlas of Tumor Pathology[12], and it is noted that a malformative mass com-

Table 1. Literature Review: Intracranial Lipomatous Lesions in Rodents

Species	Report type	Diagnosis	Occurrence / total number of animals	Frequency	Reference
Mouse	NCTR* database	Lipoma	15/45,983 (BALB/c) 0/31,427 (other strains)	0.033% (BALB/c)	Morgan KT *et al.*, 1984
	AFRC and MRC Neuropathogenesis Unit database	Lipoma	110/75,070 (some strains including BALB/c)	0.15% (some strains including BALB/c)	Fraser H *et al.*, 1986
	The Jackson Laboratory database	Lipomatous hamartoma	52 (0 in BALB/c)/nearly 10,000	0.52%	Adkison DL *et al.*, 1991
	NTP** historical data	Lipoma	1/4,894 (B6C3F1)	0.02% (B6C3F1)	Haseman JK *et al.*, 1999
Rat	NTP** historical data	Lipoma / Lipomatous hamartoma	0/7,786 (F344)	0% (F344)	Haseman JK *et al.*, 1990
	Case report (first report in rat)	Intracranial lipoma	1/Unclear (Wistar)	-	Brander P *et al.*, 1995

*NCTR: National Center for Toxicological Research. **NTP: National Toxicology Program.

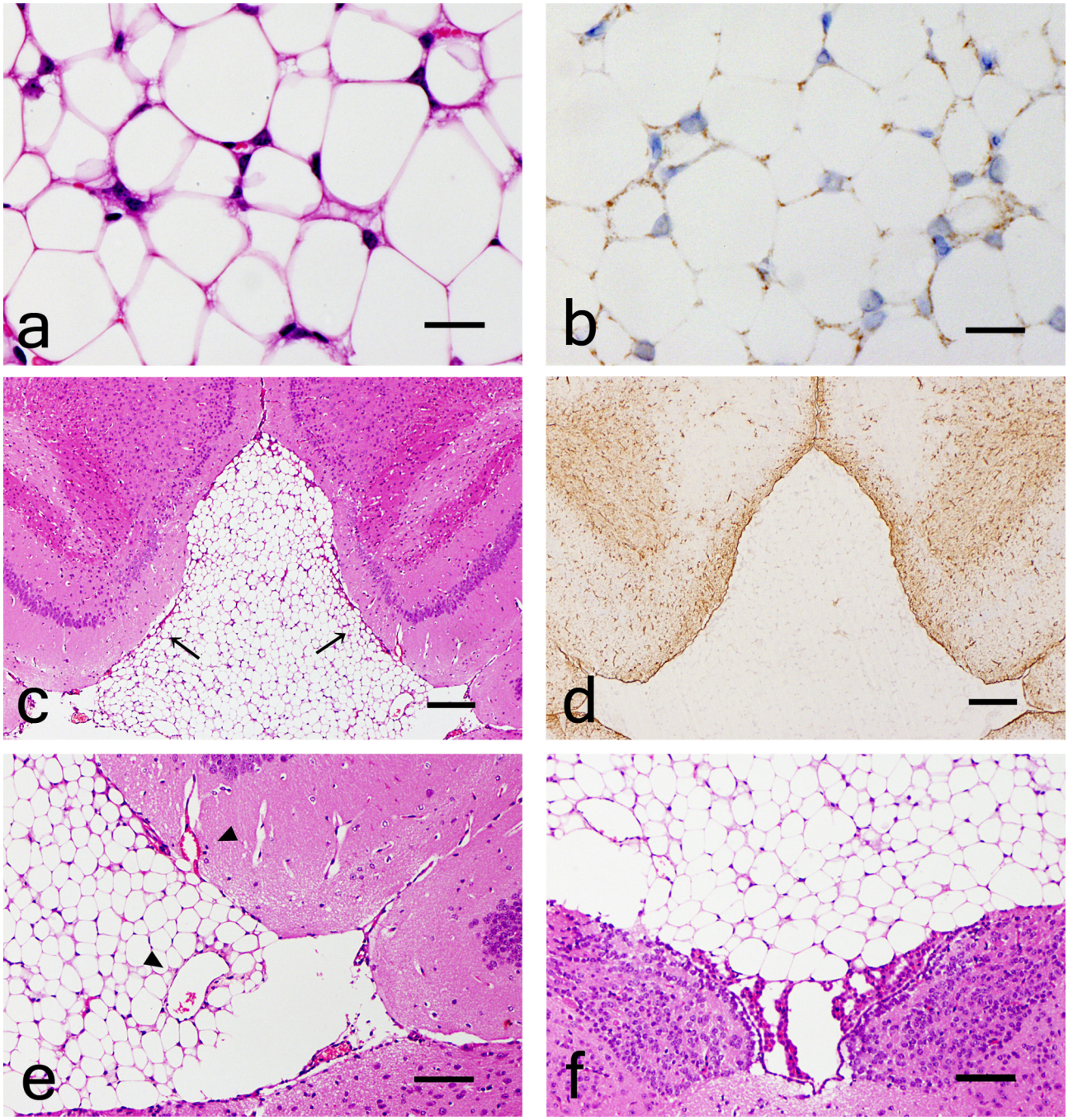

Fig. 2. Histopathological and immunohistochemical findings of a lipomatous hamartoma. (a) The mass is composed of well-differentiated adipocytes, which contain a single large fat droplet, without atypia. HE stain, bar = 25 µm. (b) PCNA signals are not seen in any nuclei of the adipocytes in the nodule. Bar = 25 µm. (c) Brain parenchyma of the retrosplenial granular cortex and the hippocampus in the cerebrum were slightly compressed (arrow). HE stain, bar = 200 µm. (d) GFAP-positive glial cells did not proliferate in the nodule and surrounding brain parenchyma. Bar = 200 µm. (e) Scattered capillary vessels penetrated the nodule from the surrounding tissue (arrowhead). HE stain, bar = 100 µm. (f) The choroid plexus was displaced downward due to compression by the nodule. HE stain, bar = 100 µm.

posed of mature adipose tissue is more appropriately called a "lipomatous hamartoma." According to the diagnostic criteria from goRENI[3], a lipomatous lesion in the cerebrum is defined as a lipomatous hamartoma in rodents. Intracranial lipomatous lesions are frequently localized in the medial line and especially the corpus callosum, where one could expect a neural tube closure defect during embryogenesis[4]. Their histogenesis remains uncertain; however, the term "lipomatous hamartoma" may be more appropriate[6,9].

Previous reports of lipomatous lesions in the rodent CNS are summarized in Table 1. According to the National Center for Toxicological Research database[4], lipomas were

found in 15 of 45,983 (0.033%) BALB/c mice and 0 of 31,427 mice from other strains. Fraser *et al.* identified lipomas in 110 of 75,070 (0.15%) mice including BALB/c mice[13]. The characteristics of the present case were similar to those of the above cases. In contrast, The Jackson Laboratory[2] evaluated nearly 10,000 mice, and lipomatous hamartomas were found in none of the BALB/c mice but were found in 52 (0.52%) mice of other strains. Regarding B6C3F1 mice, only 1 of 4,894 (0.02%) mice had a lipomatous hamartoma according to the National Toxicology Program (NTP) historical data[14]. These data indicate that intracranial lipomatous lesions in mice are extremely rare. In rats, there are only two reports of intracranial lipomas, one case in a Wistar rat[15] and none in F344 rats (NTP historical data[16]). This suggests that the occurrence of lipomatous lesions in rats is lower than in mice.

To the best of our knowledge, BALB/c mice are not commonly used in toxicity and pharmacological studies, and historical control data for BALB/c brain lesions have not been well reported. Our case provides valuable information on the histopathology of an intracranial lipomatous hamartoma in a BALB/c mouse.

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