Characterization of triple-phase computed tomography in dogs with pancreatic insulinoma

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ABSTRACT. Little information is available regarding triple-phase computed tomography (CT) of canine pancreatic insulinoma. A few case reports with small numbers of cases have indicated that hyper-attenuation in the arterial phase was a common finding on multi-phasic CT in dogs with insulinoma. Our purpose was to clarify the characteristic findings of dogs with insulinoma on triple-phase CT. Nine dogs with insulinoma that underwent triple-phase CT were included in the present study. Attenuation patterns in the arterial phase indicated hypo-attenuation in 4 cases and hyper-attenuation in 2 cases. In the remaining 3 cases, 1 case showed hypo-attenuation and 1 case showed hyper-attenuation in the pancreatic phase, and 1 case presented hyper-attenuation in the later phase. Altogether, 5 cases showed hypo and 4 cases showed hyper-attenuation in at least one phase. The enhancement pattern was homogenous in 7 cases and heterogeneous in 2 cases. Tumor margins were well-defined in 5 cases and ill-defined in 4 cases. Capsule formation was present in 5 cases and absent in 4 cases. In conclusion, it is important to note that hypo-attenuation was as common as hyper-attenuation in dogs with insulinoma in triple-phase CT in at least one phase. Additionally, mass lesions were most conspicuous not only in the arterial phase but in the pancreatic and later phases in some cases. Therefore, it is important to perform triple-phase CT and notice about variable findings for the detection of canine pancreatic insulinoma.

KEY WORDS: clinical oncology, computed tomography, imaging diagnosis

Insulinoma is most common pancreatic endocrine tumor in dog [5]. Clinical signs are related to hypoglycemia including seizure, weakness and collapse. A provisional diagnosis relies on clinical signs, laboratory data, such as the amended insulin glucose ratio (AIGR), and imaging diagnosis. While AIGR has high sensitivity in detection of pancreatic insulinoma in dogs, AIGR shows false positive result in hypoglycemic patient without insulin secreting tumor [9]. Therefore, visualization of a pancreatic mass lesion is quite essential, and surgical removal of the tumor is needed for both definitive diagnosis and treatment. For an imaging diagnosis, ultrasonography (US) can be used to visualize a mass lesion in the pancreas [14]. The sensitivity of US in detecting insulinoma was reported to range from 28% to 75% [8, 14]. However, the sensitivity of insulinoma detection is operator-dependent, and various factors, such as abdominal fat, gas contents in the gastrointestinal tract and patient characteristics, can interfere with a complete examination of the pancreas. Recently, contrast-enhanced ultrasonography (CEUS) has been applied for the detection of insulinoma in dogs [13, 16]. Although these reports describe the usefulness of CEUS with improved visualization of insulinoma lesions in dogs, this technique potentially has the same limitations described above. In contrast, computed tomography (CT) allows a full and thorough assessment of the entire pancreas. Therefore, CT is another important imaging modality for the detection of canine pancreatic insulinoma. It has been reported that conventional contrast-enhanced CT is a more sensitive imaging examination than non-contrast US or single-photon emission computed tomography (SPECT) [15]. As surgical removal is the first choice for the treatment of dogs with insulinoma, CT is superior to US for insulinoma localization and staging.

In human medicine, the preoperative diagnostic utility of dual-phase CT for pancreatic insulinoma has been well described [6, 10]. It has been reported that this technique has promising sensitivity in the detection of insulinoma. These reports suggest that the arterial phase is essential for detection; hyper-attenuation compared with the pancreatic

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parenchyma is a typical enhancement pattern in insulinoma. In addition, there is a report that mentioned triple-phase CT was more useful than dual-phase CT in the detection of insulinoma [3]. This report suggested that the pancreatic phase was more important than the arterial phase in detecting insulinoma.

In veterinary medicine, there are only 2 reports that described multi-phasic CT in dogs with insulinoma. The first report aimed to establish optimal enhancement conditions for pancreatic tumors in dogs on dynamic CT. In this report, 1 dog with insulinoma showed a hyper-enhanced lesion in the arterial phase [7]. In the second report, 3 dogs with insulinoma underwent dual-phase CT [11]. While 2 cases showed hyper-attenuation in the arterial phase, the findings in 1 case were equivocal to the surrounding pancreatic parenchyma. According to these reports, hyper-attenuation in the arterial phase was a common finding on multi-phasic CT in dogs with insulinoma, as it is in humans. However, the number of the cases was too small to draw conclusions regarding the features of multi-phasic CT in dogs with insulinoma. The purpose of the present study was to clarify the image features of dogs with insulinoma on triple-phase CT.

MATERIALS AND METHODS

A retrospective review of the medical records from the Veterinary Medical Center at The University of Tokyo (VMC-UT) was performed from April 2005 to June 2014. Inclusion criteria were as follows: (1) Dogs that suspected pancreatic insulinoma by clinical symptoms (seizure, lethargy and ataxia) and clinicopathological fidings including increased amended insulin glucose ratio (AIGR;>30); (2) Dogs underwent triple-phase CT, and these data were available for reevaluation; and (3) Dogs with histopahological confirmation of pancreatic insulinoma.

Clinical data, such as breed, age, body weight, blood glucose and insulin levels, amended insulin glucose ratio (AIGR) and presence or absence of a mass lesion in the pancreas on US were collected from medical records. Histopathological findings related to metastates to regional lymph nodes or other organs were also noted from medical records.

All patients had undergone an abdominal helical CT evaluation that included non-enhanced and contrast-enhanced triple-phase CT through the pancreas. Pancreatic triple-phase CT scanning was performed in fixed method during the study period, which described previously with slight modification [7]. In most of the cases, CT images were acquired with a 4-row multi-detector helical CT unit (Asteion Super 4, Toshiba Medical Systems Corp., Otawara, Japan). In the latest 1 case, image was obtained with a 80-row multi-detector helical CT unit (Aquilion Prime, Toshiba Medical Systems Corp.). The patient was in dorsal recumbency and under general anesthesia. The tube rotation speed was 1 sec, slice thickness was 3 mm, and beam pitch was 0.875. The non-contrast plain CT scanning was initiated at the cranial aspect of the diaphragm and extended caudally to the level of the pelvic inlet. On arterial phase of triple-phase CT, the scan was initiated at the cranial aspect of the diaphragm and

extended caudal end of pancreas. Scan area was extended caudally to the level of the pelvic inlet at pancreatic and equilibrium phases. Iohexol (300 mg I/m*l*, Omnipaque 300, Daiichi Sankyo Co., Ltd., Tokyo, Japan) was used as the contrast medium at a dose of 2 m*l*/kg and was injected with a power injector (A-300, Nemoto Kyorindo Co., Ltd., Tokyo, Japan) over 5 to 10 sec (depending on size of the patient) via the jugular vein. Scan delay was fixed and set as 15 sec for the arterial phase, 30 sec for the pancreatic phase and 90 sec for the equilibrium phase after contrast medium injection started [7].

Images were reviewed using OsiriX (Pixmeo, Geneva, Switzerland) by a single radiologist (K.F.). Before image analysis, validity of each phase was assessed depending on following criteria [3]. The phase was considered as the arterial phase, if there was enhancement of the arteries without enhancement of the cranial mesenteric vein. The phase was considered as the pancreatic phase, if there was enhancement of the cranial mesenteric vein. The subsequent phase was classified as the later phase. If any of the phases did not correspond to the criteria, these cases were excluded from the present study.

The features evaluated included location, size, margin description (well-defined or ill-defined) and presence of a tumor capsule. A tumor capsule was defined as a thin curvilinear border that surrounded the tumor and had a distinct difference in attenuation. Presence or absence of lymphadenopathy and hepatic nodule was evaluated.

Enhancement patterns were evaluated as homogenous or heterogeneous. The overall attenuation of the tumor was also noted, which was defined relative to the pancreatic parenchyma during the same phase of imaging (pre-contrast, arterial, pancreatic or later phase). If the lesion had a different CT value in Hounsfield units (HU) (>20 HU compared with the surrounding pancreatic parenchyma), we deemed it to be different and considered these lesions to have hyper- or hypo-attenuation [4]. The phase that presented the most different CT values between the lesion and pancreatic parenchyma was recorded as the most conspicuous phase.

RESULTS

Nine dogs corresponded to the inclusion criteria. Clinical features of each patient are summarized in Table 1. The median blood glucose and insulin levels were 38 mg/d*l* (range, 32–50 mg/d*l*) and 24.2 μU/m*l* (1.8–312 μU/m*l*), respectively (Table 1). The median AIGR value was 200 (range, 90–3,900). As all 9 cases underwent abdominal ultrasonography, mass lesions were identified in 2 cases by US (22.2%). The mass lesions were detected in the right lobe in a case and in the left lobe in another case. On triple-phase CT, tumors were detected in the left lobe in 5 cases, 3 cases were in the right robe, and 1 case was in the pancreatic body. The median maximum diameter of the tumors was 12 mm (range; 9–20 mm).

The overall attenuation on triple-phase CT is summarized in Table 2. Four cases were hypo-attenuated (Fig. 1), and other two cases were hyper-attenuated (Fig. 2) compared

Table 1.　Clinical features of the cases

Case No.	Breed	Sex	Age	BW (kg)	GLU (mg/d*l*)	Insulin (μU/m*l*)	AIGR	US findings	CT findings Location	CT findings Size (mm)
1	Pug	SF	8y10m	7.7	35	15.8	316	ND	Left	20
2	WCP	CM	8y3m	15.6	44	22.9	163.6	ND	Body	8.5
3	Mix	SF	7y6m	11.0	37	13.8	200	ND	Right	12
4	Maltase	SF	9y3m	3.3	32	1.8	90	ND	Left	9
5	Shi Tzu	SF	11y	6.6	34	73.9	1,848	+ (left)	Left	18
6	FCR	CM	7y11m	27.7	45	55.3	368.7	ND	Left	12
7	Mix	M	9y8m	18.6	50	27.6	137.8	ND	Right	12
8	LR	CM	8y9m	33.0	38	312.0	3,900	ND	Left	11
9	Toy Poodle	M	11y	5.8	50	24.2	120.9	+ (right)	Right	12

WCP; Welsh Corgi Pembroke; ACS; American Cocker Spaniel; FCR; Flat-Coated Retriever; LR; Labrador Retriever, M: male; F: female; CM: castrated male; SF: spayed female, AIGR: amended insulin glucose ratio, ND: not detected, Right: right lobe; Left: left lobe; body: pancreatic body.

Table 2.　CT findings in dogs with insulinoma

Case No.	Overall attenuation Non-contrast	Overall attenuation Arterial	Overall attenuation Pancreatic	Overall attenuation Later	Enhancement pattern	Margin Description	Capsule	LN enlargement (CE)
1	Iso	Hypo[a]	Hypo	Hypo	Homo	Well	+	−
2	Iso	Hypo[a]	Iso	Iso	Homo	Ill	+	+ (−)
3	Iso	Hyper[a]	Iso	Iso	Homo	Well	−	+ (arterial)
4	Iso	Iso	Hyper[a]	Iso	Homo	Well	−	−
5	Iso	Hyper[a]	Iso	Iso	Hetero	Ill	−	−
6	Iso	Iso	Iso	Hyper[a]	Homo	Well	−	+ (later)
7	Iso	Iso	Hypo[a]	Hypo	Homo	Ill	+	+ (−)
8	Iso	Hypo[a]	Iso	Iso	Hetero	Ill	+	−
9	Iso	Hypo[a]	Hypo	Iso	Homo	Well	+	−

LN: lymph node, CE: contrast enhancement, Hypo: hypo-attenuation; Iso: iso-attenuation; Hyper: hyper-attenuation, Hetero: heterogeneous; Homo: homogenous, +: present, −: absent, a) The CT value showed the greatest difference between the lesion and pancreatic parenchyma.

with the pancreatic parenchyma at the arterial phase. One case showed hypo-attenuation, and other 1 case showed hyper-attenuation at the pancreatic phase. The remaining one case showed hyper-attenuation in the later phase. Altogether, five cases showed hypo and four cases showed hyper-attenuation in at least one phase. Of these 9 cases, 6 cases were most conspicuous in the arterial phase, 2 cases were most conspicuous in the pancreatic phase (Fig. 3), and 1 case was most distinct in the later phase. Other CT findings are also summarized in Table 2. Enhancement patterns were homogenous in 7 cases and heterogeneous in 2 cases. Margins were described as well-defined in 5 cases and ill-defined in 4 cases. Capsule formation was observed in 5 cases.

Lymphadenopathy was observed in 4 cases (hepatic lymph nodes in 3 cases and splenic lymph nodes in 1 case). Of these 4 cases, a lymph node biopsy was performed in 2 cases (case Nos. 2, 6). While a case with contrast enhancement had the evidence of lymph node metastasis of insulinoma histopathologically, one case without enhancement was diagnosed as lymph node hyperplasia. Although hyper attenuated hepatic nodules were detected in one case in the arterial phase, liver biopsy was not performed and histopathological evidence of metastasis was not confirmed in this case.

DISCUSSION

In this manuscript, we describe the image features of insulinoma on triple-phase CT in a larger number of dogs than previous case reports. In previous reports of multi-phasic CT findings in canine insulinoma, an enhancement pattern of hyper-attenuation in the arterial phase was dominant [7, 11]. However, in the present study, hypo-attenuation (4 cases) was more common than hyper-attenuation (2 cases) in the arterial phase. It has been reported that hypo-attenuation was found as an atypical enhancement pattern in 13% of human insulinoma patients [3]. The reason why hypo-attenuation is common in canine insulinoma compared to human was unknown. It has been reported that histopathological features in canine insulinoma were variable in the following aspects: invasion into the surrounding pancreatic parenchyma, condensation of connective tissue and the presence or absence of a fibrous capsule [1, 2, 12]. Pathological features including condensation of connective tissue and vascular distribution inside the lesion might be related to enhancement pattern, such as hypo or hyper attenuation, in the triple-phase CT. Additionally, invasion into the surrounding parenchyma and fibrous capsule formation might be related to image findings of margin description and presence or absence of tumor capsule. Further investigation focused on histopathological
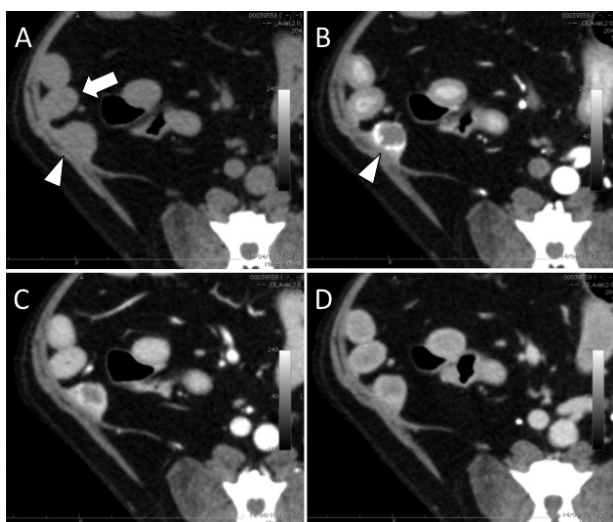
Fig. 1.   Transverse CT images of a patient with insulinoma (case 9). (A) Pre-contrast: the right lobe of the pancreas (arrowhead) was observed at the dorsal area of the duodenum (arrow). A mass lesion is not evident. (B) Arterial phase: a hypo-attenuating mass lesion with marginal ring enhancement is distinctly observed (arrowhead). The description of the margin was well-defined with a capsule. (C) Pancreatic phase: the hypo-attenuating mass lesion was still found in this phase, but gradually became equivocal. (D) Later phase: the mass lesion became more equivocal than in the early phases.
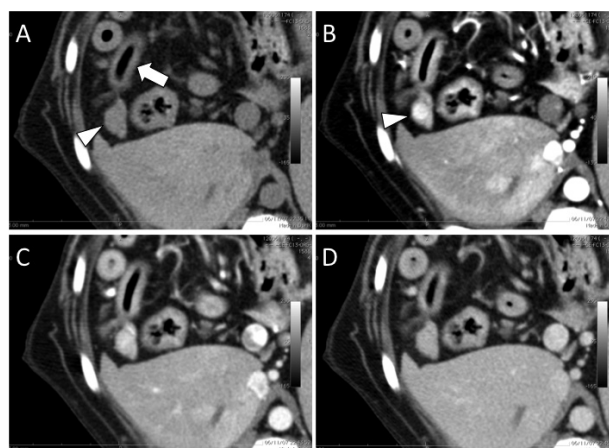

Fig. 2.   Transverse CT images of a patient with insulinoma (case 3). (A) Pre-contrast: the right lobe of the pancreas (arrowhead) was observed at the dorsal area of the duodenum (arrow). A mass lesion is not evident. (B) Arterial phase: a hyper-attenuating mass lesion is distinctly observed (arrowhead). The description of the margin was well-defined without a capsule. (C, D) Pancreatic and Later phases: the mass lesion became equivocal. It is difficult to distinguish the mass lesion from the pancreatic parenchyma.

features is needed to clarify the difference of CT findings, such as hypo or hyper-attenuation, in canine pancreatic insulinoma.

In 6 out of 9 cases, mass lesions were most conspicuous in the arterial phase and corresponded to enhancement patterns in previous reports of dogs and humans with insulinoma [6, 7, 10, 11]. However, 3 out of 9 cases presented a conspicuous mass lesion in the pancreatic or the later phase. There is a report that describes the importance of the pancreatic phase on triple-phase CT for the detection of insulinoma in humans [3]. Additionally, there is a report about CEUS in dogs with insulinoma that describes drastic changes in enhancement patterns for every moment [13]. Therefore, multi-phasic CT is essential (triple-phase must be preferred to dual-phase) to obtain adequate image for the detection of canine insulinoma. Under the triple-phase CT in the present study, however, body weight and anesthetic condition which may affect the results of enhancement pattern of the pancreatic parenchyma or the tumor lesion were not factored in. Therefore, a further study is needed to establish a more adequate protocol for multi-phasic CT on canine insulinoma, such as test injection or bolus-tracking method.

Additionally, in the present study, other CT findings of canine insulinoma demonstrated a wide variety. Seven cases presented homogeneous enhancement patterns, while the other 2 cases showed heterogeneous patterns. Capsule formation was identified in 5 cases, but absent in 4 cases. These various enhancement patterns corresponded with the variable findings in the CEUS literature reported previously
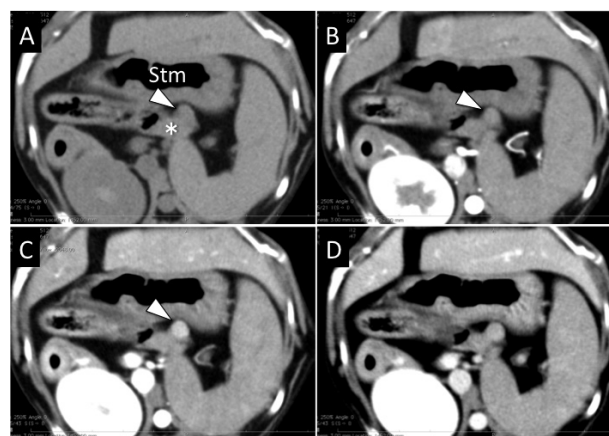

Fig. 3.   Transverse CT images of a patient with insulinoma (case 4). (A) Pre-contrast: the left lobe of the pancreas (*) was observed at the dorsal area of the stomach (stm). A raised lesion was seen, but is not evident (arrowhead). (B) Arterial phase: the mass lesion is not enhanced in this phase (arrowhead). (C) Pancreatic phase: the mass lesion is more distinctly enhanced than the pancreatic parenchyma (arrowhead). (D) Later phase: the lesion is still evident, but more equivocal than in the pancreatic phase.

[13]. It is important to note that these variable findings might be observed when we evaluate canine insulinoma on CT examinations.

Lymphadenopathy was detected in 4 cases on CT. One out of 2 cases with a lymph node biopsy showed histopathological evidence of insulinoma metastasis. Enhancement pattern was consistent with primary tumors and metastatic lymph nodes at the same phase. Another case was found to

be lymph node hyperplasia in the histopathological evaluation; contrast enhancement was not observed in all phases. An enhancement patterns comparable to that of the primary lesion in the pancreas might indicate lymph node metastasis. Although there was 1 case of suspected hepatic metastasis on CT, a biopsy was not performed. As the metastatic rate of canine insulinoma has been reported as 45 to 55% at the time of diagnosis [5], it is important to carefully assess the liver and regional lymph nodes on CT when insulinoma is suspected.

While mass lesions in the pancreas were detected only in 2 cases by US, all of the mass lesions were detected by CT. This result corresponds to that of a previous study in which low sensitivity for the detection of canine insulinoma was reported for US [15]. Additionally, a CT examination allows surgeons to consider surgical removal and plan the surgical procedure. Consequently, triple-phase CT is a superior imaging modality to non contrast-enhanced US as a diagnostic tool for canine insulinoma.

The present study had several limitations. First of all, by the nature of the retrospective study, triple-phase CT in the present study was performed in fixed scan delay, despite different body weight and anesthetic condition of each case. For the large breed dogs, it takes more time for injection of contrast medium than the small breed dogs. That may result in reduced intensity of CT value in the pancreatic parenchyma or the tumor lesion in the large breed dogs. It may affect the results of enhancement pattern in the present study. To reduce these potential technical problems, more precise method for pancreatic CT imaging should be determined, such as test injection or bolus-tracking method. Second, case number was too small in the present study. Further case accumulation of the triple-phase CT is needed to make more certain evidence about image findings in canine pancreatic insulinoma.

In summary, the present study described the characteristics of canine insulinoma on triple-phase CT. It is important to note that hypo-attenuation in at least one phase was as common as hyper- attenuation in dogs with insulinoma in triple-phase CT. Additionally, other variable features of canine insulinoma were identified including that homogenous and heterogeneous enhancement patterns were present, descriptions of tumor margins ranged from ill-defined to well-defined, and both the presence and absence of capsule formation were observed. Although the arterial phase is essential for the detection of canine insulinoma, the pancreatic and the later phases are needed to avoid missing detection of the lesion. It is important to be familiar with the findings of canine insulinoma when evaluating CT images suspicious for insulinoma.

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