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Successful treatment of feline hyperadrenocorticism with pituitary macroadenoma using radiation therapy: a case study

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ABSTRACT. A 10-year-old castrated male cat showing behavioral (irritation, prowling, and tumbling) and cutaneous abnormalities such as dermal fragility was diagnosed as hyperadrenocorticism with pituitary macroadenoma, concurrent with insulin dependent diabetes mellitus. Pituitary enlargement (18.0 mm) was observed during magnetic resonance imaging. High endogenous adrenocorticotropic hormone levels (>2,500 pg/ml) were also observed. Although trilostane treatment (5–10 mg/head, daily) was commenced, the clinical signs did not disappear. Insulin and trilostane treatment were discontinued on day 86 after first day of radiation therapy (4 Gy/12 fractions). After radiation therapy, a decreased pituitary tumor size (10.7 mm) was observed on day 301; neurological and dermatological signs exhibited remission. Radiation therapy is the treatment of choice for feline hyperadrenocorticism with pituitary macroadenoma with neurological signs.

KEYWORDS: adrenocorticotropic hormone, cortisol, dermatological sign, neurological sign, trilostane

Feline hyperadrenocorticism with pituitary tumor is an uncommon endocrine disease [1]. Treatment of feline hyperadrenocorticism includes medical therapy with trilostane, radiation therapy (RT), and hypophysectomy [10, 11]. Trilostane treatment induces improvement of clinical signs of Cushing syndrome and decreases the cortisol concentrations in cats, but does not cause remission [1]. However, in some cats with hyperadrenocorticism, trilostane treatment does not improve the clinical signs. Additionally, cats with pituitary enlargement cannot be administered trilostane, because trilostane induces further pituitary enlargement and leads to increasing endogenous plasma adrenocorticotropic hormone (ACTH) concentrations, thereby worsening the neurological signs. RT is another therapeutic option for treating hyperadrenocorticism with pituitary tumor; however, RT has been reported to be only partially successful [4, 5, 9]. Periodic diagnostic magnetic resonance imaging (MRI) or computed tomography (CT) for pre-and post-RT follow-up is yet to be adequately studied.

In this report, we successfully managed a cat with hyperadrenocorticism using RT, wherein gradual shrinkage of the pituitary gland was observed during CT and MRI examination. The current case was the first to show the detailed treatment protocol of RT and document the changes in response of the clinical signs and radiographic changes in feline hyperadrenocorticism with pituitary macroadenoma.

At day −232 (we determined day 1 as first day of RT), a 10-year-old, castrated male Abyssinian cat, weighing 7.2 kg, was brought to a local veterinary hospital. The cat exhibited obesity, polyuria, polydipsia, and hyperglycemia (255 mg/dl); the changes in the blood test results are shown in Table 1 and Fig. 1. Urinalysis revealed a high glucose concentration. The cat was then diagnosed with diabetes mellitus (DM) and started on insulin (2 units/head, twice a day; Prozinc, Boehringer Ingelheim, Tokyo, Japan) (Fig. 1); however, the clinical signs did not resolve, and the bodyweight gradually decreased from 7.2 to 5.5 kg between day −232 to −50. The cat showed behavioral abnormalities such as irritation and tumbling (on day −168), and prowling (on day −50), and cutaneous abnormalities such as endocrine alopecia (on day −168) and dermal fragility (on day −19). Changes in

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Table 1. The course of clinical test results for the cat with pituitary dependent hyperadrenocorticism

Parameters	Units	Day −232	Day −7	Day 21	Day 28	Day 119	Day 210	Day 301	Reference range
Complete blood cell counts									
Red blood cells	/μl	10.36×10^6		5.53×10^6	5.25×10^6	7.07×10^6	8.20×10^6		$6–10 \times 10^6$
Hemoglobin	g/dl	15.1		10.7	10.3	11.3	13.4		10–17
Hematocrit	%	47.1		30.7	29.6	34.9	40.0		30–45
Platelet	/μl	21.1×10^4		43.9×10^4	40.4×10^4	43.1×10^4	27.4×10^4		$20–60 \times 10^4$
White blood cells	/μl	7,300		16,800	13,800	6,400	6,600		5,500–19,500
Blood biochemical tests									
Glucose	mg/dl	255	229	249	284	119	98		69–148
Total protein	g/dl	7.5	5.8	6.2	6.1	7	7.2		5.5–7.8
Albumin	g/dl	3.4	2.2	2	2	2.3	2.2		1.9–3.2
Aspartate aminotransferase	IU/l	33	31	26	25	26	24		16–53
Alanine aminotransferase	IU/l	39	35	28	30	35	35		18–84
Alkali phosphatase	IU/l	91	60	64	63	51	43		38–165
Total cholesterol	mg/dl		162	127	142	179	139		75–176
Triglyceride	mg/dl		23	49	42	15	24		7–77
Blood urea nitrogen	mg/dl	16.1	11.7	12.4	16.2	33.4	36.3		15.6–33.0
Creatinine	mg/dl	1.05	0.76	0.71	0.77	1.36	1.66		0.75–1.85
Calcium	mg/dl	10.8	8.4	8.8	8.6	9.2	9.5		8.2–12.1
Phosphorus	mg/dl	2.9	3.2	3.1	3	4.6	4		2.6–6.0
Sodium	mEq/l	157	153	156	155	154	153		147–156
Potassium	mEq/l	3.8	3.6	3.5	3.7	4.2	4.1		3.4–4.6
Chloride	mEq/l	112	118	120	121	119	118		102–117
Adrenocorticotropic hormone	pg/ml		>2,500		>2,500	1,446	792	699	4.0–36.0

neurological and dermatological signs during days −232 to 301 are shown in Table 2. Pituitary enlargement (18 mm) was observed during MRI on day −30 at a veterinary diagnostic imaging hospital (MRI imaging could not be obtained). The ACTH stimulation test was conducted by collecting blood samples for the determination of the serum cortisol concentration pre and 1 hr after (post) the intravenous injection of 0.125 mg of ACTH (Cortrosyn, Daiichi Sankyo, Tokyo, Japan). ACTH stimulation testing showed a high cortisol concentration on day −26 (pre 13.2 μg/dl, post 17.8 μg/dl). Abdominal ultrasound examination revealed that the minor axis size of the adrenal gland was 5.3 mm on the left and 6.3 mm on the right, wherein bilateral enlargement was confirmed. The cat was diagnosed with hyperadrenocorticism with pituitary macroadenoma, concurrent with DM. Although trilostane treatment (5 mg/head, once a day; Kyoritsu Seiyaku, Tokyo, Japan) was started on day −19 (Fig. 1), the dermatological and neurological signs did not improve, and the owner requested RT nevertheless during the administration of trilostane.

On day −7, the cat was transferred to Nippon Veterinary and Life Science University Veterinary Medical Teaching Hospital (Tokyo, Japan) to undergo RT for an enlarged pituitary tumor. Physical examination revealed a bodyweight of 4.65 kg, temperature of 37.8°C, and heart rate of 240 beats/min. The cat had polyuria polydipsia, mild anorexia, mild lethargic and circling. Figure 2 (a, b) shows the cutaneous abnormality of the cat on day −7. Endogenous ACTH levels were high (>2,500 pg/ml; reference range, 4–36 pg/ml). The cat still required insulin administration (2 units/head, twice a day; Prozinc) for maintaining good glucose control (Fig. 1). Table 1 shows the course of the blood test results between days −7 and 301. Informed consent (verbal or written) was obtained from the owner or legal custodian of the animal described in this work for all procedure(s) undertaken. For the individually identifiable animal in the photographs of this publication, informed consent (verbal or written) for the use in the publication was obtained from the people involved.

RT was performed to decrease the size of the pituitary tumor and ameliorate clinical signs and insulin resistance using a linear accelerator with a beam energy of 6 MV (Elekta Synergy; Canon Medical Systems Corp., Ootawara, Japan). The cat was sedated by intravenous injection of 6 mg/kg body weight of propofol (Propofol Intravenous Injection 1%; Fresenius Kabi Japan Corp., Tokyo, Japan), and then anesthetized with isoflurane and oxygen admixture.

RT planning was performed based on a CT scan (Aquilion PRIME TSX-303A; Canon Medical Systems Corp.). The cat was placed in the prone position with a customized tooth-form device and a vacuum-mattress immobilization device. A CT scan was performed with intravenous administration of 600 mgI/kg of iopamidol (Iopamidol 300, Hikari Pharmaceutical Co., Ltd., Tokyo, Japan), and a strongly enhanced irregular mass (height 15.5 × width 17.7 × length 22.4 mm) involving the cerebral arterial circle was observed from the base of the brain to the thalamic area. The mass displaced the third ventricle to the left with partial dilation (Fig. 3a).

The treatment plan was generated using a three-dimensional CT-based computer treatment planning system (Monaco; Elekta, Tokyo, Japan). Daily patient position verification was performed using a corn beam CT. Gross tumor volume (GTV) was defined on the CT images. The planning target volume (PTV) was defined by expanding the margin of the GTV by 3 mm. The dose-volume histogram constraints for the organs at risk were as follows: brain-PTV, V46 Gy <2 cc, and Vmax <56 Gy. The D95 was

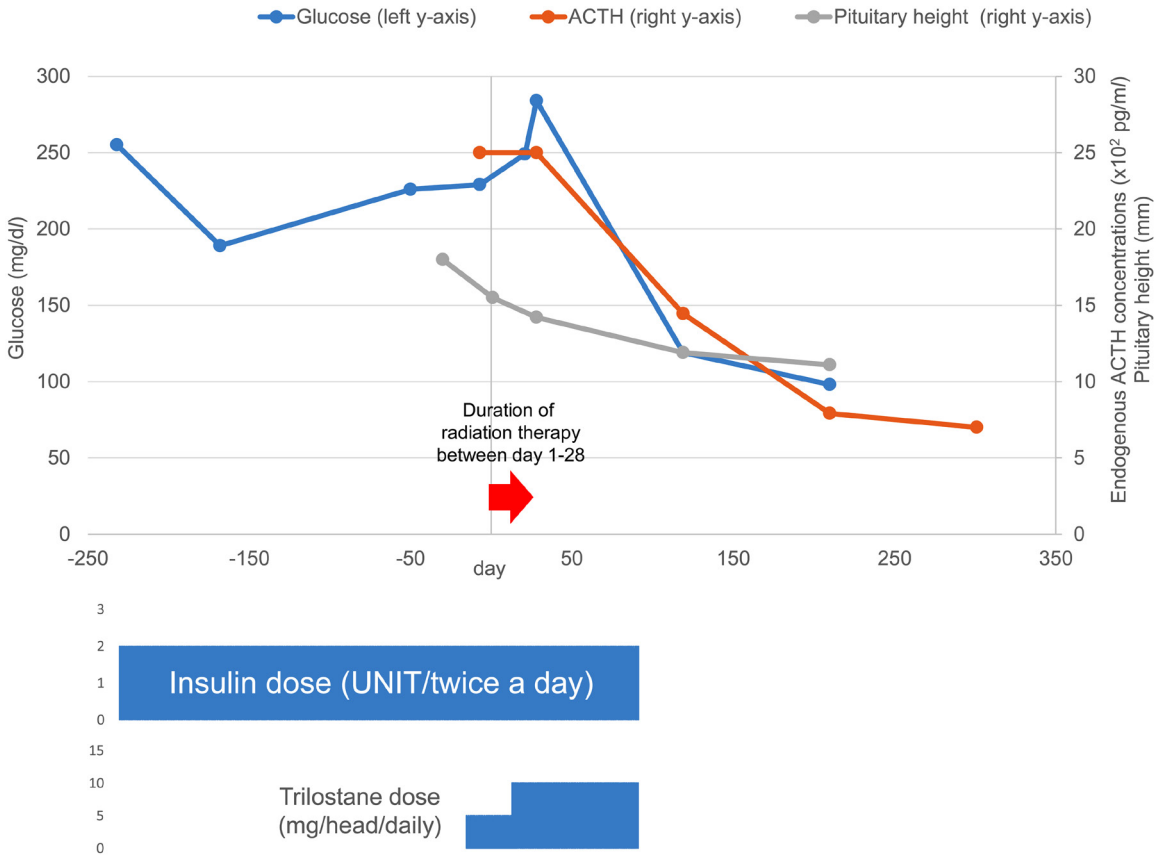

Fig. 1. The changes in serum glucose concentrations (mg/dl) (left y-axis, blue line), endogenous adrenocorticotropic hormone (ACTH) concentrations ($\times 10^2$ pg/ml) (right y-axis, orange line) and pituitary height (mm) (right y-axis, gray line) in the cat during day −232 to 301. Duration of radiation therapy between day 1–28 is shown in red arrow. Dose of insulin (UNIT/ twice a day) and trilostane (mg/head/daily) are shown in blue boxes corresponding to the treatment day.

48 Gy. The isocenter and beam arrangements were determined based on the PTV locations and adjacent critical normal structures. Beam arrangements were determined in six directions (30, 90, 150, 210, 270 and 330). The linear accelerator was equipped with a multi-leaf collimator (5 mm leaves), which was used to block adjacent normal tissues. The cat was administered 4 Gy per fraction, delivered to a total dose of 48 Gy with three fractions per week for a total of 12 fractions (day 1 to 28). The minimum, maximum, and mean doses in the GTV were 46.9, 49.1, and 50.4 Gy, respectively. Figure 4 presents examples of a dose volume histogram (DVH) and dose color wash from the treatment planning software.

No acute adverse effects were observed during the RT. However, during the course of RT, the dermatological signs gradually worsened. Dose of trilostane was increased (5 mg/head, twice a day) on day 9 (Fig. 1). However, endocrine alopecia had become widespread with dermal fragility and fracture of the skin on day 16 (Fig. 2c, 2d).

After the course of RT (4 Gy, 12 fractions from day 1 to 28), polyuria, polydipsia and cutaneous abnormalities such as endocrine alopecia and dermal fragility gradually improved on day 28 (Table 2). In addition, neurological signs showed remission (Table 2). The heart rate was 180/min, and blood pressure on day 28 was as follows: systolic, 110 mmHg; average, 76 mmHg; and diastolic, 60 mmHg.

On day 28, MRI was performed with a 3.0-Tesla unit (Signa® HDtx 3.0T, GE Healthcare Japan, Tokyo, Japan) using an 8-channel human knee array radiofrequency coil. The tumor had an inhomogeneous internal structure with an iso-low intense signal on T2-weighted (T2W) images with a transverse acquisition. Mild edema was observed around the tumor. The cerebral sulcus was obscured, and increased intracranial pressure was suspected. The tumor size on Gd-T1-weighted (Gd-T1W) images was slightly reduced (height 14.2 × width 17.1 × length 19.1 mm) than that before RT (Fig. 3b).

Polyuria and polydipsia were greatly improved. Euglycemia was confirmed, and insulin administration was discontinued from day 86. The dermatological condition greatly improved, and trilostane treatment (5 mg/head, twice a day) was discontinued from day 86 (Fig. 1).

On day 119, MRI revealed a decreased pituitary tumor size (height 11.9 × width 17.3 × length 17.3 mm; Fig. 3c). Edema around the tumor and the clearness of the cerebral sulcus were improved on T2W images. No adverse effects were observed on MRI examination of the pituitary region after RT. In addition, dermatological signs showed remission (Fig. 2e, 2f) (Table 2). Endogenous ACTH levels were high (1,446 pg/ml); however, a decrease was observed compared to the levels before RT (Table 1).

Table 2. Changes in neurological and dermatological signs during days −232 to 301 in the cat with hyperadrenocorticism with pituitary macroadenoma

Day	Neurological sign	Dermatological sign
−232	None	None
−168	Irritation and tumbling	Endocrine alopecia
−50	Irritation, tumbling and prowling	#
−30	#	#
−19	#	Endocrine alopecia and dermal fragility
−7	Mild anorexia and mild lethargic, circling	#
1	#	#
10	#	Endocrine alopecia has become widespread with dermal fragility and fracture of skin
13	#	#
21	Activity, appetite and circling improved	#
28	Remission	Endocline alopecia, dermal fragility and fracture of skin improved
86	#	Endocline alopecia, dermal fragility and fracture of skin greatly improved
119	#	Remission
210	#	#
301	#	#

[#] Clinical signs not different from previous medical interview.

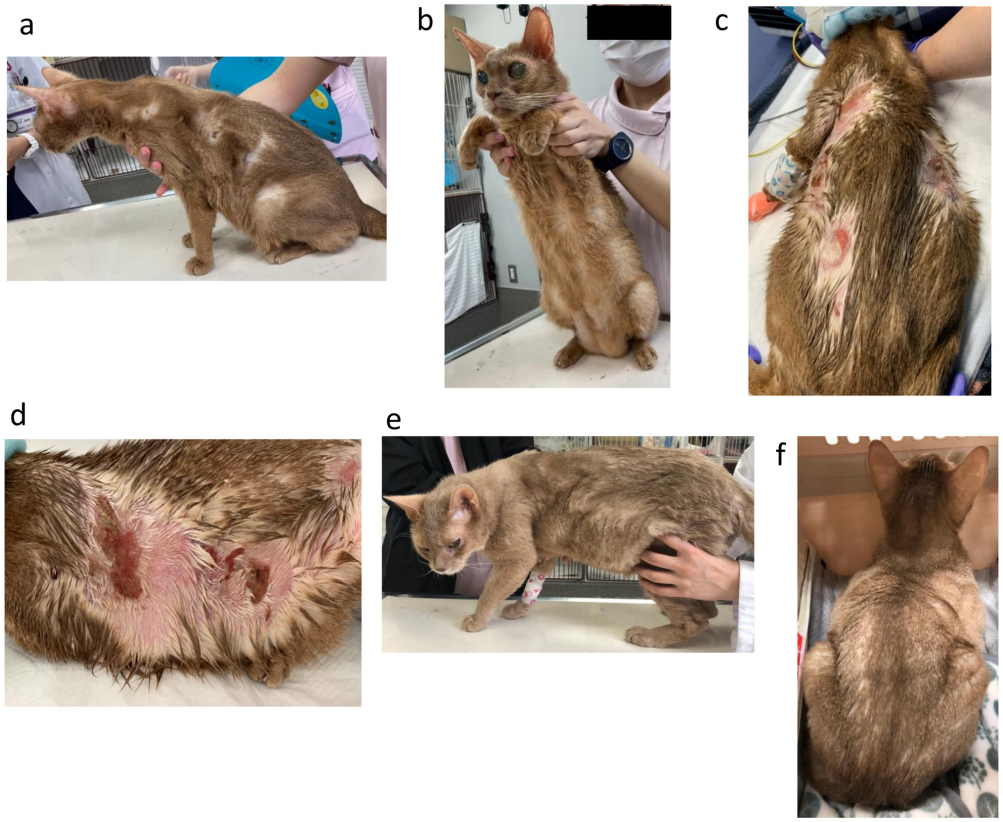

Fig. 2. The change in the clinical appearance of the cat with hyperadrenocorticism with pituitary macroadenoma on day −7 (**a**, **b**), day 16 (**c**, **d**), and day 119 (**e**, **f**). Dermatological signs such as endocrine alopecia and dermal fragility worsened from day −7 to day 16. However, after radiation therapy, the dermatological signs improved from day 16 to day 119.

On day 210, the cat weighed 7.1 kg and had an increased appetite and no neurological or dermatological signs. A further decrease in pituitary tumor size (height 11.1 × width 17.3 × length 16.0 mm) was observed on MRI examination (Fig. 3d). Further improvement of edema around the tumor and clearness of the cerebral sulcus was observed, while acute and late-onset adverse effects associated with RT were not observed. An ACTH stimulation test with similar protocol on day −26 revealed a decreased cortisol concentration (on day 210; pre 2.49 µg/dl, post 10.0 µg/dl) than that on day −26 (pre 13.2 µg/dl, post 17.8 µg/dl). The minor axis size of the adrenal gland was 4.5 mm on the left and 4.8 mm on the right, and a decreased adrenal size was observed

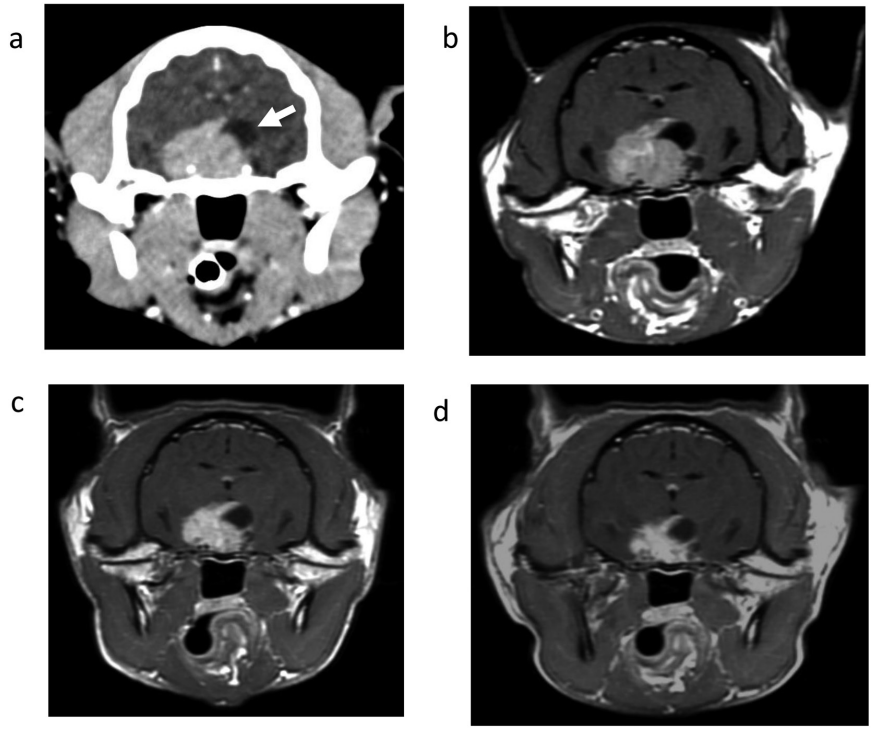

Fig. 3. Computed tomography scan of the pituitary tumor with contrast agent (iopamidol) on day −7 is shown in (**a**). A strongly enhanced irregular mass involving the cerebral arterial circle was observed from the base of the brain to the thalamic area. The mass also displaced the third ventricle to the left and partially dilated the third ventricle (arrow in (a)). Magnetic resonance imaging of the pituitary tumor is shown in (**b**) (day 28), (**c**) (day 119), and (**d**) (day 210). The presence of the pituitary tumor was evaluated using gadodiamide hydrate (Gd)-T1-weighted (T1W) images with transverse acquisitions. The pituitary tumor was demonstrated by a hyperintense signal of the pituitary area on Gd-T1W images. The pituitary tumor gradually decreased in height from day −7 (15.5 mm) to day 28 (14.2 mm), 119 (11.9 mm), and 210 (11.1 mm).

compared to that on day −26. Endogenous ACTH levels gradually decreased (792 pg/ml) compared to those before RT (>2,500 pg/ml) (Table 1). Insulin like growth factor-1 was 263 ng/ml which was within the reference range (138–673 ng/ml, Fuji FILM VET SYSTEMS, Tokyo, Japan) on day 210.

On day 301, MRI examination revealed a further decrease in pituitary tumor size (height 10.7 × width 16.3 × length 15.5 mm), and the endogenous ACTH concentration was also decreased, at 699 pg/ml (Table 1).

In this case, feline hyperadrenocorticism with pituitary macroadenoma with neurological signs was treated using RT, and full recovery from the clinical signs of Cushing syndrome and the neurological signs was observed. Feline pituitary tumors are uncommon and considered to secrete two types of hormones. The major cause of feline pituitary tumors is acromegaly secondary to an increased growth hormone-inducing tumor. Treatment for feline acromegaly has been widely reported, and RT is known to be effective [2, 7, 9, 13]. Another type of pituitary tumor is secondary to an increased ACTH-producing tumor. This type of pituitary tumor induces Cushing syndrome in cats and has discriminative clinical signs such as endocrine alopecia and dermal fragility.

Clinical cases of RT for feline hyperadrenocorticism with pituitary tumor have been reported in textbooks with partial success [4, 5, 9, 14]. The benefit of RT is that it decreases the tumor size in feline hyperadrenocorticism with pituitary tumor patients. Whether RT for feline hyperadrenocorticism with pituitary tumor ameliorates clinical signs such as endocrine alopecia and dermal fragility has not been fully reported. Feldman [5] treated seven hyperadrenocorticism with pituitary tumor cats with RT. All seven cats had obvious clinical signs of feline hyperadrenocorticism, and five had insulin-resistant DM. Four of the seven cats were treated with 15 fractions of radiation (radiation dose was unknown) divided over 3 weeks. One cat exhibited no response and was euthanized 7 months after RT. Two of the four cats appeared to exhibit improved clinical signs with healthier skin. The fourth cat responded well to RT with the resolution of DM. Three of the seven cats were treated with a single large dose of RT (the radiation dose was unknown). However, none of the cats treated with a single large dose exhibited the resolution of the clinical signs of hyperadrenocorticism. Only seven cats were mentioned in textbooks, and the detailed RT protocol and disease course were unknown. Four of eight cats with pituitary tumors had clinical signs of hyperadrenocorticism, and neurologic abnormalities (three of four cats had concurrent DM) were treated with RT [9]. Some cats with concurrent DM had reduced insulin levels. The clinical signs improved after RT, although normal endocrine test results were restored in only one cat. Another study involving 11 cats with pituitary tumors treated with RT was reported [14]. The RT protocol for eight of the 11 cats was a single 15-Gy dose of radiation. The other two of the 11 cats were treated twice with 15-Gy doses, and the last one was treated three times with 15–20-Gy doses. Two of the 11 cats had poorly regulated DM and fragile skin attributed to hyperadrenocorticism; one was euthanized 2

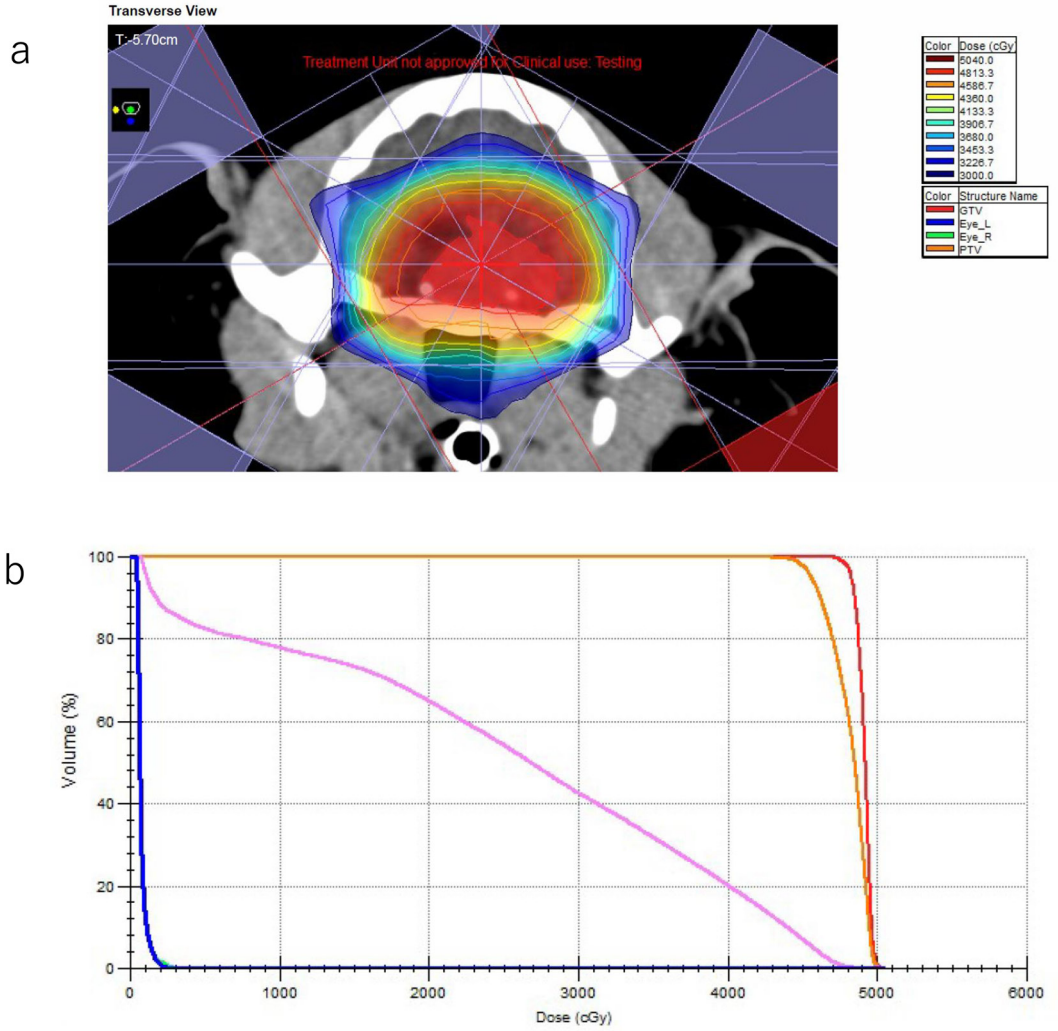

Fig. 4. (**a**) Dose color wash displaying the six-angle beam arrangement what was used most commonly in the current study. Dose color interpretation is displayed on the right side of the image with dose displayed in cGy. (**b**) Dose Volume histogram (DVH) displaying the GTV (red line) and PTV (orange line) curves. Organ at risks in this DVH include eye (blue and green line), and brain minus PTV (pink line). Y-axis displays the percentage of the total volume. The X-axis displays the absolute dose in cGy.

months after radiosurgery because of another disease associated with intra-abdominal masses. The other was alive for 14 months after completing RT; however, changes in clinical signs were not reported. Another study reported that three of 17 cats with hyperadrenocorticism were treated with RT [15]. Two of the three cats with DM and hyperadrenocorticism no longer required insulin after RT. However, in that study, the diagnostic procedure primarily focused on hyperadrenocorticism; thus, the RT protocol and disease course were also unknown. In the above studies, many cases of pituitary tumors included cats with acromegaly, which makes it difficult to parse out information specifically pertinent to those with hyperadrenocorticism and DM [3]. Although the current study only presented one case report, complete reduction of the pituitary size by CT and MRI examinations and restoration of blood hormone levels after RT were observed. Amelioration of clinical signs, including neurological signs, endocrine alopecia, and dermal fragility, as well as remission of DM were observed.

Various RT protocols (receiving doses between 15 and 48 Gy) for treating feline pituitary tumors (mainly acromegaly) have been reported in the literature [2, 6–9, 12, 14]. We used the protocol with 48 Gy in 12 fractions, as in our previous study [13], which is similar to the protocol for feline pituitary tumors with acromegaly. Stereotactic RT (SRT) is also one of the choices for RT in cats with pituitary tumors [16]. Although, that study targeted 53 client owned cats with acromegaly (not ACTH-secreted hyperadrenocorticism), safe and effective results were reported in SRT when compared to those treated with non-SRT. As such, SRT for feline hyperadrenocorticism with pituitary tumor should be studied in the future.

In the present study, no acute adverse effects of RT were observed. However, Mayer *et al*. [9] reported that two of eight cats had acute adverse effects after RT, such as epilation in the treated area and mild bilateral otitis externa. Therefore, the relationship between RT for feline pituitary tumors and acute adverse effects should be further studied in the future. Furthermore, late complications after RT for pituitary tumor have been reported as epilation, brain necrosis, blindness (including cataract

development) and hearing loss [9, 14]. The current study monitored RT related clinical signs for a relatively short term (within 1 year). As such, late adverse effects should be closely monitored with continuous and careful observation after RT.

In conclusion, we successfully treated feline hyperadrenocorticism with pituitary macroadenoma using RT. RT reduces the pituitary tumor size and plasma endogenous ACTH concentrations, ameliorating clinical signs. The detailed treatment protocol of RT and the response of the clinical signs and radiographic changes in the current study give important information for similar feline cases. Therefore, RT is the treatment of choice for feline hyperadrenocorticism with pituitary enlargement.

CONFLICT OF INTEREST. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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