Ultrasound-aided diagnosis of an insulinoma in a cat

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Key words
Endocrine neoplasia, pancreas, ultrasonography, surgery, feline insulinoma

Summary
A 15-year old, neutered female, domestic shorthaired cat was presented for evaluation of a 3-month history of paroxysmal falling over and trembling. In laboratory work the cat displayed a mild hypoglycemia. Ultrasound revealed a nodule in the left pancreatic lobe and surgical excision was performed. The histological diagnosis was an insulinoma. To the authors knowledge this is the first ultrasound description of an insulinoma in a cat. Up to date the cat has a survival time of 32 months without recurrence of symptoms.

Introduction
Insulinomas are endocrine functional tumors originating from beta-cells of the islets of Langerhans in the pancreas. The excessive insulin excretion by the tumor can lead to serious functional disorders of the whole organism like seizures, weakness, muscle tremors, lethargy or bizarre behavior. Some animals will also show polyphagia and weight gain (3). Ferrets are the species with the highest prevalence to suffer from an insulinoma in veterinary medicine, whereas these tumors are uncommon in dogs and rare in cats (1, 20). The published cases of insulinomas in cats are dealing with clinical and histological aspects and one report characterizes the molecular sides of neoplastic beta-cells (5, 6, 8, 9, 15, 19). The current case report presents the first description of the sonographic appearance of an insulinoma in a cat.

Case report
History, clinical examination and laboratory diagnostics
A 15-year old, neutered female, domestic shorthaired cat weighing 3.9 kg was presented with a 3-month history of paroxysmal falling over and trembling. According to the owner the seizures lasted from a few minutes to an hour.

The cat was bright, alert and responsive and showed mild generalized muscle tremors. Body condition score was 4/9. The body temperature was 38.8°C, heart and pulse rate were 160 beats per minute. The mucosal membranes were pink and the capillary refill time was below 2 seconds. Abdominal palpation was unremarkable and the palpable lymph nodes were of physiological size and consistence. The thyroid gland could not be palpated. The neurological examination showed no abnormalities.

In a blood sample collected from the cephalic vein a glucose level of 2.38 mmol/l (reference range: 3.05–6.93 mmol/l) was measured using a hand glucometer (Accu-Check Compact Plus, Roche, Mannheim). Another plasma sample sent to a laboratory...
validated this result (2.33 mmol/l). In addition, there was a slightly increased T4-level of 4.9 µg/dl (reference range: 1–4 µg/dl). Fructoseamine level was 164 µmol/l (reference range: up to 340 µmol/l). The other parameters of blood chemistry and hematology were within normal limits.

**Diagnostic imaging**

Right and left lateral as well as ventrodorsal radiographs of the thorax and left lateral and ventrodorsal radiographs of the abdomen were taken. In the subcutaneous tissue caudal to the scapulae an oval shaped calcification was visible. Ventral at L7/S1, arising from the ventral endplates, a mild spondylosis was visible. Otherwise the radiographs showed no abnormalities and no cause for hypoglycemia, e.g. neoplasia within the thorax, could be found.

A first ultrasound examination (Logiq P5 + 11L linear probe, GE, Solingen) was performed in the awake, not fasted cat. The bladder was moderately filled with anechoic fluid and showed a smooth wall. The normal sized kidneys showed a good corticomedullary distinction. Both adrenal glands displayed a hypechoic adrenal medulla, which was surrounded by a hypoechoic adrenal cortex. The transverse diameter of the left and right adrenal gland was 3.5 mm and 3.9 mm respectively (reference range: 3–4.6 mm) (13). The spleen had a medium echogenicity and a homogenous echotexture. The liver was hypoechoic in comparison to the spleen and showed a homogenous echotexture. The gallbladder was mildly filled with anechoic content. There was a moderate filling of the gastrointestinal tract with ingesta and gas. The gas-filled ascending and transverse colon were concealing the view of the pancreas.

**Further course**

Since the diagnostics did not reveal any cause for the hypoglycemia a serum sample was taken to determine the insulin level and an ACTH stimulation test was performed. Insulin level was <1.0 µU/ml (reference range: 12–97 µU/ml) and the ACTH stimulation test was inconspicuous with a baseline value of 0.7 µg/dl (reference range: < 4.0 µg/dl) and a stimulated value of 7.9 µg/dl (reference range: < 17 µg/dl).

Presumptive diagnosis based on low blood glucose and case history was insulinoma. The cat was scheduled for surgery. After induction of general anesthesia with an intramuscular injection of ketamine (10 mg/kg) and xylazine (1 mg/kg) the cat was intubated and a vein catheter was placed in the right cephalic vein.

Before surgery a second ultrasound examination was performed. The right pancreatic lobe and the pancreatic body appeared homogenous and slightly hypoechoic to the surrounding tissue. At the mid-part and caudal border of the left pancreatic lobe a mildly hyperechoic, homogenous round nodule was detected. It measured 9 x 9 x 9 mm and showed few small anechoic areas in its center. The nodule was demarcated from the residual pancreatic tissue by a fine hypoechoic line (Fig. 1). In the color- and power-Doppler coded images of the nodule no blood flow was detectable. Vessels in normal pancreatic tissue at the edge of the nodule were displaced and lined to the nodules contour (Fig. 2).

Ultrasonographic findings supported the presumptive diagnosis of insulinoma. Anesthesia was continued with inhalation of isoflurane in oxygen and a laparotomy was performed. At the caudal border of the left limb of the otherwise grossly normal pancreas a solitary mass with a diameter of approximately 10 mm was

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Fig. 1  a) Sonogram of the left pancreatic lobe in transverse view. The pancreas (P) is visible between the stomach (St) and the spleen (Sp). It is homogenous and of medium echogenicity. Note the slightly hypechoic nodule (N) at the caudal border of the pancreas with a larger vessel (arrow) crossing cranially within the normal pancreatic tissue. The nodule protrudes slightly above the surface of the pancreas. b) Pancreatic mass (arrows) in sagittal view. Some anechoic round areas are visible.

Abb. 1  a) Ultraschallbild des linken Pankreaslappens im Transversalschnitt. Das Pankreas (P) ist zwischen dem Magen (St) und der Milz (Sp) sichtbar. Es ist homogen und von mittlerer Echogenität. Am kaudalen Rand zeigt sich eine geringgradig hyperechogene Zunahme (N) dar, kranial davon verläuft ein Blutgefäß (Pfeil). Die Zunahme ist geringgradig über die Oberfläche des Pankreasehens. b) Zunahme im Pankreas (Pfeile) im Sagittalschnitt. Es sind mehrere anechogene Areale zu erkennen.

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Histopathological findings

Histopathology of the excised mass revealed epithelial-like cells which were lined in a string like pattern forming a sectional adenoma-like structured tumor with central retention of secretions. Cell morphology was suspicious for pancreatic islet cells (islet cell adenoma). Immunohistochemically the diagnosis of an insulinoma could be confirmed, as the cells were highly positive for insulin. Due to the good differentiation of the cells and the non-invasive growth, the mass was classified as benign.

Discussion

Ultrasound has a low sensitivity on the detection of insulinomas. In humans, sensitivity for detection of insulinomas by transabdominal ultrasound varies between 9 to 79% (2). In dogs the sensitivity for detection of pancreatic neoplasias is reported to be 75% (11, 23). Due to the low number of cats with pancreatic nodules, a determination of sensitivity for nodules in the pancreas was not possible (7).

On one hand gas and ingesta in the gastrointestinal tract can cause artifacts, which prevent visualization of the pancreas. On the other hand the size of the nodules can be a limiting factor as they are too small in size to be detected in diagnostic ultrasonography (10, 17, 23). Besides that the differentiation of pancreas from the surrounding tissue can be challenging depending on the experience of the examiner and the quality of the ultrasonographic equipment. In the actual case the nodule had a size of 9 mm in diameter and was comparatively large and easy to detect. A smaller nodule would have been more challenging in diagnosis.

In the dog insulinomas are described as hypoechoic nodules in the pancreas (10, 23). Deviant from these finding, the insulinoma in the presented case was hyperechoic to the surrounding tissue.
Differential diagnosis for pancreatic nodules include changes due to chronic pancreatitis, adenomas, adenocarcinomas, endocrine-active tumors of other cell types (e.g. gastrinoma, somatostatinoma), abscesses and cysts. Cysts and abscesses can be differentiated from solid masses of other origin by their ultrasonographic appearance. Whereas further differentiation of a solid mass into benign or malignant is only possible with a histological examination of a tissue sample (17). Cytology alone cannot predict the biological behavior for sure and a potential malignancy must always be expected (4).

Overall the diagnosis of an insulinoma with diagnostic imaging can be challenging. As radiographs from thorax and abdomen, ultrasound is useful in excluding other causes for hypoglycemia, e.g. tumors of other origin. Transabdominal ultrasound is highly operator- and machine-dependent and good quality images can be difficult to obtain (18, 20, 23). An alternative technique is endoscopic ultrasound. In endoscopic ultrasound the ultrasound probe is implemented in the tip of a so called echoendoscope and the ultrasound examination of the pancreas is performed directly through the gastric wall. In one case an insulinoma could be detected in a dog by endoscopic ultrasound which could not be visualized by transabdominal ultrasound (3). Another technique for detection of mass lesions in the pancreas is the contrast enhanced ultrasound. Studies for the sensitivity and specificity in veterinary medicine are still pending (4). Very good results are retrieved using a CT angiography or a somatostatin receptor scintigraphy (14, 18). In human medicine the somatostatin receptor scintigraphy is considered the method with the highest sensitivity and specificity (22, 23). However, it is a very costly procedure and therefore will be reserved for only a few specialized institutes in veterinary medicine. Somatostatin receptor scintigraphy does not allow an exact localization of the primary tumor and differentiation from near metastases can be difficult (18). Unfortunately none of these advanced techniques was available at our clinic.

Clinical symptoms are due to hypoglycemia and the concomitant neuroglycopenia, that shows the dependency of the CNS on a continuous glucose supply. Symptoms are similar in dogs and in cats, including seizures, ataxia, weakness, lethargy and muscle tremor (5). Hence it can easily lead to a false diagnosis of a neurological disease.

Like in the present case, all reported cases of cats with insulinoma shared seizures, muscle tremors and weakness as clinical symptoms (5, 6, 8, 9, 15, 19). In a case previously published, the cat initially showed gastrointestinal symptoms like anorexia and diarrhea after an episode of feebleness and lethargy. Two to three weeks afterwards it had first neurological signs (9). Thus in older cats with similar clinical signs an insulinoma should always be considered as a differential diagnosis to a primary neurologic disorder. Measurement of blood glucose is the diagnostic method of choice and a hand glucometer seems to be well suitable for this. In the presented case the difference between the values measured using the hand glucometer and the laboratory value was negligible.

The plasma-insulin level was below 1 µU/ml in the current case. It could not be clarified whether this was a measurement error of the laboratory, since the test used is validated only for dogs and horses. An error during sample procession might also have occurred.

In human medicine descriptions of hypoglycemia with hypoinsulinemia exist, although this is considered rare. It is discussed whether highly specific tests for insulin are less suitable to proof an insulinoma than less specific tests based on radioimmunooassays that detect also certain amounts of proinsulin apart from insulin. Proinsulin is known to have a hypoglycemic effect as well and if a tumor secretes nominal amounts of proinsulin instead of insulin it can also lead to hypoglycemia, despite low insulin levels (12). It remains unclear whether this is a possible explanation in the present case.

Fructosamines are also discussed as a potential indicator for an insulinoma in dogs. One reported case had typical clinical signs and the only measurable deviations were low fructosamine values whereas glucose values were within normal limits (16). Fructosamine level in the presented case was 164 µmol/l. Retrospectively this can be evaluated as a slightly decreased fructosamine level and may be considered as a hint for chronic hypoglycemia.

Laparotomy with complete inspection of the abdominal cavity is still considered the method of choice for a diagnostic and prognostic statement in case of insulinoma (20, 23). This must be seen critically as liver metastases might not be visible during laparotomy if they are deep in the parenchyma. Therfore a combination of an imaging technique with surgery may prove to be superior. In humans sensitivity of surgery in combination with intraoperative ultrasound is reported to be 90–100% (23).

Surgical excision of an insulinoma is the therapy of choice. With complete resection of the insulinoma and lack of metastases the symptoms should resolve immediately. The value of biopsies from liver and lymphnodes, even if no signs for metastases are present, is discussed controversially in the literature (10). This option was waived here, as in all other reported cases of insulinoma in cats (5, 6, 8, 9, 15, 19).

Medical treatment is necessary prior to surgical treatment or if a surgical treatment is not wanted by the owner or is no option because of metastases.

Conclusions for practice
With today’s diagnostic possibilities it can be challenging to detect insulinomas by laboratory work or diagnostic imaging. Diagnostic imaging should be used for the recognition of a primary tumor and possible metastases. It can also help in decision making and planning of surgery. Despite its low sensitivity ultrasound should always be performed. As in the presented case, it can lead to a positive diagnosis and may reveal possible metastases in lymph nodes or in the liver or at least allows the exclusion of other differential diagnosis.
Although the cat reported herein did not show symptoms for hypoglycemia up to 18 months after the diagnosis of an insulinoma the prognosis should always be considered as guarded. Based upon the low case numbers a dignity classification of insulinomas in cats is not possible until now.

Conflict of interest
The authors declare that there is no conflict of interest.

References