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Contrast-Enhanced Ultrasonographic Detection and Dual-Phase Computed Tomographic Angiography in a 5-Year-Old Boxer with Pancreatic Insulinoma—Case Report

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Abstract

This case report describes the findings in a canine histopathologically confirmed pancreatic insulinoma using contrast-enhanced ultrasound (CEUS) and dual-phase computed tomographic angiography (CTA). The insulinoma was better demarcated in CEUS and CTA compared with conventional B-mode ultrasound. On the other hand, only one of two nodules visible in CTA was detected in CEUS. In this case, the insulinoma had an atypical non-contrast-enhancing appearance in both CEUS and CTA. Lack of enhancement in CEUS and CTA has previously been reported in human and canine studies, but this was the first report using both CEUS and CTA for detecting canine insulinoma.

Keywords

Pancreas, Insulinoma, Dog, Contrast-Enhanced Ultrasound, Contrast-Enhanced Computed Tomography

1. Introduction

Insulinoma is the most common tumor of pancreatic islet cells in dogs. The typical insulinoma patient is a me-

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dium- to large-breed dog with a mean age of 8 - 9 years [1]. Most insulinomas are malignant [2]. The general life expectancy for insulinoma patients is about one year [1]. Metastatic lesions are detected in approximately 50% of canine insulinomas [2]. Insulinomas are usually solitary and discrete, but multiple tumors and diffuse infiltrates have also been reported. Malignant insulinomas (carcinomas) are larger, multilobular masses that invade the parenchyma and contain areas of hemorrhage and necrosis. Insulinomas autonomously produce insulin despite falling blood glucose concentrations, resulting in a paraneoplastic syndrome of episodic hypoglycemia. Common clinical signs include confusion, bizarre behavior, episodic muscle weakness, tremors, ataxia, hindlimb weakness and collapse, and even epileptiformic convulsions. The physical examination is usually normal apart from some weight gain [1]. A diagnosis of insulinoma can be made based on typical history and repeatedly high serum insulin despite hypoglycemia in a fasting blood sample [1].

Imaging studies are often used in evaluation of insulinoma patients. Ultrasound examination is relatively inexpensive, repeatable, and does not always require anesthesia. However, the sensitivity and specificity of ultrasound can be poor [3] [4]. A normal-appearing pancreas on ultrasound does not exclude insulinoma since isoechoic pancreatic lesions may go unnoticed in baseline ultrasound [3]. Furthermore, considerable overlap exists in the ultrasonographic appearance of various pancreatic diseases. A differential diagnosis for nodular changes in the pancreas includes nodular hyperplasia, hematoma, and neoplasia. In addition, some pancreatic neoplasias may also mimic pancreatitis due to concurrent inflammed and necrotic areas and possible abscessation. The accuracy of ultrasound examination depends on the technician's skill, the size of the lesion, and the quality of the sonograms [5]. The relatively low sensitivity in canine studies may arise from factors decreasing image quality such as motion artifact caused by movement of unsedated patients, deep-chested body conformation, and intestinal contents or gas [5].

Previous canine studies have shown an increased number of nodules in the pancreas and improved anatomic localization with CEUS (contrast-enhanced ultrasound) compared with conventional ultrasound [4]. In addition, the nodule margins have been better demarcated with CEUS [4] [6]. However, in a recent case series of three dogs with pancreatic nodules with histologically confirmed insulinoma the nodules were visible using both conventional and CEUS [6]. In a study performed on humans, an overall accuracy of CEUS for the differential diagnosis in solid pancreatic masses was 81%, and CEUS had good diagnostic accuracy in differentiating contrast-enhancing and non-contrast-enhancing pancreatic solid lesions [7].

In a case series of three dogs with pancreatic insulinoma, each of the three nodules showed different enhancement patterns (first enhancing then non-enhancing). One of the dogs had an insulinoma with an untypical enhancement pattern in CEUS. After injection of the contrast agent, the nodule remained hypoechoic to the adjacent pancreatic parenchyma and became more clearly demarcated for over 30 seconds [6]. In a study with humans, most endocrine tumors had a hyperenhancing pattern in CEUS (140/190), but some lesions had a hypoenhancing (28/190) or isoenhancing (9/190) pattern [8].

The appearance of insulinoma in CTA has been shown to be variable in both veterinary and human studies. CTA has revealed pancreatic insulinomas not seen in conventional ultrasonography in multiple canine studies. Most of the canine insulinomas have shown typical strong enhancement during the arterial phase, but lack of enhancement has also been reported [9] [10]. The conclusion has been that multiphasic CTA has a moderate sensitivity in the detection of insulinomas, and most tumors are more conspicuous during the earlier phases of enhancement [11].

This case report describes the findings in a canine pancreatic insulinoma using CEUS and CTA. The insulinoma was better demarcated in CEUS and CTA compared with conventional B-mode ultrasound. In this case, the insulinoma had an atypical non-contrast-enhancing appearance in both CEUS and CTA.

2. Case Report

2.1. Case

A 5-year-old female boxer was referred to the Veterinary Teaching Hospital of the University of Helsinki, Finland, for further examinations and diagnostic imaging because of hypoglycemia and episodic weakness/seizures and suspected insulinoma. The dog had been examined three weeks earlier by a veterinarian and two weeks earlier by a veterinary neurologist. Blood glucose values during these visits had been 3.8 mmol/l (3.3 - 6.1 mmol/l) and 1.7 mmol/l (3.5 - 5.5 mmol/l), respectively. The blood insulin level had also been examined at two weeks, yielding a borderline value of 17.8 mU/l (10 - 20 mU/l), indicating possible insulinoma, high/normal insulin

level.

The dog had been on prednisolone medication (0.19 mg/kg eod) for a long time because of atopic skin. One week earlier, the prednisolone dose had been increased to 0.19 mg/kg bid. The dog had had polydipsia and polyuria for a long time, likely due to long-term corticosteroid use.

At presentation, the physical examination was normal. The following blood analyses were performed: complete blood cell count, serum biochemistry, serum fructosamine, CRP and clotting factors, and urinalysis. Laboratory findings indicated a mild hypoglycemia (2.9 mmol/l, 4.0 - 6.4 mmol/l) and an increase in alanine aminotransferase (ALAT) (209 U/l, 18 - 77 U/l). All other blood values were within normal ranges. Repeated blood glucose measurements were performed when the dog visited the University Hospital Clinic. The lowest blood glucose measurement that day was 2.2 mmol/l. Insulin measurement was performed simultaneously, revealing an abnormally high result (S-Insulin 200: 59.5 mU/l, 0.10 - 20.0 mU/l), indicating insulinoma. Thoracic radiographs were taken to rule out pulmonary metastases; no abnormal findings emerged. Abdominal ultrasonography (Philips iU22, C5-8 curvilinear transducer, Philips Oy Healthcare, Finland) was performed to evaluate the pancreas for presence of nodular or mass lesions indicating insulinoma. The pancreas was focally enlarged at the region of the corpus (thickness 2.2 - 2.6 cm) with a heterogeneous echo pattern, but no focal nodular or mass lesions were detected. In addition, several hypoechoic nodules were noted in the spleen (max size 1.1 cm). Cytological examination of ultrasound-guided splenic aspirates revealed findings consistent with benign nodular hyperplasia.

The following week, the dog came back to the hospital for further diagnostic imaging. The blood glucose measurements were normal (4.2 mmol/l) that day. The dog underwent contrast-enhanced ultrasonography (CEUS) and dual-phase computed tomographic angiography (CTA) under general anesthesia (anesthesia: premedication butorphanol, induction: midazolam and alfaxalone, general anesthesia: sevofluran).

2.2. Materials and Methods

CEUS was performed using the same ultrasound machine as in the previous abdominal ultrasonography with a C5-8 curvilinear transducer. The ultrasound machine has a contrast-specific software (QLAB), and the system was optimized for harmonic signal display.

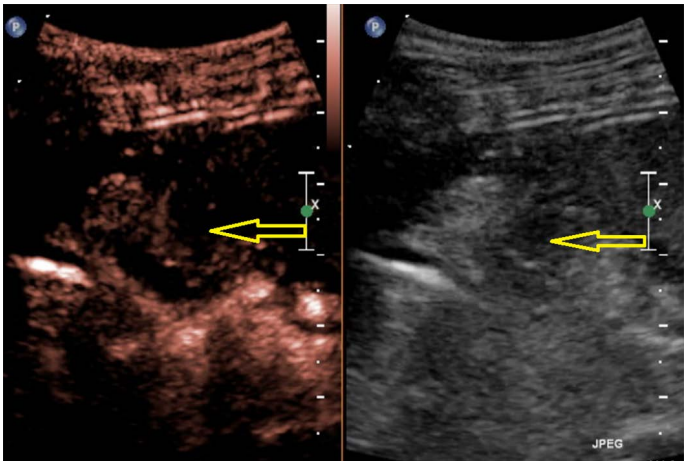
The mechanical index was maintained at 0.07 - 0.08. Standardized parameters included depth (3 cm), time gain compensation, and focal zones. One focal zone was placed at the level of or just below the organ imaged. The dog received multiple 0.52 ml bolus injections (0.2 ml/10kg) of ultrasound contrast medium (Sonovue, Bracco Imaging S.p.A., Italy 8 µg), followed by a saline bolus (5 ml). The contrast media were administered via a 20G catheter placed on the left cephalic vein. A three-way stopcock was placed at the catheter to avoid any delay between the injection of the contrast medium and the saline. The contrast medium was prepared by shaking according to the manufacturer's instructions before the injection. The region of previously noted abnormal pancreas was centered on the screen, and the contrast-specific imaging mode was turned on. Between the injections, the residual microbubbles in the vascular system and the targeted organ were destroyed by increasing acoustic power to the level of normal ultrasound and scanning over the aorta near the pancreas and the pancreas to avoid attenuation artifacts.

A two-slice helical CT unit (Siemens Emotion Duo) was used with 120 kVp and 130 mA settings and a tube rotation speed of 1 s, a slice width of 3 mm, and collimation of 2 mm. Dual-phase study of the pancreas was done with precontrast series, with intravenous contrast and 5 min post-contrast from the diaphragm to L5. Contrast media was injected using a power injector at 4 ml/s at a dosage of 600 mg iodine/kg (Iomeron 300 mg I/ml, dose: 2 ml/kg). We used a protocol previously published for canine pancreatic insulinoma [9].

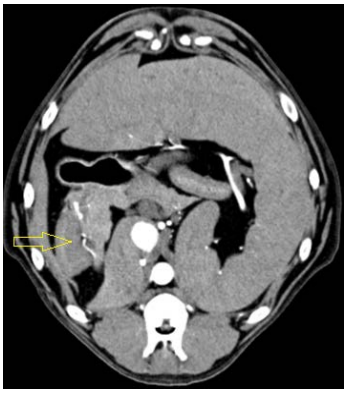
2.3. Findings

The corpus area of the pancreas had an irregular hypervascular appearance during both arterial and parenchymal phases in CEUS compared with B-mode ultrasound. In addition, a small nodule in the corpus region of the pancreas (diameter 1.7 cm) was found with CEUS. The nodule had a clear feeding vessel, but was otherwise non-contrast-enhancing during both arterial and parenchymal phases (**Figure 1(a)**).

The focal enlargement of the corpus area of the pancreas (diameter exceeding 2 cm) was noted also in the CT study. The contrast enhancement of the pancreas was diffusely slightly heterogeneous during both arterial and portal phases (**Figure 1(b)**). There were two oval, poorly marginated non-contrast-enhancing lesions in the



(a)



(b)

Figure 1. Poorly marginated non-contrast-enhancing lesions in the pancreatic body, arterial phase (CEUS, B-mode ultrasound, CTA).

region of the focal enlargement/corpus (1.7 × 1 cm, 1.3 × 1 cm) during arterial and portal phases. During the delayed phase (5 min post-contrast) these lesions appeared slightly contrast-enhancing. In addition, two small, round, well-delineated non-contrast-enhancing lesions were observed in the liver.

2.4. Imaging Diagnosis

The lesions seen in the pancreas had an atypical appearance for insulinoma in both CEUS and CTA with an atypical contrast enhancement pattern in both examinations. Based on the appearance and the contrast enhancement of the lesions, pancreatic neuroendocrine tumors and adenocarcinoma were considered as the differential diagnosis.

The owner chose a palliative treatment for the dog to prevent hypoglycemia. The dog was medicated with diatzoxide (Proglicem) 5 mg/kg po bid, hydrochlorothiazide (Hydrex semi) 1 mg/kg po bid, and prednisolone (Prednisolon) 0.4 mg/kg po bid. Dietary changes (fat- and protein-rich food) and exercise restriction were additionally instructed for the dog.

The dog showed no clinical symptoms at physical exams performed during follow-up visits at one week and three months after diagnosis. After three months, the dog began to have episodic seizures despite medical management. Because of the clinical symptoms and the poor prognosis, the owner elected euthanasia and refused further treatments at this point. A complete post-mortem examination was performed. The pathological examination revealed an oval-shaped, hard 3 cm × 2 cm × 1.5 cm pancreatic mass. Histopathological diagnosis was probable malignant insulinoma with evidence of spread to the adjacent pancreatic parenchyma and pancreatic vessels. There were no abnormal findings in liver in either the pathological or the histopathological examination.

3. Discussion

To the author's knowledge, this is the first confirmed canine pancreatic insulinoma case diagnosed using both CEUS and CTA. In this case, the dog had typical clinical features, symptoms, and laboratory findings. US was shown to have a relatively low sensitivity in detecting insulinoma in a previous canine study [5], consistent with our experience in diagnosing this canine insulinoma patient. In addition, CTA revealed pancreatic insulinomas not seen in conventional ultrasonography in a case series of three dogs [9], as was also the case here, where only focal thickening of the pancreatic corpus region was noted in baseline ultrasound. CEUS has resulted in clearer demarcation of the nodule margins in some previous studies [4] [6], which we also found. In this case, only one of nodules visible in CTA was detected in CEUS. This is likely due to better anatomic detail available in CT studies than in ultrasound, especially with deep-chested patients like the patient in this case report.

A typicaI enhancement pattern for pancreatic tumors in dogs was described in a previous case series of four dogs using CEUS [4]. Two pancreatic adenocarcinomas were non-contrast-enhancing during both arterial and parenchymal phases, and two insulinomas had a contrast-enhancing appearance with a rapid intense wash-in of contrast during the arterial phase and a rapid disappearance of contrast during the parenchymal phase [4]. In a CTA study of 13 dogs, the lesions considered to be primary pancreatic insulinomas were slightly hypoattenuating compared with the liver in the precontrast series. The lesions were contrast-enhancing, but remained slightly hypoattenuating compared with the contrast-enhanced liver tissue [5]. In another canine study, a dynamic CT detected an insulinoma in the pancreas and it was hyperattenuating in the arterial phase, similar to findings of most studies performed in humans [10]-[12]. In our case, the enhancement of the insulinoma was atypical in both CEUS and CTA. This atypical non-contrast-enhancing appearance has also been previously reported in canine CEUS and CTA studies with histopathologically proven neoplastic invasion to the adjacent parenchyma [6] [9], as was also the case here. It is therefore possible that the malignant and invasive nature of the insulinoma had an effect to the enhancement pattern of the tumor in CEUS and CTA. Further, it is possible that the lack of arterial phase enhancement in CTA in our case might have been caused by the two-slice CT system being too slow to detect it. However, this would not explain the atypical enhancement pattern observed in CEUS.

4. Conclusion

This report concentrates in different methods of diagnostic imaging in a case of canine pancreatic insulinoma. The insulinoma was diagnosed using both CEUS and CTA in addition to typical clinical features, symptoms, and laboratory findings. In this case, only one of nodules visible in CTA was detected in CEUS. This is likely due to better anatomic detail available in CT studies than in ultrasound, especially with deep-chested patients. In our case, the enhancement of the insulinoma was atypical in both CEUS and CTA. This atypical non-contrast-enhancing appearance has also been previously reported in canine CEUS and CTA studies with histopathologically proven neoplastic invasion to the adjacent parenchyma [6] [9], as was also the case here. It was therefore possible that the malignant and invasive nature of the insulinoma had an effect to the enhancement pattern of the tumor in CEUS and CTA.

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