Hypoglycaemia associated with gastrointestinal and extragastrointestinal stromal tumour in two dogs

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HYPOGLYCAEMIA ASSOCIATED WITH GASTROINTESTINAL AND EXTRAGASTROINTESTINAL STROMAL TUMOUR IN TWO DOGS.

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Abstract:	Gastrointestinal stromal tumours (GISTs) are uncommon mesenchymal tumours that originate from the interstitial cells of Cajal (ICC). As these tumours are difficult to distinguish from gastrointestinal smooth muscle tumours using standard histological techniques, their true prevalence may be underestimated. Metabolic and systemic consequences of GISTs are not well described in any species. More rarely, neoplasms with histological and immunohistochemical features similar to GISTs may occur outside the gastrointestinal tract, so-called Extra-gastrointestinal Stromal Tumours (EGIST). EGISTs have never been described in the veterinary literature. In this article we present and describe clinical findings, management and treatment of two dogs with clinical hypoglycaemia induced by histologically confirmed GIST and EGIST. Hypoglycaemia resolved immediately and long-term after tumour excision. To the authors' knowledge this is the first report of hypoglycaemia associated with a canine GIST and the first case report of an EGIST in the dog.

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TITLE OF CASE ***Do not include "a case report"***

HYPOGLYCAEMIA ASSOCIATED WITH GASTROINTESTINAL AND EXTRAGASTROINTESTINAL STROMAL TUMOUR IN TWO DOGS.

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

Gastrointestinal stromal tumours (GISTs) are uncommon mesenchymal tumours that originate from the interstitial cells of Cajal (ICC). As these tumours are difficult to distinguish from gastrointestinal smooth muscle tumours using standard histological techniques, their true prevalence may be underestimated. Metabolic and systemic consequences of GISTs are not well described in any species. More rarely, neoplasms with histological and immunohistochemical features similar to GISTs may occur outside the gastrointestinal tract, so-called Extra-gastrointestinal Stromal Tumours (EGIST). EGISTs have never been described in the veterinary literature. In this article we present and describe clinical findings, management and treatment of two dogs with clinical hypoglycaemia induced by histologically confirmed GIST and EGIST.

Hypoglycaemia resolved immediately and long-term after tumour excision. To the authors' knowledge this is the first report of hypoglycaemia associated with a canine GIST and the first case report of an EGIST in the dog.

BACKGROUND ***Why you think this case is important – why did you write it up?***

GISTs are mesenchymal tumours that occur in the GIT of dogs (1, 2), cats (3, 4), humans (5-8), horses (9) and non-human primates (10). They can occur in any segment of the GIT, however most of them develop in the stomach and small intestine. Clinically, they can lead to focal obstruction, vomiting and diarrhoea as well as chronic low grade GIT blood loss, resulting in iron deficiency anaemia. Surgical removal usually results in excellent outcomes (11) while only a few case reports have been published demonstrating a response to tyrosine kinase inhibitors (12-14).

More rarely, neoplasms with histological and immunohistochemical features similar to GISTs may occur outside the gastrointestinal tract, so-called Extra-gastrointestinal Stromal Tumours (EGISTs).

These tumours are difficult to distinguish from gastrointestinal smooth muscle tumours such as leiomyoma or leiomyosarcoma (11) using standard histological techniques, therefore their true prevalence may be underestimated. It has been established that GISTs can be differentiated by the expression of KIT (CD117), a receptor tyrosine kinase encoded by the proto-oncogene *c-KIT* (11, 15). One study also suggests that the immunohistochemical application of DOG1 (discovered on GIST protein 1) achieves higher specificity and sensitivity than KIT for differentiating between canine GISTs and leiomyosarcomas. Inclusion of both DOG1 and KIT IHC in diagnostic panels offers improved overall accuracy of canine GIST diagnosis (16).

No previous cases of GIST-associated hypoglycaemia have been described in the veterinary literature. To our knowledge there are also no case reports describing an EGIST in veterinary medicine.

Hypoglycaemia in dogs, defined as a blood glucose concentration of less than 3.3mmol/L (17), can be a life-threatening disorder that necessitates swift and decisive treatment to prevent lasting

neuronal damage. Most frequently reported causes of severe hypoglycaemia in adult dogs are insulinoma, excessive insulin administration, and non-pancreatic neoplasia (18, 19). Sepsis, severe hepatopathy, and hypoadrenocorticism are usually associated with only a mild decrease in blood glucose concentration (18).

In human medicine, non-islet cell tumour hypoglycaemia (NICTH) is a well-recognised paraneoplastic syndrome (20) and has been described in association with gastrointestinal stromal tumours (GISTs) in humans (21). In dogs, NICTH has been described with neoplasms of hepatic (22, 23), smooth muscle (24, 25), mammary (26) and renal origin (27, 28), but not with neoplasms of the gastrointestinal tract (GIT). Different mechanisms have been proposed to explain the paraneoplastic syndrome. NICTH may be caused by increased tumour utilization of glucose; decreased hepatic glycogenolysis or gluconeogenesis; or secretion of insulin or insulin-like growth factor 1 (IGF1) and insulin-like growth factor 2 (IGF2)(29) . However, in human medicine it has been established that IGF2 is the main cause of NICTH, including in GISTs (30). Two different studies suggest that IGF2 is also a relevant factor in dogs (25, 26). Some mesenchymal and epithelial tumours can overexpress IGF2, resulting in the secretion of partially processed precursors of IGF2 ('big' IGF2). This molecule binds to insulin receptors, resulting in insulin-like hypoglycaemic effects (31). The purpose of this paper is to describe clinical findings and treatment in two dogs with marked hypoglycaemia associated with GIST and EGIST that resolved after tumour excision.

CASE PRESENTATION *Presenting features, clinical and environmental history*

DOG 1

A 13-year-old, male intact Golden retriever canine presented to the referring emergency service with a history of intermittent diarrhoea and acute onset weakness and collapse. Symptomatic hypoglycaemia (2.4-2.6 mmol/l; reference range 4.11-7.95 mmol/l) causing weakness episodes was detected by the referring veterinary surgeon on multiple measurements and the dog was referred to the Royal (Dick) School of Veterinary Studies for investigation of hypoglycaemic

episodes and a palpable cranial abdominal mass. The initial treatment by the referring veterinarian included 2.5% glucose constant rate infusion. On physical examination the dog was quiet, alert and responsive. Ptyalism was noted and a large mass was palpated in the cranial abdomen. Initial investigations included complete blood count and serum biochemistry that revealed low urea and confirmed hypoglycaemia of 2.58 mmol/l (reference range 4.11-7.95 mmol/l). Despite glucose supplementation, the glucose was consistently low at 2.4 mmol/l and 2.6 mmol/l on subsequent measurements taken over a 24-hour period using a hand-held glucometer. To rule out hepatic dysfunction as cause of low urea and glucose, a bile acid stimulation test was performed, and this ruled out severe functional loss.

Abdominal ultrasound scan confirmed the presence of a large round heterogeneous mass containing small cavities in the right cranial abdomen dorsal to the duodenum (Fig. 1). Its exact origin could not be established but neoplasia was considered the most likely differential diagnosis**.** No other abdominal abnormalities were identified (including in the liver) and thoracic radiography did not show any evidence of metastatic disease or any other abnormality. The patient was stabilised on glucose infusion and surgery was scheduled.

Ventral midline exploratory coeliotomy was performed. The mass was associated with the junction of the central and right pancreatic regions and pancreatic origin was suspected but not surgically confirmed, given multiple adhesions to the duodenum, gastric wall and transverse colon. The common bile duct and the gastric pylorus were not involved. No other abnormalities were found during surgery and, given the normal liver morphology and lack of significant laboratory changes, liver biopsies were not taken. The mass was successfully excised and submitted for histopathology. Glucose supplementation was gradually discontinued 12 hours after the surgery. The hypoglycaemia resolved quickly and all the measurements during the post-operative period were within normal limits. The dog was managed on pain relief and discharged four days later.

Macroscopically, the mass was fluctuant to firm, mottled dark purple to grey and spherical, measuring 14cm diameter, with fat attached to its surface. On cut section, it was solid and mottled

pink, red and orange, with a soft consistency. Histopathology of the mass confirmed an intra-abdominal malignant spindle cell tumour (sarcoma) that was completely excised with narrow margins and no evidence of pancreatic or GIT involvement. The only recognisable architecture consisted of fat and smooth muscle. This was effaced by a well-demarcated, expansile and encapsulated proliferation of spindle cells arranged in interlacing fascicles with a faint herringbone pattern. The spindle cells breached the capsule and invaded the surrounding fat. The spindle cells contained fibrillar, eosinophilic cytoplasm and elongated or "cigar shaped" nuclei. Anisokaryosis was mild and the mitotic index averaged 3 per hpf at 400X. There were multifocal areas of necrosis and haemorrhage, with occasional cystic degeneration. Immunohistochemically, ~10% of the spindle cells labelled strongly with antibody against CD117, confirming a diagnosis of EGIST.

In addition to surgical removal, treatment in this patient consisted of single-agent chemotherapy (four doses of doxorubicin (30mg/m^2) given every 3 weeks). Six months after the initial diagnosis a new 8mm nodule next to the pancreas was noticed on a routine recheck ultrasound. Fine needle aspirate (FNA) confirmed mesenchymal neoplasia, indicating probable recurrence of the previously diagnosed EGIST. Blood glucose levels were tested and were within normal limits on subsequent chemotherapy consultations. Five months later multiple pancreatic nodules and a liver mass were identified on ultrasound (Fig. 2). The owners opted for no further treatment and the dog was humanely euthanised at the referring practice.

DOG 2

A 13-year-old, female neutered Labrador canine was referred for investigation of an abdominal mass. A few episodes of vomiting and diarrhoea were reported but they had resolved by the time of presentation. The owner also reported a 2-month history of progressive weight loss. On physical examination the patient was bright alert and responsive with a body condition score of 2/9 (32). A grade I/VI heart murmur was auscultated and abdominal palpation indicated the presence of a mass in the cranial abdomen. Initial investigations included complete blood count and serum biochemistry. Mild leukopenia with mild neutropenia (no left shift) and lymphopenia,

and minimal (non-significant) normocytic-normochromic anaemia were noted. Biochemical abnormalities consisted of moderate elevations in both alanine transaminase (ALT) and alkaline phosphatase (AP). Mildly raised basal bile acids were not considered significant, but a bile acid stimulation test was not performed. Due to the non-specific presenting complaints and mild hypercholesterolemia, TT4 and TSH were assessed but were not suggestive of hypothyroidism.

Abdominal ultrasound confirmed the presence of a very large cranial abdominal mass, for which the exact origin could not be established. Results of an FNA suggested chronic haemorrhage**.** Computed tomography (CT) of the abdomen indicated that the mass was most likely of gastric origin. Additional findings on thoracic CT images showed changes consistent with aspiration pneumonia, though there was no history or clinical signs typical of that. Elective surgery was scheduled and the patient was discharged on the same day with a course of antibiotics to treat the presumed subclinical aspiration pneumonia prior to surgery. The dog re-presented to the R(D)SVS emergency service a few hours later due to a collapsing episode. The dog was dull but responsive, with continued ptyalism. In addition, pyrexia and tachypnoea with increased inspiratory effort had developed. The heart rate was 104 beats per minute, with good quality synchronous pulses, and blood pressure was 155mmHg. Blood analysis revealed more severe lymphopenia and neutropenia with a glucose of 4.3 mmol/l (reference range 4.11-7.95 mmol/l). Oxygen therapy and intravenous antibiotic therapy were initiated and the patient was closely monitored. Two hours later the glucose levels had dropped to 3mmol/l. At this point a dextrose bolus was administered and repeat (every 2 hours) glucose measurements using hand-held glucometer were commenced. These were consistently low therefore a 5% dextrose continuous rate infusion (CRI) was started.

The respiratory status of the patient remained stable in the following days but glucose remained low despite CRI supplementation. Administration of an anti-inflammatory dose of dexamethasone achieved a mild improvement in glucose levels. However, they decreased again once dexamethasone was discontinued. Leukocytes returned to normal, although lymphopenia persisted. Once the respiratory status of the patient was stable, a ventral midline exploratory

coeliotomy was performed. It revealed a mass arising from the dorsal aspect of the pyloric antrum with omentum wrapped around it; this was removed and submitted for histopathology. Glucose levels were closely monitored during surgery and due to initial hypoglycaemia of 2.8mmol/l, supplemental dextrose injections were given. Once the mass was excised the consecutive glucose readings were within normal limits and no further supplementation was required. Recovery from the surgery was uneventful. The hypoglycaemia resolved completely after the mass excision and the patient was discharged four days later.

Macroscopically, the mass was ovoid and multinodular, measuring 14cm diameter at its widest dimension, with an attached fragment of omentum. Histopathologically it comprised an expansile, non-encapsulated but well demarcated proliferation of spindle cells similar to those described above (Fig.3). Anisokaryosis was moderate to marked but mitoses were rare. There were large areas of necrosis and some haemorrhage. The spindle cell proliferation merged with the muscularis layer of the pyloric stomach. Immunohistochemically, 20% of the spindle cells labelled moderately strongly with antibody against CD117, supporting a diagnosis of GIST (Fig.4). Different chemotherapy protocols were discussed but declined by the owners. At the last follow up appointment (three months after initial diagnosis) the dog was free of clinical signs.

INVESTIGATIONS ***If relevant***

DIFFERENTIAL DIAGNOSIS ***If relevant***

TREATMENT ***If relevant***

OUTCOME AND FOLLOW-UP

DISCUSSION ***Include a very brief review of similar published cases***

As far as the authors are aware, there are no previous reports of GIST-associated hypoglycaemia in the dog. To date, only one case report of GIST-associated hypoglycaemia in a veterinary patient has been published, and that was in a horse (33). However, GISTs are a relatively new entity. An immunohistochemical review of previously diagnosed gastrointestinal leiomyomas and leiomyosarcomas has resulted in most of these tumours being re-classified as GISTs (11, 15, 34). All the cases describing hypoglycaemia secondary to leiomyomas/sarcomas (19, 24, 25, 35, 36) were published prior to this new classification. Therefore, it is possible that some of these previous cases were actually GISTs.

Paraneoplastic syndromes are common manifestations of many malignancies and have been reported with GIST (37, 38). Multiple articles on GIST-associated hypoglycaemia are available in human medicine (39-42) but no information on its systemic effects is available in the veterinary literature. Hypoglycaemia was a common presenting abnormality in both of the dogs reported here. In dog 1, the hypoglycaemia was considered to be the most likely cause of the clinical sings (weakness and collapse), given the lack of other physical and laboratory abnormalities. However, other unrelated causes (such as a transient arrhythmia or syncopal episode) were not ruled out. Liver dysfunction was considered an unlikely explanation for the hypoglycaemia. A bile acid stimulation test was not consistent with severe liver dysfunction and no imaging abnormalities were identified in the liver. Furthermore, the dog became normoglycaemic after the tumour was resected, providing more support for a paraneoplastic mechanism.

During surgery the mass was adjacent to the pancreas, but pancreatic involvement was not confirmed histopathologically. A concomitant, undetected insulinoma cannot be ruled out as a

potential cause for hypoglycaemia as insulin levels were not measured but the presence of two different neoplasms is considered unlikely.

Interestingly, histopathological examination of the mass in dog 1 did not indicate a direct connection between the mass and the GIT. EGISTs have been described in human medicine widely but nothing has been reported in the veterinary literature. In recent years, ICC or ICC-like cells have been found in extraintestinal organs (43). For example, in the genitourinary tract, KIT-positive specialized pacemaker cells have been described in the human bladder, urethra, uterus, and prostate (44-48). The presence of these cells in various organs or soft tissue could provide an explanation for the rare cases of GISTs that occur as primary tumours outside the GIT, such as in the mesentery, omentum, retroperitoneum, liver, gallbladder, vagina, uterus, urinary bladder, or prostate (44, 49-58). In some of these tumours, the origin remains unclear (59).

In addition to its hypoglycaemia, dog 2 was also diagnosed with aspiration pneumonia and, considering the clinical findings (dyspnoea, pyrexia), laboratory abnormalities (neutropenia), and timeframe, sepsis with secondary hypoglycaemia was a possibility. However, hypoglycaemia persisted after sepsis resolved. It also responded to glucocorticoid administration and, as with case 1, resolved after mass removal, such that sepsis as a sole cause was unlikely.

The main limitation of this report is the fact that the exact underlying mechanism for the hypoglycaemia was not determined. Given that the main cause of NICTH seems to be the secretion of IGF2, this should ideally have been measured to confirm the source of hypoglycaemia. Consequently, other causes of hypoglycaemia (insulinoma or liver disease in case 1 and sepsis in case 2), although unlikely, cannot be completely excluded. Furthermore, while an antibody panel was not applied in these two cases, both samples labelled strongly with antibody against CD117 which, given the other histological features, was considered sufficiently diagnostic of GIST and EGIST.

To the authors' knowledge these are the first cases describing hypoglycaemia associated with GIST and EGIST in the dog. GIST and EGIST should be considered as a differential diagnosis in dogs presenting with an abdominal mass and hypoglycaemia.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- EGISTs do occur in dogs.
- GIST and EGIST should be considered as a differential diagnosis in dogs presenting with an abdominal mass.
- GIST and EGIST should be considered as a differential diagnosis in dogs presenting hypoglycaemia.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Fig. 1

Ultrasonographic image from dog 1 showing large round heterogeneous mass (between callipers) with multiple hypoechoic cavitations (asterisk shows the largest one) which was identified in the right cranial abdomen dorsal to the duodenum.

Fig. 2

Ultrasonographic image from dog 1 showing multiple different sized, hypoechoic nodules within the pancreatic parenchyma (between callipers) discovered five months after initial presentation. Note hepatic parenchyma in the near field (margin delineated with arrows).

Fig. 3

Abdominal gastrointestinal stromal tumour from dog 2 [HE]. The mass comprises a partially necrotic proliferation of moderately pleomorphic spindle cells arranged in interlacing streams.

Fig. 4

Immunohistochemistry of abdominal gastrointestinal stromal tumour from dog 2. Spindle cells label moderately strongly with antibody against CD117.

OWNER'S PERSPECTIVE ***Optional***

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TITLE OF CASE ***Do not include "a case report"***

HYPOGLYCAEMIA ASSOCIATED WITH GASTROINTESTINAL AND EXTRAGASTROINTESTINAL STROMAL TUMOUR IN TWO DOGS.

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

Gastrointestinal stromal tumours (GISTs) are uncommon mesenchymal tumours that originate from the interstitial cells of Cajal (ICC). As these tumours are difficult to distinguish from gastrointestinal smooth muscle tumours using standard histological techniques, their true prevalence may be underestimated. Metabolic and systemic consequences of GISTs are not well described in any species. More rarely, neoplasms with histological and immunohistochemical features similar to GISTs may occur outside the gastrointestinal tract, so-called Extra-gastrointestinal Stromal Tumours (EGIST). EGISTs have never been described in the veterinary literature. In this article we present and describe clinical findings, management and treatment of two dogs with clinical hypoglycaemia induced by histologically confirmed GIST and EGIST.

Hypoglycaemia resolved immediately and long-term after tumour excision. To the authors' knowledge this is the first report of hypoglycaemia associated with a canine GIST and the first case report of an EGIST in the dog.

BACKGROUND ***Why you think this case is important – why did you write it up?***

GISTs are mesenchymal tumours that occur in the GIT of dogs (1, 2), cats (3, 4), humans (5-8), horses (9) and non-human primates (10). They can occur in any segment of the GIT, however most of them develop in the stomach and small intestine. Clinically, they can lead to focal obstruction, vomiting and diarrhoea as well as chronic low grade GIT blood loss, resulting in iron deficiency anaemia. Surgical removal usually results in excellent outcomes (11) while only a few case reports have been published demonstrating a response to tyrosine kinase inhibitors (12-14).

More rarely, neoplasms with histological and immunohistochemical features similar to GISTs may occur outside the gastrointestinal tract, so-called Extra-gastrointestinal Stromal Tumours (EGISTs).

These tumours are difficult to distinguish from gastrointestinal smooth muscle tumours such as leiomyoma or leiomyosarcoma (11) using standard histological techniques, therefore their true prevalence may be underestimated. It has been established that GISTs can be differentiated by the expression of KIT (CD117), a receptor tyrosine kinase encoded by the proto-oncogene *c-KIT* (11, 15). One study also suggests that the immunohistochemical application of DOG1 (discovered on GIST protein 1) achieves higher specificity and sensitivity than KIT for differentiating between canine GISTs and leiomyosarcomas. Inclusion of both DOG1 and KIT IHC in diagnostic panels offers improved overall accuracy of canine GIST diagnosis (16).

No previous cases of GIST-associated hypoglycaemia have been described in the veterinary literature. To our knowledge there are also no case reports describing an EGIST in veterinary medicine.

Hypoglycaemia in dogs, defined as a blood glucose concentration of less than 3.3mmol/L (17), can be a life-threatening disorder that necessitates swift and decisive treatment to prevent lasting

neuronal damage. Most frequently reported causes of severe hypoglycaemia in adult dogs are insulinoma, excessive insulin administration, and non-pancreatic neoplasia (18, 19). Sepsis, severe hepatopathy, and hypoadrenocorticism are usually associated with only a mild decrease in blood glucose concentration (18).

In human medicine, non-islet cell tumour hypoglycaemia (NICTH) is a well-recognised paraneoplastic syndrome (20) and has been described in association with gastrointestinal stromal tumours (GISTs) in humans (21). In dogs, NICTH has been described with neoplasms of hepatic (22, 23), smooth muscle (24, 25), mammary (26) and renal origin (27, 28), but not with neoplasms of the gastrointestinal tract (GIT). Different mechanisms have been proposed to explain the paraneoplastic syndrome. NICTH may be caused by increased tumour utilization of glucose; decreased hepatic glycogenolysis or gluconeogenesis; or secretion of insulin or insulin-like growth factor 1 (IGF1) and insulin-like growth factor 2 (IGF2)(29) . However, in human medicine it has been established that IGF2 is the main cause of NICTH, including in GISTs (30). Two different studies suggest that IGF2 is also a relevant factor in dogs (25, 26). Some mesenchymal and epithelial tumours can overexpress IGF2, resulting in the secretion of partially processed precursors of IGF2 ('big' IGF2). This molecule binds to insulin receptors, resulting in insulin-like hypoglycaemic effects (31). The purpose of this paper is to describe clinical findings and treatment in two dogs with marked hypoglycaemia associated with GIST and EGIST that resolved after tumour excision.

CASE PRESENTATION *Presenting features, clinical and environmental history*

DOG 1

A 13-year-old, male intact Golden retriever canine presented to the referring emergency service with a history of intermittent diarrhoea and acute onset weakness and collapse. Symptomatic hypoglycaemia (2.4-2.6 mmol/l; reference range 4.11-7.95 mmol/l) causing weakness episodes was detected by the referring veterinary surgeon on multiple measurements and the dog was referred to the Royal (Dick) School of Veterinary Studies for investigation of hypoglycaemic

episodes and a palpable cranial abdominal mass. The initial treatment by the referring veterinarian included 2.5% glucose constant rate infusion. On physical examination the dog was quiet, alert and responsive. Ptyalism was noted and a large mass was palpated in the cranial abdomen. Initial investigations included complete blood count and serum biochemistry that revealed low urea and confirmed hypoglycaemia of 2.58 mmol/l (reference range 4.11-7.95 mmol/l). Despite glucose supplementation, the glucose was consistently low at 2.4 mmol/l and 2.6 mmol/l on subsequent measurements taken over a 24-hour period using a hand-held glucometer. To rule out hepatic dysfunction as cause of low urea and glucose, a bile acid stimulation test was performed, and this ruled out severe functional loss.

Abdominal ultrasound scan confirmed the presence of a large round heterogeneous mass containing small cavities in the right cranial abdomen dorsal to the duodenum (Fig. 1). Its exact origin could not be established but neoplasia was considered the most likely differential diagnosis**.** No other abdominal abnormalities were identified (including in the liver) and thoracic radiography did not show any evidence of metastatic disease or any other abnormality. The patient was stabilised on glucose infusion and surgery was scheduled.

Ventral midline exploratory coeliotomy was performed. The mass was associated with the junction of the central and right pancreatic regions and pancreatic origin was suspected but not surgically confirmed, given multiple adhesions to the duodenum, gastric wall and transverse colon. The common bile duct and the gastric pylorus were not involved. No other abnormalities were found during surgery and, given the normal liver morphology and lack of significant laboratory changes, liver biopsies were not taken. The mass was successfully excised and submitted for histopathology. Glucose supplementation was gradually discontinued 12 hours after the surgery. The hypoglycaemia resolved quickly and all the measurements during the post-operative period were within normal limits. The dog was managed on pain relief and discharged four days later.

Macroscopically, the mass was fluctuant to firm, mottled dark purple to grey and spherical, measuring 14cm diameter, with fat attached to its surface. On cut section, it was solid and mottled

pink, red and orange, with a soft consistency. Histopathology of the mass confirmed an intra-abdominal malignant spindle cell tumour (sarcoma) that was completely excised with narrow margins and no evidence of pancreatic or GIT involvement. The only recognisable architecture consisted of fat and smooth muscle. This was effaced by a well-demarcated, expansile and encapsulated proliferation of spindle cells arranged in interlacing fascicles with a faint herringbone pattern. The spindle cells breached the capsule and invaded the surrounding fat. The spindle cells contained fibrillar, eosinophilic cytoplasm and elongated or "cigar shaped" nuclei. Anisokaryosis was mild and the mitotic index averaged 3 per hpf at 400X. There were multifocal areas of necrosis and haemorrhage, with occasional cystic degeneration. Immunohistochemically, ~10% of the spindle cells labelled strongly with antibody against CD117, confirming a diagnosis of EGIST.

In addition to surgical removal, treatment in this patient consisted of single-agent chemotherapy (four doses of doxorubicin (30mg/m^2) given every 3 weeks). Six months after the initial diagnosis a new 8mm nodule next to the pancreas was noticed on a routine recheck ultrasound. Fine needle aspirate (FNA) confirmed mesenchymal neoplasia, indicating probable recurrence of the previously diagnosed EGIST. Blood glucose levels were tested and were within normal limits on subsequent chemotherapy consultations. Five months later multiple pancreatic nodules and a liver mass were identified on ultrasound (Fig. 2). The owners opted for no further treatment and the dog was humanely euthanised at the referring practice.

DOG 2

A 13-year-old, female neutered Labrador canine was referred for investigation of an abdominal mass. A few episodes of vomiting and diarrhoea were reported but they had resolved by the time of presentation. The owner also reported a 2-month history of progressive weight loss. On physical examination the patient was bright alert and responsive with a body condition score of 2/9 (32). A grade I/VI heart murmur was auscultated and abdominal palpation indicated the presence of a mass in the cranial abdomen. Initial investigations included complete blood count and serum biochemistry. Mild leukopenia with mild neutropenia (no left shift) and lymphopenia,

and minimal (non-significant) normocytic-normochromic anaemia were noted. Biochemical abnormalities consisted of moderate elevations in both alanine transaminase (ALT) and alkaline phosphatase (AP). Mildly raised basal bile acids were not considered significant, but a bile acid stimulation test was not performed. Due to the non-specific presenting complaints and mild hypercholesterolemia, TT4 and TSH were assessed but were not suggestive of hypothyroidism.

Abdominal ultrasound confirmed the presence of a very large cranial abdominal mass, for which the exact origin could not be established. Results of an FNA suggested chronic haemorrhage**.** Computed tomography (CT) of the abdomen indicated that the mass was most likely of gastric origin. Additional findings on thoracic CT images showed changes consistent with aspiration pneumonia, though there was no history or clinical signs typical of that. Elective surgery was scheduled and the patient was discharged on the same day with a course of antibiotics to treat the presumed subclinical aspiration pneumonia prior to surgery. The dog re-presented to the R(D)SVS emergency service a few hours later due to a collapsing episode. The dog was dull but responsive, with continued ptyalism. In addition, pyrexia and tachypnoea with increased inspiratory effort had developed. The heart rate was 104 beats per minute, with good quality synchronous pulses, and blood pressure was 155mmHg. Blood analysis revealed more severe lymphopenia and neutropenia with a glucose of 4.3 mmol/l (reference range 4.11-7.95 mmol/l). Oxygen therapy and intravenous antibiotic therapy were initiated and the patient was closely monitored. Two hours later the glucose levels had dropped to 3mmol/l. At this point a dextrose bolus was administered and repeat (every 2 hours) glucose measurements using hand-held glucometer were commenced. These were consistently low therefore a 5% dextrose continuous rate infusion (CRI) was started.

The respiratory status of the patient remained stable in the following days but glucose remained low despite CRI supplementation. Administration of an anti-inflammatory dose of dexamethasone achieved a mild improvement in glucose levels. However, they decreased again once dexamethasone was discontinued. Leukocytes returned to normal, although lymphopenia persisted. Once the respiratory status of the patient was stable, a ventral midline exploratory

coeliotomy was performed. It revealed a mass arising from the dorsal aspect of the pyloric antrum with omentum wrapped around it; this was removed and submitted for histopathology. Glucose levels were closely monitored during surgery and due to initial hypoglycaemia of 2.8mmol/l, supplemental dextrose injections were given. Once the mass was excised the consecutive glucose readings were within normal limits and no further supplementation was required. Recovery from the surgery was uneventful. The hypoglycaemia resolved completely after the mass excision and the patient was discharged four days later.

Macroscopically, the mass was ovoid and multinodular, measuring 14cm diameter at its widest dimension, with an attached fragment of omentum. Histopathologically it comprised an expansile, non-encapsulated but well demarcated proliferation of spindle cells similar to those described above (Fig.3). Anisokaryosis was moderate to marked but mitoses were rare. There were large areas of necrosis and some haemorrhage. The spindle cell proliferation merged with the muscularis layer of the pyloric stomach. Immunohistochemically, 20% of the spindle cells labelled moderately strongly with antibody against CD117, supporting a diagnosis of GIST (Fig.4). Different chemotherapy protocols were discussed but declined by the owners. At the last follow up appointment (three months after initial diagnosis) the dog was free of clinical signs.

INVESTIGATIONS ***If relevant***

DIFFERENTIAL DIAGNOSIS ***If relevant***

TREATMENT ***If relevant***

OUTCOME AND FOLLOW-UP

DISCUSSION ***Include a very brief review of similar published cases***

As far as the authors are aware, there are no previous reports of GIST-associated hypoglycaemia in the dog. To date, only one case report of GIST-associated hypoglycaemia in a veterinary patient has been published, and that was in a horse (33). However, GISTs are a relatively new entity. An immunohistochemical review of previously diagnosed gastrointestinal leiomyomas and leiomyosarcomas has resulted in most of these tumours being re-classified as GISTs (11, 15, 34). All the cases describing hypoglycaemia secondary to leiomyomas/sarcomas (19, 24, 25, 35, 36) were published prior to this new classification. Therefore, it is possible that some of these previous cases were actually GISTs.

Paraneoplastic syndromes are common manifestations of many malignancies and have been reported with GIST (37, 38). Multiple articles on GIST-associated hypoglycaemia are available in human medicine (39-42) but no information on its systemic effects is available in the veterinary literature. Hypoglycaemia was a common presenting abnormality in both of the dogs reported here. In dog 1, the hypoglycaemia was considered to be the most likely cause of the clinical sings (weakness and collapse), given the lack of other physical and laboratory abnormalities. However, other unrelated causes (such as a transient arrhythmia or syncopal episode) were not ruled out. Liver dysfunction was considered an unlikely explanation for the hypoglycaemia. A bile acid stimulation test was not consistent with severe liver dysfunction and no imaging abnormalities were identified in the liver. Furthermore, the dog became normoglycaemic after the tumour was resected, providing more support for a paraneoplastic mechanism.

During surgery the mass was adjacent to the pancreas, but pancreatic involvement was not confirmed histopathologically. A concomitant, undetected insulinoma cannot be ruled out as a

potential cause for hypoglycaemia as insulin levels were not measured but the presence of two different neoplasms is considered unlikely.

Interestingly, histopathological examination of the mass in dog 1 did not indicate a direct connection between the mass and the GIT. EGISTs have been described in human medicine widely but nothing has been reported in the veterinary literature. In recent years, ICC or ICC-like cells have been found in extraintestinal organs (43). For example, in the genitourinary tract, KIT-positive specialized pacemaker cells have been described in the human bladder, urethra, uterus, and prostate (44-48). The presence of these cells in various organs or soft tissue could provide an explanation for the rare cases of GISTs that occur as primary tumours outside the GIT, such as in the mesentery, omentum, retroperitoneum, liver, gallbladder, vagina, uterus, urinary bladder, or prostate (44, 49-58). In some of these tumours, the origin remains unclear (59).

In addition to its hypoglycaemia, dog 2 was also diagnosed with aspiration pneumonia and, considering the clinical findings (dyspnoea, pyrexia), laboratory abnormalities (neutropenia), and timeframe, sepsis with secondary hypoglycaemia was a possibility. However, hypoglycaemia persisted after sepsis resolved. It also responded to glucocorticoid administration and, as with case 1, resolved after mass removal, such that sepsis as a sole cause was unlikely.

The main limitation of this report is the fact that the exact underlying mechanism for the hypoglycaemia was not determined. Given that the main cause of NICTH seems to be the secretion of IGF2, this should ideally have been measured to confirm the source of hypoglycaemia. Consequently, other causes of hypoglycaemia (insulinoma or liver disease in case 1 and sepsis in case 2), although unlikely, cannot be completely excluded. Furthermore, while an antibody panel was not applied in these two cases, both samples labelled strongly with antibody against CD117 which, given the other histological features, was considered sufficiently diagnostic of GIST and EGIST.

To the authors' knowledge these are the first cases describing hypoglycaemia associated with GIST and EGIST in the dog. GIST and EGIST should be considered as a differential diagnosis in dogs presenting with an abdominal mass and hypoglycaemia.

LEARNING POINTS/TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- EGISTs do occur in dogs.
- GIST and EGIST should be considered as a differential diagnosis in dogs presenting with an abdominal mass.
- GIST and EGIST should be considered as a differential diagnosis in dogs presenting hypoglycaemia.

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FIGURE/VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Fig. 1

Ultrasonographic image from dog 1 showing large round heterogeneous mass (between callipers) with multiple hypoechoic cavitations (asterisk shows the largest one) which was identified in the right cranial abdomen dorsal to the duodenum.

Fig. 2

Ultrasonographic image from dog 1 showing multiple different sized, hypoechoic nodules within the pancreatic parenchyma (between callipers) discovered five months after initial presentation. Note hepatic parenchyma in the near field (margin delineated with arrows).

Fig. 3

Abdominal gastrointestinal stromal tumour from dog 2 [HE]. The mass comprises a partially necrotic proliferation of moderately pleomorphic spindle cells arranged in interlacing streams.

Fig. 4

Immunohistochemistry of abdominal gastrointestinal stromal tumour from dog 2. Spindle cells label moderately strongly with antibody against CD117.

OWNER'S PERSPECTIVE ***Optional***

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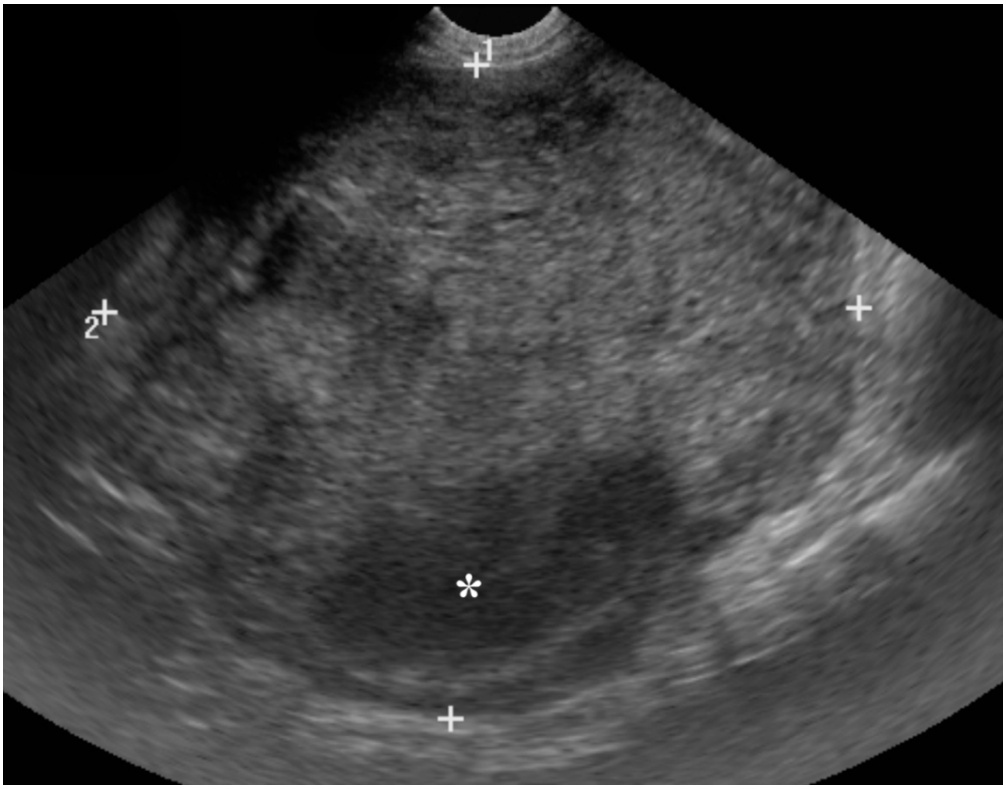
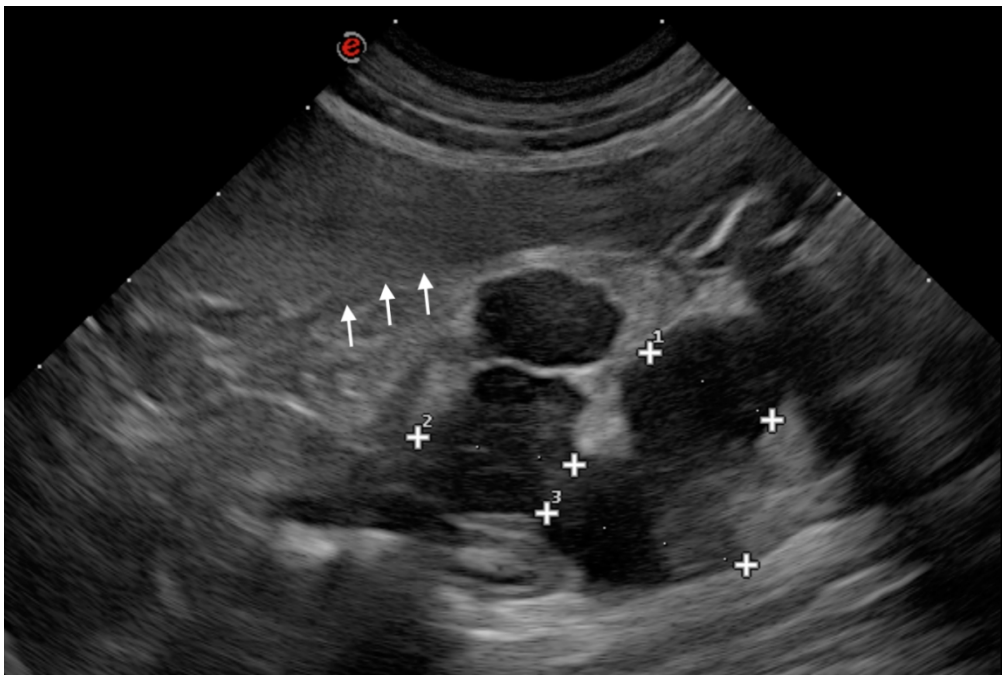


Ultrasonographic image from dog 1 showing large round heterogeneous mass (between callipers) with multiple hypoechoic cavitations (asterisk shows the largest one) which was identified in the right cranial abdomen dorsal to the duodenum.

102x79mm (300 x 300 DPI)



Ultrasonographic image from dog 1 showing multiple different sized, hypoechoic nodules within the pancreatic parenchyma (between callipers) discovered five months after initial presentation. Note hepatic parenchyma in the near field (margin delineated with arrows).

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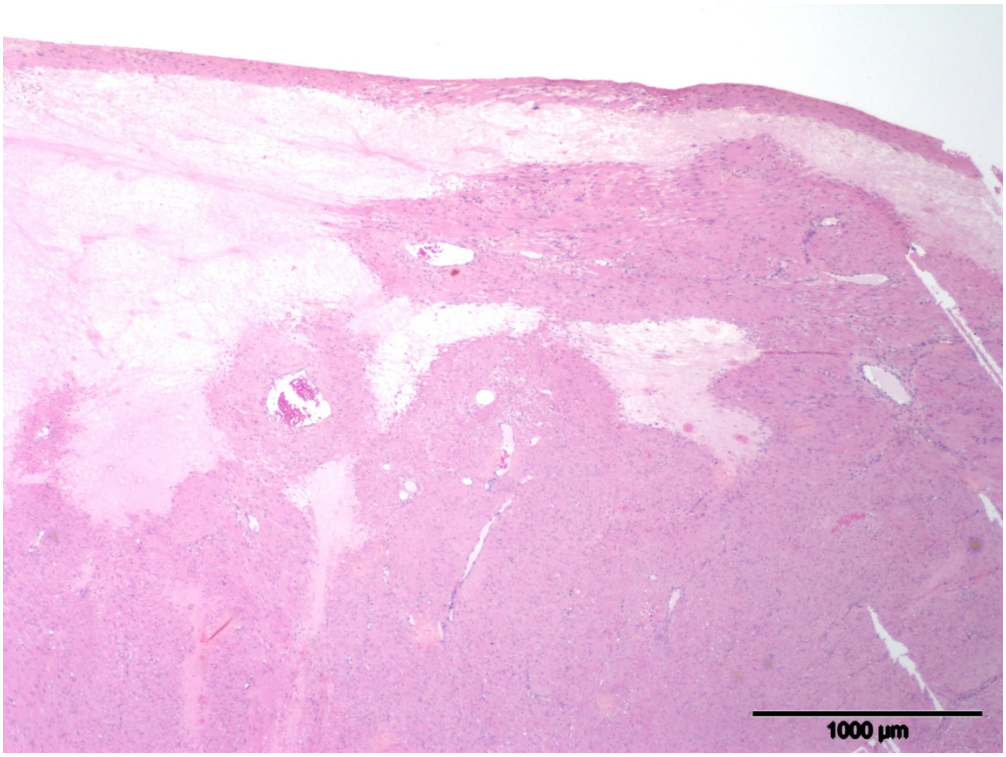
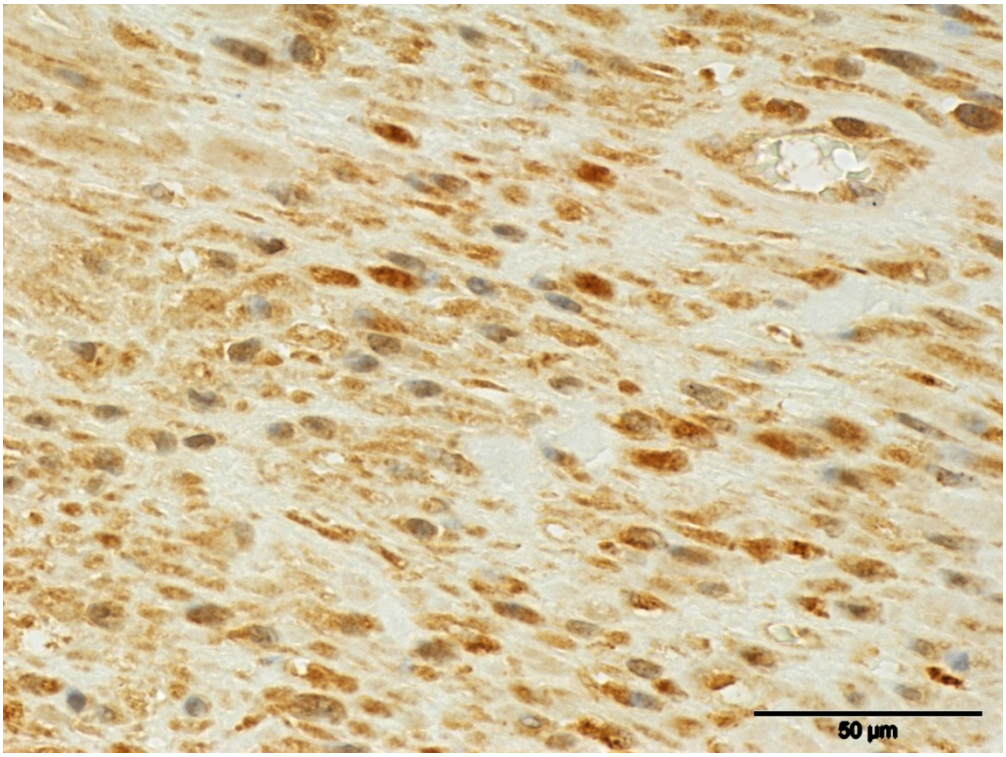


Abdominal gastrointestinal stromal tumour from dog 2 [HE]. The mass comprises a partially necrotic proliferation of moderately pleomorphic spindle cells arranged in interlacing streams.

59x44mm (600 x 600 DPI)



Immunohistochemistry of abdominal gastrointestinal stromal tumour from dog 2. Spindle cells label moderately strongly with antibody against CD117.

59x44mm (600 x 600 DPI)