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Computed Tomography of Monkey Brain Tumors

Toru Satoh, Susumu Nakasone, Kengo Matsumoto, Akira Nishimoto, Hajime Ogura, Takashi Fujiwara, and Kazuo Tabuchi

Abstract: Thirty-five Japanese monkeys were inoculated intracerebrally with chick embryo fibroblasts that were producing Schmidt-Ruppin strain of Rous sarcoma virus. Tumors were induced in 54.3% (19/35). Computed tomography detected tumors in 10 symptomatic animals with an average latency of 32.6 (15–43) days. At autopsy, the brains were sectioned into 5 mm slices, coplanar to the CT image. Various CT features of high- and low-density area correlated well with the histopathological findings, such as tumor, hemorrhage, necrosis, and peritumoral edema. Contrast-enhanced CT detected 10 tumors >4 mm in diameter, and there was ±2 mm potential error in determining tumor size. Follow-up CT revealed growth of tumors in four animals and stabilization of tumor in two animals. Large brain size, 90–110 g in adult monkeys, and availability of induced tumors offer an excellent brain tumor model for CT studies.
Index Terms: Brain, neoplasms—Animal studies—Computed tomography.

Experimental brain tumor in large animals provides a number of advantages. Particularly important is the fact that CT is easily obtainable, even serially, and CT images can be correlated with autopsy specimens (1–3).

We have tried to induce experimental brain tumors in Japanese monkeys (*Macaca fuscata*), which have brains as large as 90–110 g in weight, by intracerebral inoculation of chick embryo fibroblasts that were producing Schmidt-Ruppin strain of Rous sarcoma virus (RSV). In this report we describe our initial experience with CT of virally induced monkey brain tumors as well as the correlation between CT images and autopsy specimens.

MATERIALS AND METHODS

Thirty-five Japanese monkeys, 20 males and 15 females, 2–15 years old, and weighing 2.0–12.6 kg, were used. A monolayer culture of chick embryo fibroblasts (CEF) was prepared and infected with a Schmidt-Ruppin strain (subgroup D) of RSV. A burr hole was made in the right frontoparietal region of the monkeys' skulls under anesthesia with ketamine hydrochloride. The RSV-producing CEF were inoculated into the monkeys' brains with a 21-gauge needle ~10 mm deep from the cerebral surface. After the inoculation, the general condition and neurological symptoms or signs were closely observed and CT studies were carried out under anesthesia. Axial and/or coronal sections, with a slice thickness of 5 mm and scan time of 9.0 s, were obtained in supine position. Contrast-enhancement (CE) was accomplished with intravenous administration of 60% meglumine iothalamate (Conray-60), 1–3 ml/kg.

At autopsy, brains were cut in 5 mm thick slices coplanar to CT scans. Formalin fixed and paraffin embedded specimens were stained by hematoxylin and eosin and were compared with CT images.

RESULTS

Autopsy verified tumors were induced in 19 of 35 inoculated animals (54.3%). The brain tumor-bearing animals became anorexic and hypokinetic and exhibited various neurological signs, such as left hemiplegia, nystagmus, and generalized convulsion. Computed tomography could be performed in 10 symptomatic animals; the latency period before the detection of tumor development by

From the Department of Neurological Surgery (T. Satoh, S. Nakasone, K. Matsumoto, and A. Nishimoto), and Division of Virology, Cancer Institute (H. Ogura), Okayama University Medical School, Okayama, and the Department of Neurosurgery (T. Fujiwara and K. Tabuchi), Kagawa Medical College, Kagawa, Japan. Address correspondence and reprint requests to Dr. T. Satoh at Department of Neurological Surgery, Okayama University Medical School, 2–5–1 Shikata-cho, Okayama, 700 Japan.

1a–d

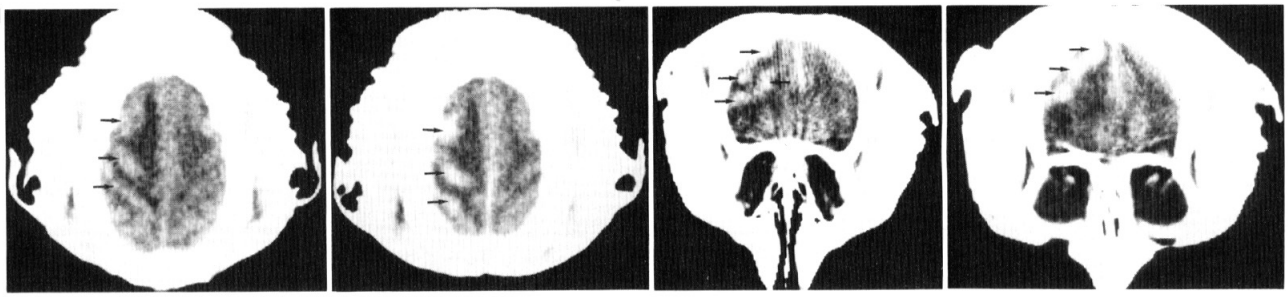

FIG. 1. a: Axial CT scan 24 days after intracerebral inoculation of Rous sarcoma virus-producing chick embryo fibroblasts, demonstrates isodense nodules (arrows) surrounded by perifocal edema in right frontoparietal region. Postcontrast scans (axial **b** and coronal **c and d**) reveal well-demarcated mass lesions (arrows) with slight shift of midline structures toward the left.

CT ranged from 17 to 43 days (average 32.6 days). On plain CT the tumor appeared as a relatively well demarcated, isodense mass surrounded by a perifocal low-density area. Marked enhancement was observed after contrast medium administration (Fig. 1). Ten serial, follow-up CT scans were performed in six of those 10 animals. During the observation period of 17–270 days, tumor growth as judged by CT was observed in four animals (Fig. 2).

Autopsy revealed that the tumors had developed mostly subcortically, at the site of inoculation, but some extended deeply into the ipsilateral ventricle. Except for one case of multiple tumors (Fig. 1), the neoplasms grew as a single mass. The CT images showed a good correlation with the brain specimen features, such as size and extent of tumor, and presence of hemorrhage, necrosis, and peritoneal edema (Figs. 3 and 4). A comparison of autopsy specimens and CE-CT images revealed that the maximum potential error in the tumor size estimation by CT was in the order of ±2 mm. The smallest tumor that could be detected by CT was 4.0 × 5.9 mm.

Histologically, the tumors proved to be fibrosarcomas (17/19) or gliomas (2/19), both showing predominant elongated bipolar cells and occasional large cells with oval nuclei (Fig. 5). At electron microscopy, no RSV particles were observed. Chromosomal analysis of the cultured tumor cells revealed that the mode of diploid number was 42, i.e., identical to that of the monkey (4).

DISCUSSION

At present, CT is one of the most useful neuroradiological examinations for the diagnosis and management of human brain tumors. Site and size of the tumor as well as degree and extent of peritumoral edema can be easily evaluated by CT. To assess the effect of steroids and the various therapeutic modalities of brain tumors, a suitable animal brain tumor model should be established (5–7). It is essential to obtain an experimental brain tumor in a large animal, in which useful CT images can be obtained and compared with neuropathological findings.

Induction of experimental brain tumors in various experimental animals has been carried out

2a,b

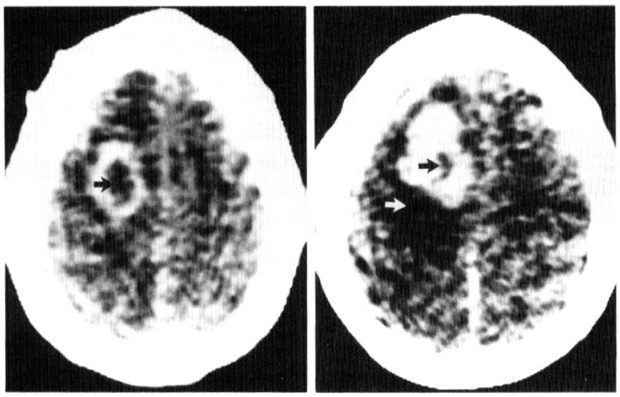

FIG. 2. Postcontrast axial CT scans 15 **(a)** and 32 **(b)** days after inoculation. A dense, irregular mass with central lucency (black arrows) is detected. The mass has increased from 11.3 × 17.3 to 15.4 × 22.7 mm during the 17 follow-up days. Perifocal edema area (white arrow, b) and midline shift are also increased at 32 days.

3a,b

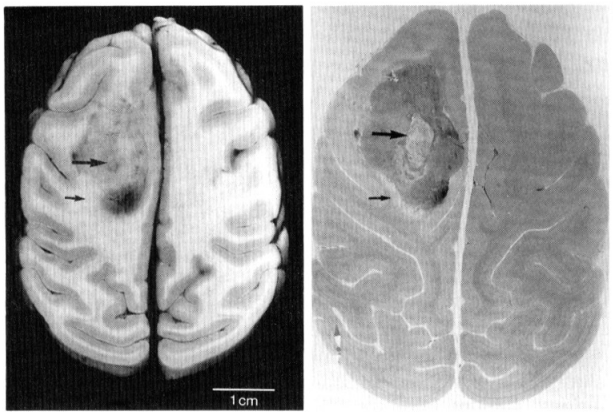

FIG. 3. Gross **(a)** and histological **(b)** specimen of the same monkey shown in Fig. 2 (32 days). CT features (Fig. 2b) correlate well with pathological findings such as central necrosis (large arrows) and peritumoral edema (small arrows). Calculated tumor size in the gross specimen (14.9 × 21.4 mm) is close to that calculated by CT (15.4 × 22.7 mm).

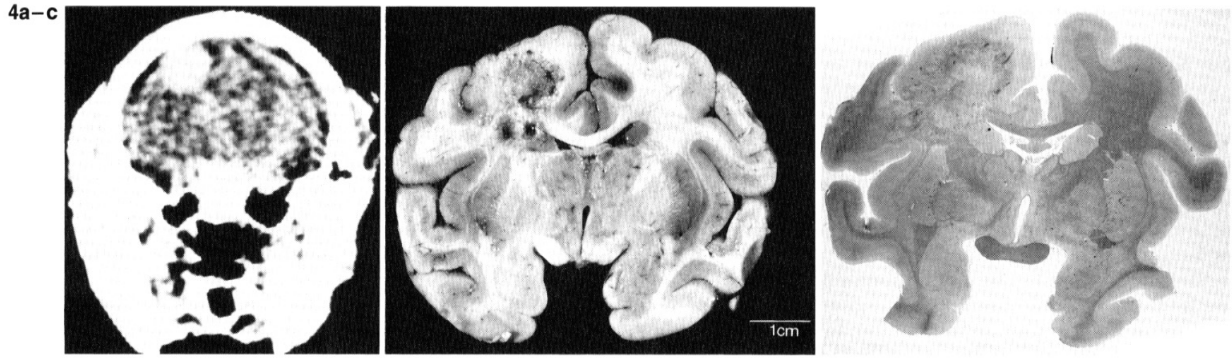

FIG. 4. Postcontrast coronal CT scan **(a)** coplanar to gross **(b)** and histological **(c)** specimen of monkey scanned and killed at 37 days after inoculation. Tumor size estimation by CT was within 2 mm of autopsy finding. (CT: 12.6 × 15.2 mm; gross specimen: 10.6 × 14.2 mm.)

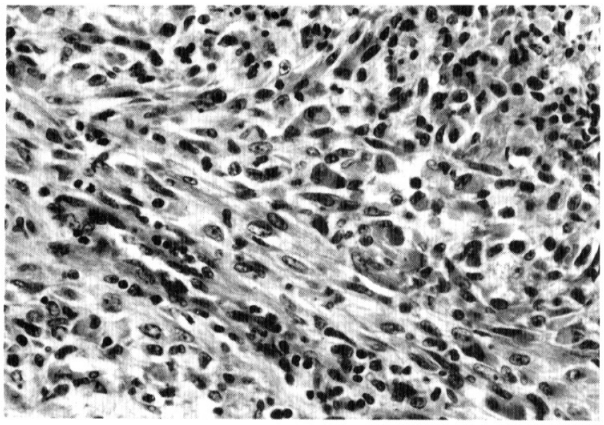

FIG. 5. Tumor induced by Rous sarcoma virus shows predominant bipolar elongated cells. Hematoxylin/eosin. ×300.

since the first successful experiment by Zimmerman and Arnold (8). However, only a few reports on experimental brain tumors in large animals, such as cats, dogs, and monkeys are found in the literature (9,10). We succeeded in producing experimental brain tumors in >50% of the cases (19 of 35 animals) in Japanese monkeys by intracerebral inoculation of RSV-producing CEF. There are only four reports (1,9,11,12) dealing with virally induced monkey brain tumors in the literature (Table 1). Our brain tumor model shows biological similarities with human tumors and is suitable for multimodal therapeutic experiments.

Computed tomography of experimental brain tumors of rats (13), dogs (2,3), and monkeys (12) has been reported sporadically. Kapp and Holla (13) found a high rate of false-negative CT examinations (four of nine animals) in their study of rat brain tumors. Groothuis et al. (2) inoculated RSV in the brains of seven newborn dogs and induced four astrocytomas and two sarcomas. They compared the CT images with pathological specimens and found the extent of CE and the distribution of peroxidase permeability to correlate well. Rieth et al. (1) inoculated JC virus in 26 brains of adult owl monkeys and 10 of adult squirrel monkeys, producing four gliomas. They could detect the tumors on CT before the appearance of symptoms in three cases. However, the rate of induction was as low as 11.1% and the latency period was >1 year. Furthermore, the mean brain weight of these two monkey species is low (<20 g).

We could produce brain tumors at a relatively high incidence rate in adult monkeys. The latency prior to CT detection was 15–43 days (average 32.6 days). Enlargement of the tumor could be observed by serial follow-up CT. Since the mean brain weight of adult Japanese monkeys is as large as 90–110 g, the CT images are of satisfactory quality. The comparative examination of CT images and autopsied brains corresponded well with the findings.

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TABLE 1. *Virally induced monkey brain tumors*

Investigators	Year	Species	Virus	Incidence (%)
Jänish et al. (11)	1968	Rhesus monkey (newborn)	Rous sarcoma virus (RSV)	3/8 (37.5)
Ikuta and Kumanishi (9)	1973	Crab-eating monkey (adult)	RSV	4/9 (44.4)
London et al. (12)	1978	Owl monkey (adult)	Polyomavirus (JC virus)	2/4 (50.0)
Rieth et al. (1)	1980	Owl monkey (adult); squirrel monkey (adult)	Polyomavirus (JC virus)	3/26 (11.5) 1/10 (10.0)
Satoh et al. (this study)	1985	Japanese monkey (adult)	RSV	19/35 (54.3)

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