Original Article

Normal thymus evaluation using radiographs and computed tomographic images in young and adult dogs

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Abstract

The thymus generally presents as a sail-shaped soft-tissue opacity on thoracic radiographs in young, pre-pubescent dogs. After puberty, lymphatic tissue is replaced by adipose tissue and can usually no longer be identified on radiographs; however, thymic remnants have often been observed in adult dogs. The objective of this retrospective descriptive study was to investigate the incidence of thymic remnants using thoracic radiographs and to analyze the incidence in dogs by age, sex and breed. We analyzed the data from 1,464 dogs that underwent both thoracic ventrodorsal and right lateral radiography, of which 40 underwent both radiography and computed tomography (CT). The frequency of thymus identification on thoracic radiographs decreased with age in 184 dogs aged < 1 year (P = 0.024). Of 1,280 dogs aged > 1 year, thymic remnants were observed in 81 dogs (6.33%), with a greater frequency in intact female dogs than intact male dogs (P = 0.015). Thymic remnants were observed more frequently in castrated male dogs than in intact male dogs, with borderline significance (P = 0.051). The frequency of thymic remnants was not related to age, body size or breed. Thymic remnants were identified in 20 out of 40 dogs that underwent CT examination, of which two showed thymic remnants on both thoracic radiographs and CT images, and 18 showed thymic remnants only on CT images. In conclusion, although the thymus involutes with aging, thymic remnants may be observed in adult dogs, at an incidence of approximately 6.3%. The frequency of thymic remnants on thoracic radiographs was higher in intact females than in intact males but was not related to age, body size or breed. Additionally, CT could be more useful than radiography for detecting thymic remnants.

Keywords: computed tomography, dog, radiography, thymus, thymic remnants

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Introduction

The thymus is an immunological organ located in the cranioventral mediastinal reflection, which, in dogs, presents as a sail-shaped soft-tissue opacity in the pericardial mediastinum, cranial to the heart and ventral to the base of the heart and aortic arch on thoracic radiographs (Haley PJ, 2003). In dogs, the thymus is normally identifiable until puberty, which begins at between 6 and 12 months, after which the lymphatic tissue is replaced by adipose tissue (Nishino M *et al.*, 2006; Press CM and Landsverk T, 2006; Suster S and Rosai J, 1990) and is not detected on radiographs.

Thymic diseases reported in dogs and cats include thymic bronchial cyst formation or cystic change, thymic hyperplasia, congenital hypoplasia, thymic hemorrhage, thymic amyloidosis and thymic tumors, including thymic lymphoma, thymoma, thymofibrolipoma and thymolipoma (Day MJ, 1997; Morini M *et al.*, 2009). Various opinions have been suggested to explain the relationship between thymic diseases and thymic remnants. A previous study suggested that thymolipoma, defined as fatty neoplasia or hyperplasia of fat tissue, may occur incidentally with thymic remnants (Moran CA *et al.*, 1995; Ramírez GA, *et al.*, 2008). Another study in cats suggested that the histological relationship between malignant thymomas and thymic remnants is evident (Banks WJ, 1993).

Most previously reported thymus diseases were diagnosed pathologically (Day MJ, 1997; Morini M *et al.*, 2009) and a few cases have been diagnosed using diagnostic imaging modalities. In addition, there have been few studies on radiography, ultrasonography or computed tomography (CT) of the thymus in dogs. However, in human medicine, many studies have reported normal thymus and thymic appearance according to sex, age, obesity and smoking on CT (Araki T *et al.*, 2016; Simanovsky N *et al.*, 2012). Thymic remnants are often identified on thoracic radiographs in adult dogs. Thymic remnants should be differentiated from other mediastinal lesions. In addition, previous studies have indicated the necessity for considering the possibility of progression of thymic remnants to thymic disease (Banks WJ, 1993; Moran CA *et al.*, 1995; Ramírez GA *et al.*, 2008; van der Linde-Sipman JS and van Dijk JE, 1987). However, no study has been reported on the incidence of thymic remnants. Based on the author's clinical experience, thymic remnants are often seen as soft tissue or faint fat opacity on radiographs or CT. So, we hypothesized that the incidence of thymic remnants detected by radiographs or CT is relatively high and that thymic remnants may be related to age, sex and breed in dogs.

This study aimed to investigate the incidence of thymic remnants using thoracic radiographs and to analyze the effects of age, sex and breed in dogs.

Materials and Methods

***Animals*:** For this retrospective and descriptive study, the database was screened for thoracic radiographs performed at the Veterinary Medical Teaching Hospital of Kyungpook National University and the Hyundae Animal Vet Clinic between February 2017 and September 2019. All clients had previously signed informed consents for the use of their dogs' data in research. The medical records were reviewed, and the following data was recorded: age, sex, body weight, breed, radiographic features, CT findings at the time of CT acquisition, history of steroid medication and hyperadrenocorticism and diagnosis.

Considering the period of puberty and neutering, dogs aged < 1 year were divided into four age groups: 1–3, 4–6, 7–9 and 10–12 months. Dogs aged > 1 year were divided into six age groups: 1.1–3, 3.1–5, 5.1–7, 7.1–9 and 9.1–11 years, and 11.1 years or older. In the age notation, the decimal point was expressed by dividing the number of months by 12 and rounding from the second decimal place to the first decimal place.

Purebred dogs were divided into four groups according to body size: toy, small, medium and large. This classification was based on that presented by the American Kennel Club (www.akc.org). Mixed-breed dogs were classified by their body weight, as follows: toy (< 5 kg), small (5–10 kg), medium (10.1–25 kg) and large (> 25 kg).

***Radiographic and CT study*:** This study included at least two orthogonal thoracic radiographs obtained at peak inspiration without sedation, including right lateral and ventrodorsal (VD) projections. All of the thoracic radiographs were acquired using a digital radiographic system (AccuRay-603R; DK Medical Systems, Seoul, Korea). Thoracic radiography was performed at 2.0 mAs with a kilovoltage peak (kVp) that gradually increased with increasing body weight as follows: 66 kVp for ≤5 kg, 70 kVp for 5.1–10 kg, 76 kVp for 10.1–15 kg., 80 kVp for 15.1–20 kg, 86 kVp for 20.1–30 kg and 92 kVp for 30.1–40 kg.

For inclusion in this study, all CT scans had to have been performed with a 32-Multislice CT scanner (Alexion; Toshiba Medical System, Otawara, Japan) under general anesthesia. All dogs were appropriately premedicated if necessary. Anesthesia was induced with an intravenous dose of 2 mg/kg propofol (Provive; Myungmoon Pharm, Seoul, Korea) and maintained with 2% isoflurane (Forane; Choongwae Pharm, Seoul, Korea) for the CT scan. The scanning parameters were as follows: 120 kV, 150-200 mA, 1.0 mm slice thickness and 0.75 sec rotation time. Thoracic CT images obtained from the thoracic inlet to the caudal lung field were included in the study. All CT data was reconstructed as three cross-sectional (transverse, sagittal, and dorsal planes) images. Non-contrast and post-contrast CT images were evaluated using a soft-tissue window (window width, 450 Hounsfield unit (HU); window level, 40 HU). Based on the medical records, contrast studies were performed in all dogs included in this study with intravenous administration of 600 mgI/kg iohexol (Bonorex 300 Inj.; Daehan Pharm, Seoul, Korea) for 20 secs using an autoinjector (Medrad, Bayer HealthCare LLC, Whippany, USA).

***Imaging assessment: Radiographs*:** Digital radiographs were reviewed using a picture archiving and communication system (PACS) (INFINITT; INFINITT Healthcare, Seoul, Korea). To detect thymic remnant, images were analyzed for the presence of a triangular soft-tissue opacity, extending from the midline towards the left side, the so called "thymic sail" in VD views (Fig. 1A and B); and/or the presence of a crescent-shaped, soft-tissue opacity, paralleling the cranial border of the heart in the cranioventral thorax in the right lateral view. Other features such as the presence of cranioventral mediastinal reflection, changes in pulmonary parenchymal opacity and pleural fluid were recorded if present. Patients with any condition that increased the opacity of the left cranial thorax on the VD view or cranioventral thorax on the lateral view were excluded. When repeated radiographs were taken of the same dog, only the data from the first radiograph was recorded if no thymus was identified in all radiographs.

Imaging assessment: CT Non-contrast and post-contrast CT images were reviewed and analyzed in a soft-tissue window using the same PACS. The reviewer localized the thymic remnant using the reconstructed images of the system. The thymic remnant located in the cranioventral mediastinum was identified as a predominantly soft-tissue attenuated thymic gland with minimal spotted fat, a triangular thymic gland with half solid tissue and half fat attenuation, or reticulonodular remnants of the thymus with predominantly fat attenuation according to the degree of fatty degeneration in the transverse plane (Fig. 1C and D). It was considered that no thymic remnant existed when complete fatty replacement and no identifiable soft-tissue attenuation in the thymic bed were identified on the transverse plane.

Statistical analysis: Statistical analyses were performed using a commercial software (SPSS 25.0, IBM SPSS Statistics, New York, USA). The analysis was conducted in dogs aged < 1 year and > 1 year, separately. The chi-square test was applied to confirm the relationship between the identification of thymic remnants and age, sex, breed, gonadal status and body size on thoracic radiography in dogs aged > 1 year and to confirm the relationship between the identification of thymus and the four age groups in dogs aged < 1 year. Odds ratio between radiograph and CT was calculated for determining the presence of the thymus or thymic remnant. A *P*-value less than 0.05 was considered statistically significant in all analyses.

Table 1 Distribution of age, sex, and body size in dogs (n = 1464).

	< 1 year (n = 184)		> 1 year (n = 1280)	
Age			1.1–3 years	202
	1–3 months	44	3.1–5 years	168
	4–6 months	58	5.1–7 years	157
	7–9 months	28	7.1–9 years	212
	10–12 months	54	9.1–11 years	173
			Over 11 years	368
Sex	Intact female	73	Intact female	255
	Spayed female	18	Spayed female	383
	Intact male	62	Intact male	176
	Castrated male	31	Castrated male	466
Body size	Toy	141	Toy	739
	Small	26	Small	370
	Medium	15	Medium	117
	Large	2	Large	54

Table 2 Relationships between thymus and age, sex, and body size in dogs aged < 1 year (n = 184).

		1–3 months		4–6 months		7–9 months		10–12 months	
		Yes	No	Yes	No	Yes	No	Yes	No
Thymus identification		9	35	18	40	0	28	6	48
Sex	IF	6	16	6	17	0	11	2	15
	SF	0	1	1	3	0	3	3	7
	IM	3	16	9	16	0	6	0	12
	CM	0	2	2	4	0	8	1	14
Body size	Toy	8	34	13	32	0	18	5	31
	Small	1	1	3	6	0	7	0	8
	Medium	0	0	2	2	0	2	1	8
	Large	0	0	0	0	0	1	0	1

CM, castrated male; IF, intact female; IM, intact male; SF, spayed female

Results

Data was initially obtained from 1,477 dogs, including 1,174 dogs that underwent only one radiography and 303 dogs that underwent radiography more than twice. Among these, 13 dogs were excluded: 5 for mediastinal mass, 4 for increased pulmonary opacity of the left cranial lung field, 3 for pleural effusion affecting thymus identification and 1 for left mediastinal shift. A total of 1,464 dogs were included in this study, including 184 aged < 1 year and 1,280 aged > 1 year. The mean age of dogs aged < 1 year was 7 months and the mean age of dogs aged > 1 year was 8.4 years (range, 1.1–22.4 years). The numbers of dogs according to age, sex and body size are summarized in Table 1. Forty-six different breeds were represented, of which Maltese (n=355, 27.7%), toy poodle (n=150, 11.7%), Shih-tzu (n=131, 10.2%), Yorkshire terrier (n=116, 9.1%), mixed breed (n=113, 8.8%) and Pomeranian (n=104, 8.1%) were the most commonly encountered breeds. In addition, Chihuahua (3.0%), Miniature Schnauzer (2.3%), Cocker Spaniel (1.9%), Bichon frise (1.4%), German Shepherd (1.3%), Miniature Pinscher (1.3%) and Pekingese (1.3%) were relatively common breeds.

The frequency of thymus identification was 20.5, 31.0, 0 and 11.1% at 1–3, 4–6, 7–9, and 10–12 months of age, respectively. In dogs aged < 1 year, the frequency of thymus identification showed a significant linear relationship with age (P = 0.024). The frequency of thymic identification in dogs aged 1–3 and 4–6 months was significantly higher than that in dogs aged 7–9 and 10–12 months (P = 0.002). The thymus was not identified in any dogs aged 7–9 months. However, in dogs aged 10–12 months, the thymus was identified in six dogs. Although there was no difference between the two groups, the frequency of neutralization in dogs aged 10–12 months (46.3%) was higher than that in dogs aged 7–9 months (39.3%) (Table 2).

Thymic remnants were identified in 81 (6.3%) of 1,280 dogs aged > 1 year. The relationships between thymic remnants and age, sex and body size in dogs aged > 1 year are summarized in Table 3. The relationships between thymic remnants and age (P = 0.172) and between thymic remnants and body size (P = 0.089) were not significant. There was no significant difference in the frequency of thymic remnants among the four gonadal status (P = 0.096). However, thymic remnants were observed more frequently in intact female dogs than in intact male dogs (P = 0.015). Thymic remnants were observed more frequently in castrated male dogs than in intact male dogs, with borderline significance (P = 0.051). There was no significant difference in the frequency of thymic remnants among breeds.

Forty of the 1464 dogs who had thoracic radiographs, also underwent thoracic CT scanning. One dog was 4 months old, and the others were aged > 1 year, with a mean age of 9.5 years (range, 2.0–18.4 years). Of the 40 dogs that underwent CT examination, thymic remnants were identified in 20. Two dogs showed thymic remnants on both thoracic radiographs and CT images, and 18 showed thymic remnants only on CT images (Table 4). Odds ratio for radiography and CT indicated that the odds for CT were 19 times greater than for radiography to determine the presence of the thymus or thymic remnant in dogs.

Steroid medication was identified in 48 of the 1,464 dogs, all of which were aged > 1 year. Thirty-seven dogs received short-term administration within 4 weeks and five had a history of treatment for up to 3 months. Six dogs had been administered steroids for more than 3 months in the last 6 months or for the last few years. The most common reasons for steroid use were skin diseases (n = 23), respiratory diseases (n = 7), gastrointestinal diseases (n = 4) and tumors (n = 4). Forty-three of the 1,464 dogs had hyperadrenocorticism. Involution and regeneration of the thymus were detected on serial radiographs in two dogs treated with hormone-affecting medications. One dog diagnosed with eosinophilic pneumonia due to heartworm infection showed thymic remnants on the first thoracic radiograph; however, none was identified on thoracic radiograph after treatment with steroids for 1 month. Another dog diagnosed with adrenal tumor showed no thymic remnants on the first thoracic radiograph; however, after 1 year of trilostane (Vetoryl; Dechra Ltd, North Yorkshire, United Kingdom) administration, thymic remnants were detected on thoracic radiographs.

Table 3 Relationships between thymic remnant and age, sex, and body size in dogs over 1 year of age (n = 1,280).

		Visible thymic remnant		**Total**	***P*-value**
		Yes (%)	**No (%)**		
Age	1.1–3 years	21 (10.4)	181 (89.6)	202	0.172
	3.1–5 years	9 (5.4)	159 (94.6)	168	
	5.1–7 years	8 (5.1)	149 (94.9)	157	
	7.1–9 years	15 (7.1)	197 (92.9)	212	
	9.1–11 years	9 (5.2)	164 (94.8)	173	
	Over 11 years	19 (5.2)	349 (94.8)	368	
Sex	Intact female	22 (8.6)	233 (91.4)	255	0.096[a] 0.015[b] 0.051[c]
	Spayed female	22 (5.7)	361 (94.3)	383	
	Intact male	5 (2.8)	171 (97.2)	176	
	Castrated male	32 (6.9)	434 (93.1)	466	
Body size	Toy	39 (5.3)	700 (94.7)	739	0.089
	Small	24 (6.5)	346 (93.5)	370	
	Medium	12 (10.3)	105 (89.7)	117	
	Large	6 (11.1)	48 (88.9)	54	

[a]Among the four sex groups; [b]Between intact female and intact male; [c]Between intact male and castrated male

Table 4 Thymus or thymic remnants detection on radiographs or CT in 40 dogs

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		Visible thymus or thymic remnant				Total
		Radiographs		CT		
		Yes	No	Yes	No	
Age	< 1 year	0	1	1	0	1
	> 1 year	2	37	19	20	39

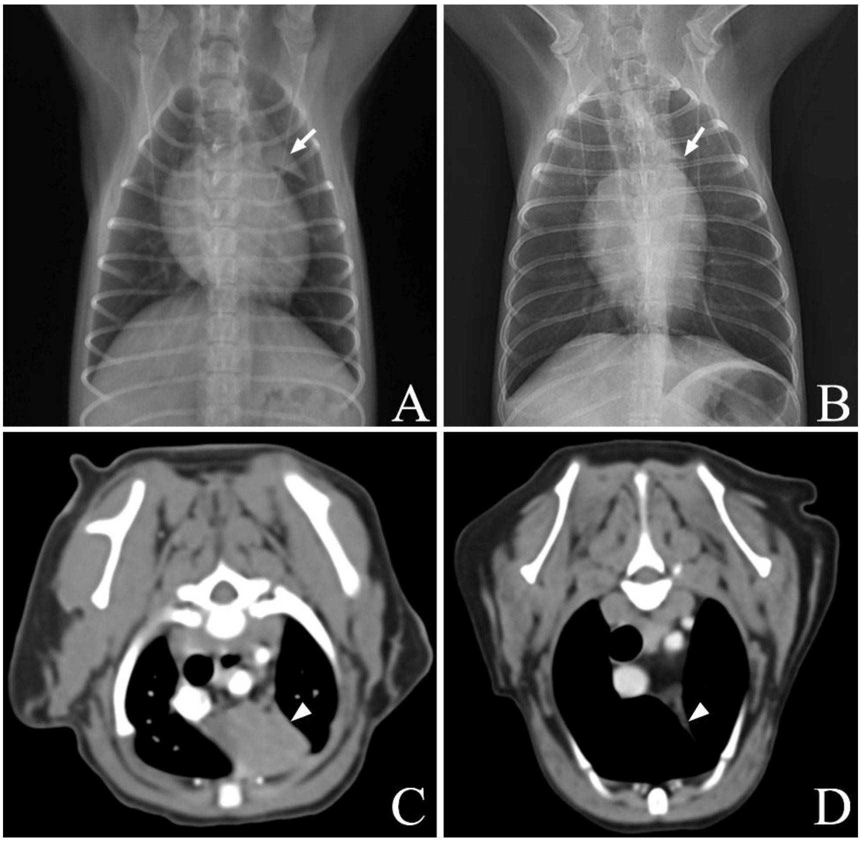

Figure 1 Example thoracic radiographs (A, B) and post-contrast transverse computed tomography (CT) images (C, D) of the cranial thorax in dogs. In dogs under 1 year (A) and over 1 year (B), the thymus can be observed as a triangular soft-tissue opacity extending from the midline towards the left side in left cranial mediastinum, often termed the thymic sail (arrows). On CT images, predominantly soft-tissue attenuating thymus is identified in a 4 months old dog (C, arrowhead), and triangular thymic gland with half soft-tissue and half fatty attenuation is identified in a 12 years old dog (D, arrowhead).

Discussion

The thymus is generally identifiable on thoracic radiographs in puppies up to 6 months (Thrall DE and Robertson ID, 2016), after which it gradually degenerates. Therefore, the present study divided the dogs into groups under and over 1 year of age, to assess the difference in thymic identification.

The thymus is generally identified on thoracic radiography before puberty and degenerates during puberty, which occurs between 6 and 12 months (Press CM and Landsverk T, 2006). In this study, the frequency of thymus identification was also significantly higher in dogs < 6 months of age than in those aged 6–12 months. Unexpectedly, the thymus was not identifiable in 74% of dogs < 6 months of age on thoracic radiographs in this study. There are several possible reasons for this finding. First, on thoracic radiographs, especially in young patients, a small thymus is difficult to discriminate from a cardiac silhouette (Manchanda S *et al.*, 2017; Nasseri F and Eftekhari F, 2010). Second, canine distemper virus infection (Alves CM *et al.*, 2006) and conditions such as immunodeficiency (Jana M *et al.*, 2016) can cause hypotrophy and hypoplasia of the thymus, respectively, making it more difficult to discern. In addition, involution of the thymus can occur due to infection, immunosuppression, surgery or glucocorticoid use (Frush DP, 2008).

Interestingly, in this study, the thymus was not identified on radiographs in dogs aged 7 to 9 months. This may be due to changes in the concentration of growth and sex hormones. A previous study demonstrated that a decrease in growth hormone is involved in the involution of the thymus by confirming that the thymus regenerates after injection of growth hormone (Monroe WE *et al.*, 1987). Leposavic suggested that involution of the thymus coincided with an increase in sex steroid levels as sexual maturation took place (Leposavić G and Perisić M, 2008). This theory suggests that changes in sex hormones play important roles in thymus involution

(Min H *et al.*, 2006). Previous studies have shown that thymus regeneration following orchidectomy or chemical castration demonstrates the effects of sex hormones on the thymus (Fitzpatrick FT *et al.*, 1985; Kendall MD *et al.*, 1990).

Unlike dogs aged 7 to 9 months, the thymus was identified in six dogs aged 10 to 12 months, of which four were neutered. This thymic re-identification may be due to neutralization. Previous studies have reported that neutralizing decreases sex hormones (Kendall MD *et al.*, 1990) and castration in rodents may induce re-growth of the thymus (Greenstein BD *et al.*, 1987; Kendall MD *et al.*, 1990). In addition, sex hormones are directly related to the involution of the thymus (Fitzpatrick FT *et al.*, 1985; Kendall MD *et al.*, 1990; Monroe WE *et al.*, 1987). In another study, castration induced temporary regeneration of the thymus, with the thymus eventually involuting (Min H *et al.*, 2006). This suggests that the thymus, which involutes after puberty, may temporarily regrow after neutralization at 7 to 9 months of age.

A previous study in humans reported that thymic remnants are associated with age and sex (Araki T *et al.*, 2016). As age increases, the soft tissue thymus is replaced by fat and women show less fatty thymus compared to men in their 40s to 60s (Araki T *et al.*, 2016). However, in this study, thymic remnants were not correlated with age. This may be due to fact that, unlike humans, many dogs are neutered. Another human study reported that men aged 20 to 30 years showed earlier fat replacement of the thymus than women (Ackman JB *et al.*, 2013). In addition, in rodents, males show earlier thymic involution than females (Aspinall R and Andrew D, 2001). The difference in thymic involution by sex may result from hormonal differences, particularly, differences in sex-steroid hormone (Ackman JB *et al.*, 2013). In the present study, the frequency of thymic remnants was higher in intact females than in intact males, which is consistent with the results of previous studies.

In large breeds such as Burmese mountain dogs, Great Danes, and Dogue de Bordeaux, the thymic involution begins earlier in life compared to that of small breeds such as Jack Russell terriers and Yorkshire terriers (Holder A *et al.*, 2016). However, we identified no significant relationship between thymic remnants and body size in the present study. It may be that the number of large breeds was insufficient and other factors, such as disease, neutralization and sex, may have influenced the results. To determine the relationship between thymic remnants and body size, further studies are required to assess thymic remnants by subdividing the age groups into large and small breeds.

In this study, involution and regeneration of the thymus were detected in dogs treated with hormone-affecting medications. One dog diagnosed with eosinophilic pneumonia due to heartworm infection showed thymic remnants on thoracic radiographs; however, no thymic remnant was identified on thoracic radiographs after treatment with steroids for a month. This phenomenon is consistent with previous studies showing that the thymus involutes after steroid medication and regenerates when steroids are discontinued (Kong FK *et al.*, 2002). Another dog diagnosed with adrenal tumor showed no thymic remnant on the first thoracic radiograph; however, after 1 year of trilostane administration, a thymic remnant was detected on thoracic radiographs. This change may be due to the decreased release of growth hormone in dogs administered trilostane. Previous studies have shown that release of growth hormones decreases in dogs with hyperadrenocorticism, which supports this finding (Peterson ME and Altszuler N, 1981; Suda T *et al.*, 1980). In addition, other studies have shown that the thymus is involuted in adrenocorticotropic hormone medication or cortisol treatment, while thymus regeneration in rodents with adrenalectomy also supports this(Weaver JA, 1955).

CT characteristics of the normal thymus, identification of lesions and thymic remnants have been described in several human studies (Ackman JB *et al.*, 2013; Araki T *et al.*, 2016; Park CH *et al.*, 1990; Simanovsky N *et al.*, 2012). CT scans are becoming more important because a normal thymus at mid- and old age can be misdiagnosed as other mediastinal lesions (Araki T *et al.*, 2016). In this study, comparison of the detection of normal thymus or thymic remnant between radiographs and CT showed that only two dogs with thymic remnants were identified on thoracic radiographs among 20 dogs where the thymic remnant was confirmed by CT. This is probably because the thymus with fatty replacement is difficult to identify by radiography but relatively easy to identify with CT. In addition, a lack of identification of the thymus on radiographs does not indicate complete involution of the thymus. Therefore, CT could be more useful than radiography for identifying thymic remnants. Further studies on the CT characteristics of the normal thymus and thymic remnants in dogs are warranted.

This study had several limitations which should be noted. First, a relatively small number of dogs were included in the study, especially large dogs, and the distribution of sex, breed and age was unbalanced. Confirmation of thymic remnant or diseased thymus by histopathology was not performed in this study. In addition, clinical information related to autoimmune disease, thyroid disease, malignant tumor, thymus involution and re-growth may have been incomplete as we depended on medical records for this information.

In conclusion, this study is the first to present the relationship between thymic remnants and sex, age and breed in dogs using radiographs. In dogs aged < 1 year, the frequency of thymus identification on thoracic radiographs declines with age. Although the thymus is involuted with aging, it can persist even after puberty. The frequency of thymic remnants on thoracic radiographs was 6.3%, which was higher in intact females than in intact males. The thymic remnants were not related to age, body size or breed.

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