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Canine gastrinoma: A case study and literature review of therapeutic options

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Clinical Communication

Canine gastrinoma: A case study and literature review of therapeutic options

SM Hughes*

Abstract

CASE HISTORY: A 6.2 kg, 8-year-old, spayed female Australian Terrier was presented with weight loss, inappetence, lethargy and a 2-day history of intermittent vomiting.

CLINICAL FINDINGS: The dog had cranial abdominal pain and there was melaena present on digital rectal examination. Haematology revealed a marked, acute leucogram.

DIAGNOSIS AND TREATMENT: Fasting serum gastrin levels were markedly elevated and gastrinoma was suspected. Treatment was initiated with omeprazole, ranitidine and sucralfate. The dog remained clinically normal for 26 months, at which time exploratory surgery was undertaken and the dog subsequently euthanised due to extensive metastases. Histopathology and immunocytochemistry confirmed the diagnosis of metastatic gastrinoma.

CLINICAL RELEVANCE: This is a rare condition infrequently reported. Although the number of cases treated with omeprazole are too few to draw firm conclusions, it would appear that proton pump inhibitors are useful and should be considered for cases of gastrinoma managed medically. Long-term prognosis is poor, and survival times range from 1 to 147 weeks. Many treatment options are discussed in the medical literature though not all are feasible in veterinary patients.

KEY WORDS: ***Canine, gastrin, gastrinoma, proton pump inhibitors, pancreatic tumours, Zollinger Ellison syndrome, gastric hyperacidity***

Introduction

Gastrinomas are rare non-β-islet cell tumours of the pancreas that result in a syndrome of gastric acid hypersecretion and gastrointestinal ulceration (Brooks and Watson 1997; Simpson 2000). This syndrome was first described in human medicine by Zollinger and Ellison (1955), who reported a triad of gastric hypersecretion, pancreatic islet cell tumour and gastrointestinal ulceration. The secretagogue and ulcerogen were subsequently identified as the hormone gastrin (Rousseaux 1987; Simpson 2000).

The first reported case of a gastrinoma in veterinary medicine was described in 1976 (Jones et al 1976). The disease usually develops in middle-aged dogs, and no breed predilection has been reported (Feldman and Nelson 1987; Zerbe 1992).

The clinical manifestations most frequently reported in patients with gastrinoma are vomiting, weight loss, depression, lethargy, anorexia and diarrhoea (Happe et al 1980; Zerbe 1992; Brooks and Watson 1997; Simpson and Dykes 1997). Diagnosis is most commonly deduced from the presence of hypergastrinaemia in fasted patients, coupled with exploratory laparotomy and biopsy/resection of the tumour and subsequent histopathological examination. Immunocytochemical evaluation of excised pancreatic tumours ensures a definitive diagnosis (Lurye and Behrend 2001; Hoenerhoff and Kiupel 2004), although not all gastrinoma cells stain positively for gastrin (Brooks and Watson 1997; Hayden and Henson 1997). The long-term prognosis of dogs with gastrinomas is grave, and survival times after diagnosis ranged from 1 week to 18 months in one study (Green and Gartrell 1997).

Presented here are the clinical findings, retrospective diagnosis and palliative treatment of a dog with metastatic gastrinoma, and a review of possible therapeutic options reported in the medical and veterinary literature.

Case history

An 8-year-old, spayed female Australian Terrier that weighed 6.2 kg was presented with weight loss, inappetence and lethargy, and a 2-day history of intermittent vomiting. Clinical examination revealed cranial abdominal pain, a temperature of 38.7°C, and melaena following digital rectal examination. Serum and whole blood samples were obtained for a complete blood count (CBC) and serum biochemistry, respectively, and a faecal sample was collected to test for occult blood.

The initial haemogram identified a marked acute leucogram with 57.4 (reference range 6.0–15.0) x 10^9/L white blood cells, comprising 5.17 (reference range 0–0.54) x 10^9/L band neutrophils, 45.92 (reference range 3.6–11.5) x 10^9/L segmental neutrophils, and 3.44 (reference range 0.2–1.5) x 10^9/L monocytes. Serum biochemistry revealed mildly decreased levels of calcium (1.80, reference range 2.03–2.91, mmol/L), albumin (25.1, reference range 28.7–38.7, g/L), potassium (3.8, reference range 4.2–6.7, mmol/L), and chloride (86, reference range 98–107, mmol/L). The faecal sample was positive for occult blood.

The dog was placed on intravenous fluids, comprising lactated Ringers solution (Compound Sodium Lactate; Baxter Healthcare, NSW, Australia) containing 10 mEq KCl/L (Potassium Chloride 1.5 g in 10 ml; AstraZeneca Ltd, Auckland, NZ), at 35 ml/h. Antibiotic therapy was instituted, comprising 1 ml amoxycillin/clavulanic acid 50 mg/ml (Clavulox RTU; Pfizer Animal Health, Auckland, NZ) subcutaneously for 3 days. The dog remained

CBC	Complete blood count
DAB	Diaminobenzidine
H&E	Haematoxylin and eosin
HRP	Horseradish peroxidase
MEN	Multiple endocrine neoplasia
PO	*Per os*
ZES	Zollinger-Ellison syndrome

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anorectic, and continued to vomit intermittently. A second blood sample was obtained for CBC and serum biochemistry (Table 1). The animal had a severe non-regenerative anaemia, which was unlikely to be solely attributable to anaemia of chronic disease. This finding, coupled with marked hypoalbuminaemia, suggested per-acute blood loss, most likely into the gastrointestinal tract, given the presence of melaena.

In an attempt to reduce gastrointestinal bleeding and alleviate cranial abdominal pain, a trial treatment of 1 mg/kg omeprazole (Losec 10 mg; AstraZeneca Ltd, Auckland, NZ) *per os* (PO) once daily, for suspected gastric ulceration, was instigated. By the following day, the dog was much brighter and the vomiting and diarrhoea had stopped. The dog continued to make an uneventful recovery, leading to its discharge 2 days later.

The consideration of a possible diagnosis of gastrinoma based on clinical findings, CBC, serum biochemistry and successful amelioration of clinical signs following medication with omeprazole prompted a measurement of plasma gastrin 1 month after initiation of omeprazole therapy. Surgery would have provided a definitive diagnosis, but was declined by the owners.

A fasting blood sample was collected, and plasma gastrin was measured using radioimmunoassay (Gastrin ^{125}I Radioimmunoassay Kit; ICN Pharmaceuticals, NSW, Australia), and com-

Table 1. Haematological and serum biochemistry data from an 8-year-old female dog with metastatic gastrinoma, 6 days after initial presentation.

Test	Case study	Units	Reference range
Red blood cells (RBC)	2.8 (L)	x 10^{12}/L	5.5–8.5
Haemoglobin	65 (L)	g/L	120–180
Packed cell volume	0.2 (L)	L/L	0.37–0.55
Reticulocytes	0.5	%	0.0–1.0
RPI	0.1		
Nucleated RBC	1	/100 WBC	
WBC	78.0 (H)	x 10^9/L	6.0–15.0
Band neutrophils	22.6 (H)	x 10^9/L	0.00–0.54
Segmented neutrophils	42.9 (H)	x 10^9/L	3.6–11.5
Lymphocytes	3.1	x 10^9/L	1.0–4.8
Monocytes	7.8 (H)	x 10^9/L	0.2–1.5
Calcium	1.75 (L)	mmol/L	2.03–2.91
Phosphorus	1.34	mmol/L	1.01–3.53
Alkaline phosphatase	332 (H)	IU/L	9–185
Creatine phosphokinase	314	IU/L	53–821
Aspartate aminotransferase	55	IU/L	2–79
Alanine aminotransferase	35	IU/L	3–58
Amylase	644	IU/L	350–920
Glucose	7.3 (H)	mmol/L	3.8–5.8
Urea	5.9	mmol/L	2.5–8.4
Creatinine	36 (L)	µmol/L	83–152
Bilirubin	9.4 (H)	µmol/L	0–6
Cholesterol	2.7 (L)	mmol/L	3.2–9.3
Total protein	32.9 (L)	g/L	47.4–69.6
Albumin	15.0 (L)	g/L	28.7–38.7
Globulin	17.9	g/L	14–35
Albumin:globulin ratio	0.84	:1	0.83–2.01
Lipase	1,067 (H)	IU/L	14–252
Sodium	155	mmol/L	140–160
Potassium	3.3 (L)	mmol/L	4.2–6.7
Bicarbonate	22.4	mmol/L	13–29
Chloride	114 (H)	mmol/L	98–107
Anion gap	22	mmol/L	12–29

(L) = low; (H) = high; RPI = reticulocyte production index; WBC = white blood cells

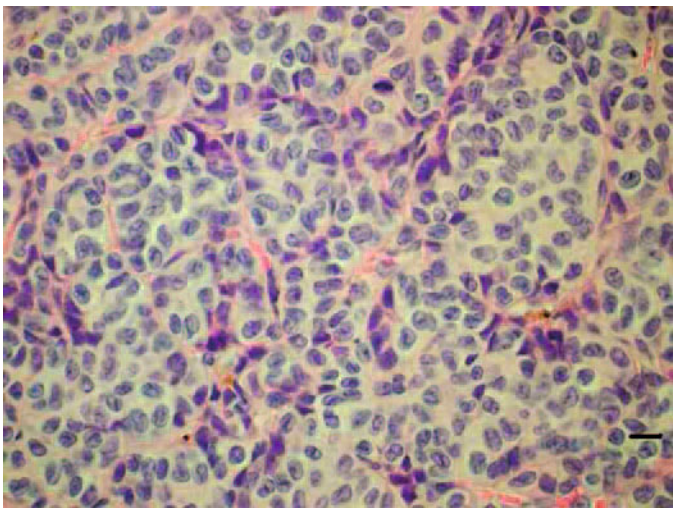

Figure 1. Light photomicrograph of a section of pancreas from a dog with gastrinoma showing hyperchromatic ribbons of neoplastic gastrinoma cells loosely packaged by a light fibrous stroma (H&E, bar=50 µm).

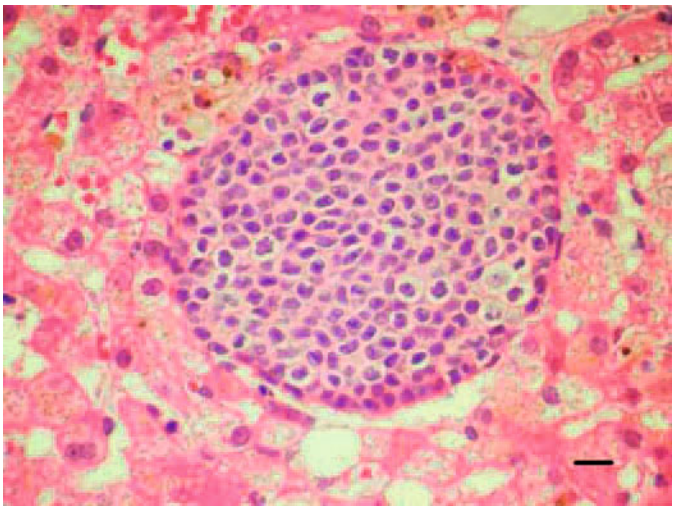

Figure 2. Light photomicrograph of a section of liver from a dog with gastrinoma, depicting a metastasis within the parenchyma (H&E, bar=50 µm).

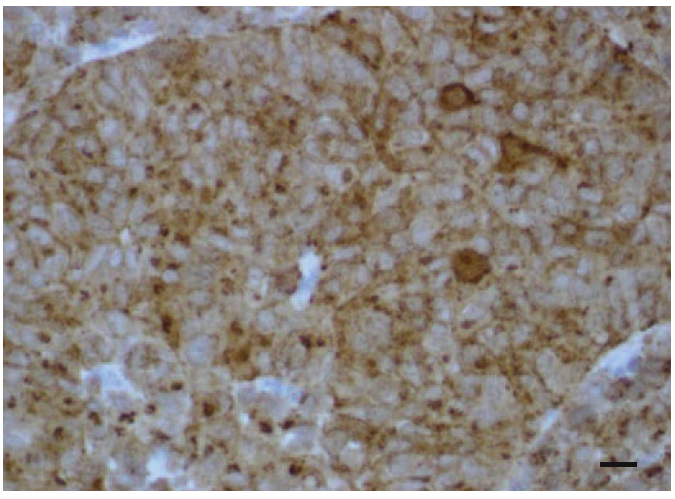

Figure 3. Immunohistochemical staining of a pancreatic neoplasm in a dog exhibiting positive immunoreactivity to antibodies against gastrin. (Envision + HRP, rabbit DAB + biotin-free Envision + horseradish peroxidase-labelled polymer, DAB chromogenic substrate, haematoxylin counter-stain, bar=50 µm).

pared with a fasting blood sample from a healthy dog. The assay revealed a fasting plasma gastrin level of 826 ng/L in the patient, compared with 48 ng/L in the healthy dog, leading to an interim diagnosis of gastrinoma.

The dog remained asymptomatic for 14 months, at which time there were anorectic episodes and sporadic vomiting. The animal was placed on a palliative treatment trial of 3 mg/kg ranitidine PO twice daily (Zantac; GlaxoWellcome, Auckland, NZ) and 0.5 g sucralfate PO twice daily (Carafate 1 g; Hoechst Marion Roussel, Auckland, NZ). The vomiting ceased and the dog's appetite returned, so the administration of ranitidine, omeprazole and sucralfate were continued indefinitely.

Twenty-six months following the tentative diagnosis, the dog was presented with a 1-month history of intermittent anorectic episodes in which meals were not consumed once or twice a week. Although the lack of appetite concerned the owners, there was no obvious clinical manifestation of disease other than a marginal weight loss of 500 g. The dog had a fasting plasma gastrin level of 9,515 ng/ml (control = 30 ng/ml).

An exploratory laparotomy was proposed, to confirm the presence of neoplasia and, if present, allow the suspected mass to be examined surgically with the aim of de-bulking or removing the tumour *en bloc*, to lower the serum gastrin level sufficiently to ameliorate the developing anorexia. As metastatic disease was likely, given the time frame since initial diagnosis, prior permission was given for euthanasia if the tumours were found to be too extensive or non-resectable. In retrospect, the decision to euthanise may have been reached following abdominal ultrasound, however this diagnostic avenue was not available at the time and the owners declined referral.

At surgery, there were multiple firm, finely-capsulated nodular masses on the body, right and left lobes of the pancreas, 2–25 mm in diameter. Multiple masses in the right lateral and medial, left lateral and quadrate lobes of the liver varied in size from 3–35 mm diameter. A 15-mm firm, spherical mass was present in the distal ileum, and a 12-mm irregular mass in the greater omentum. No other observable abnormalities were present, but due to the multi-organ involvement and difficulty in effective debulking without considerable loss of blood, the decision was made to euthanise the dog.

Following necropsy, sections of affected tissue were fixed in 10% formalin and embedded in paraffin wax, using routine methods. Sections were cut at 5 µm and stained with haematoxylin and eosin (H&E). Histopathology of the macroscopic masses in the pancreas, liver, distal ileum and omentum revealed all to be of the same type of cell. The pancreas contained a multi-lobular neoplastic infiltrate comprising hyperchromatic cells packaged into pseudorosettes and ribbons by a light fibrous stroma in a neuroendocrine pattern. Individual cells had a faint eosinophilic cytoplasm, mildly pleomorphic oval nuclei, and occasional mitotic figures (Figure 1). There was evidence of lymphatic invasion and multiple metastatic nodular tumour infiltrates in the liver (Figure 2).

Immunohistochemical evaluation involved de-waxing sections of formalin-fixed neoplastic tissue and subsequent incubation with polyclonal rabbit anti-human gastrin coupled to bovine serum albumin. The samples were then visualised with Envision + HRP (DAKO, Carpinteria CA, USA) and horseradish peroxidase (HRP)-labelled polymer using diaminobenzidine (DAB) as the chromagen, and counterstained with haematoxylin. Tumour masses in the pancreas (Figure 3), liver and distal ileum all stained positively for gastrin, confirming the diagnosis of gastrinoma.

Discussion

The dog in this report presented with clinical signs typical of gastrinoma (Zerbe 1992; Simpson and Dykes 1997). This led to a provisional diagnosis of gastrinoma, based on clinical signs, serum biochemistry, response to supportive treatment and later, markedly raised plasma gastrin levels. Recently, Dhillo et al (2006) reported that measurement of gastrin in plasma could not be used for diagnosis of gastrinoma whilst the patient was concurrently on proton pump inhibitors or histamine type-2-receptor antagonists, as there was considerable overlap between gastrinoma and control patient groups. However, those authors did report that medicated patients with gastrinoma had significantly higher plasma gastrin levels than medicated control patients, and both groups had levels that were up to eight times greater than the upper reference limit. However, the dog reported here had levels over 200 times greater than reference values, which would suggest that although gastrin levels in the dog cannot be used diagnostically, such elevated levels could increase the index of suspicion for canine gastrinoma.

The response to omeprazole produced rapid amelioration of clinical signs, which further supported the possibility of gastrinoma in this case (Brooks and Watson 1997), but histopathology/immunohistochemistry was required for a definitive diagnosis.

Earlier surgical intervention in this case would have resulted in an earlier final diagnosis and may well have increased the possibility of a surgical cure (Norton 1998), although the duration of time in which the dog had no clinical signs whilst on medication supports the effectiveness of proton pump inhibitors as a palliative treatment option for gastrinomas (Arnold 1990).

Gastrin is a polypeptide hormone that is normally secreted by the G-cells of the pyloric antrum and, to a lesser extent, the proximal duodenum (English et al 1988; Strombeck and Guilford 1990a; Zerbe 1992; Guyton and Hall 1996). It is then absorbed into the bloodstream, where it carried to the body of the stomach and acts to stimulate secretion of hydrochloric acid by gastric parietal cells, and exerts trophic effects on the mucosa of the gastrointestinal tract (Breitschwerdt et al 1986; Zerbe 1992; Green and Gartrell 1997). Gastrin also stimulates acid secretion indirectly by releasing histamine from fundic enterochromaffin-like cells (Schubert 2003).

Secretion of gastrin is regulated by both cholinergic neurons, that cause inhibition of somatostatin thereby stimulating secretion of gastrin (disinhibition), and by non-cholinergic neurons, that cause direct stimulation of secretion of gastrin by releasing the neurotransmitter bombesin (Schubert and Shamburek 1990). Other hormones involved in the release of gastrin include secretin, glucagon, neurotensin and catecholamines (Strombeck and Guilford 1990a; Hattori et al 1992). The complex nature of regulation of secretion of gastrin lends itself to more specific treatment options, for example the long-acting somatostatin analogue octreotide binds to somatostatin receptors on the tumour and decreases release of gastrin (Altschul et al 1997; Simpson 2000).

In human medicine, refractory peptic ulcer disease and gastric hypersecretion in the presence of a non-β-islet cell tumour of the pancreas is referred to as Zollinger-Ellison syndrome (ZES; Eiseman and Maynard 1956). ZES is widely regarded to exist in two forms, a sporadic form which is often solitary and located in the pancreas or duodenum, and ZES-associated multiple endocrine neoplasia (MEN) type 1, which is frequently multi-centric and is predominantly of duodenal origin (Donow et al 1991; Pipeleers-Marichal et al 1993; Mignon and Cadiot 1998). Approximately 25% of human cases of ZES are due to MEN1 (Gibril and Jensen

2004), and there is a longer period of survival with ZES/MEN than sporadic ZES (Melvin et al 1993).

It has been hypothesised that many canine gastrinomas may originate in the duodenum or gastric antrum, and that a pancreatic islet cell tumour found in cases of gastrinoma is non-gastrin-producing and represents a form of MEN (Hoenerhoff and Kiupel 2004). A recent study (Vergine et al 2005) reported a gastrinoma of duodenal origin causing extrahepatic biliary tract obstruction.

From the 22 previously reported cases in canines, 17 had masses in the pancreas and of these one did not reveal the site of the diagnostic biopsy. Three found no evidence of neoplasia in the pancreas during exploratory laparotomy, though no post mortem was performed, and one showed focal invasion of the pancreas by a duodenal gastrinoma. Therefore, 85% of dogs reported with a diagnosis of gastrinoma have had pancreatic masses.

In two of the canine gastrinoma cases reported, the only tumours found during exploratory laparotomy were in lymph nodes (Green and Gartrell 1997). The occurrence of primary lymph-node gastrinomas in human medicine has been investigated (Herrmann et al 2000), and the findings supported the hypothesis of entrapment of neuroendocrine cells during development, and the presence of primary nodal gastrinomas. It has been approximated that 10% of sporadic ZES cases in humans are due to primary lymph-node gastrinomas (Norton et al 2003).

In the 11 cases of canine gastrinoma in which immunohistochemical staining was performed on biopsies/samples, 64% showed positive staining in the pancreas and one showed positive staining in the duodenum. Due to the small number of cases, it is difficult to draw any conclusions about the origins of canine gastrinomas. A greater reporting of cases that includes thorough exploratory laparotomy/post mortem, and close examination and sampling of the pancreas, duodenum, gastric antrum as well as any other masses found, coupled with immunohistochemical staining, may shed light on this topic.

Although the treatment of choice for gastrinoma remains surgical removal of the neoplasm (Simpson 2000; Li and Norton 2001), in humans the 5-year cure rate is only 30–50% (Jensen and Fraker 1994; Mignon et al 1996), although a figure of 82% has been stated (Ellison et al 1987). In human patients without metastases, surgical cure is possible in 30% (Hung et al 2003), and will decrease the development of liver metastases and may improve survival (Norton and Jensen 2003). Surgery also offers a chance for excision of deep or perforated ulcers, as the subsequent development of peritonitis is a likely sequel (Feldman and Nelson 1987). Although surgery is indicated to potentially cure the patient, a reported 60% of gastrinomas metastasise in humans (Norton 1998), and this value is likely to be similar in canines as an incidence of 72% was reported by Zerbe (1992).

The primary determinants of survival in human patients with gastrinoma are the size of the primary tumour and liver metastases (Bornman and Radebold 1998), the latter being the most important (Kisker et al 1998). Therefore, an aggressive approach towards curative excision of the tumour is imperative in improving surgical outcomes (Stabile et al 1984). Liver transplantation as the ultimate therapeutic, or at least palliative, option for hepatic metastases in humans has produced contradictory results over the past decade; however, when coupled with other treatment modalities some success has been achieved (Gottwald et al 1998). Likewise, hepatic cryosurgery has been shown to dramatically relieve symptoms and reduce burdens of the tumour, and is therefore a useful adjuvant in symptomatic patients with refractory hepatic neuroendocrine metastases (Bilchik et al 1997).

Debulking surgery for tumours is a well-recognised approach to reduce the clinical effects of hypergastrinaemia, and as a complement to medical therapy (Rothmund et al 1991; Li and Norton 2001). Ablation of tissues using radiofrequency may prove to be a safe and efficient method of debulking liver metastatic tumours, as this can be performed percutaneously as well as intra-operatively (Hellman et al 2002). An alternative percutaneous treatment option described for liver metastases is ultrasound-guided intra-lesional injection of ethanol, to shrink tumours prior to surgical excision, though indications for this appear to be limited (Livraghi et al 1991).

Chemotherapy provides another therapeutic avenue, and mixed responses are discussed in the medical literature. After six cycles of chemotherapy with doxorubicin, cyclophosphamide and etoposide, a patient remained well for 1 year but then relapsed and died 6 months later despite an initial response to salvage radiotherapy and chemotherapy with carboplatin and dacarbazine (O'Byrne et al 1994). Another case study reported excellent responses to dacarbazine therapy in two patients diagnosed with gastrinoma and multiple liver metastases (Ohshio et al 1998).

Sreptozotocin is a chemotherapeutic agent which has been shown to be effective against metastatic gastrinoma, either as a sole treatment (Hayes et al 1976) or combined with fluorouracil (Ruffner 1976; Ruszniewski et al 1991). An alternative to intravenous and/or oral chemotherapy for liver metastases is hepatic arterial chemo-embolisation. This involves injection of a chemotherapeutic emulsion (usually doxorubicin) into an artery supplying the tumour, followed by arterial occlusion with gelatine sponge particles. This approach compared favourably with other treatment options in that it produced less morbidity than systemic chemotherapy and appeared to be more effective (Ruszniewski et al 1993; Perry et al 1994). The extrapolation and application to veterinary patients is questionable and is unlikely to ever become a feasible therapeutic option.

Receptor-mediated radiotherapy of tumours holds some promise with regards to metastatic gastrinoma. A case in a human using a radionucleotide-labelled somatostatin analogue showed good results (Leimer et al 1998), although the efficacy of nuclear medicine with regards to long-term and survival rate data is lacking (Virgolini et al 2005).

The slow onset of clinical severity and subsequent delay in early diagnosis in the veterinary field coupled with the infiltrative nature of the tumour and the high likelihood of metastasis (Zerbe 1992; Norton 1998) often makes medical management a viable if not sole option in the palliative treatment of this disease. Medical management involves reducing the clinical effects of hyperacidity, reducing the hypersecretion of acid, and/or inhibiting hormonal secretion from the tumour itself. The use of gastric mucosal protectants such as sucralfate has limited efficacy on its own, but is of use in combination with other treatment modalities.

Reducing the secretion of gastric acid has been the mainstay of medical management in human patients with gastrinoma (Altschul et al 1997; Quatrini et al 2005). H_2-receptor antagonists such as ranitidine, cimetidine and famotidine reduce gastric acid production by competitively binding to H_2-histamine-receptor sites on gastric mucosal parietal cells, preventing histamine-induced gastric acid secretion (Strombeck and Guilford 1990b). H_2-receptor antagonists have been used for many years in both veterinary and human medicine (Shearman 1976; Drazner 1981, Fukushima et al 2004ab), but more recently have been superseded by more efficacious inhibitors of gastric acid secretion.

The use of proton pump inhibitors such as omeprazole, lansoprazole and pantoprazole have proved to be very effective in control-

ling gastric acid hypersecretion in humans (Arnold 1990; Desir and Poitras 2001; Konturek et al 2002) and canines (Altschul et al 1997; Brooks and Watson 1997). Proton pump inhibitors act by inhibiting the enzyme H^+-K^+-ATP-ase, the acid pump. This effect on the final step of the process of gastric acid formation provides highly effective inhibition of both basal and stimulated acid secretion, irrespective of the stimulus (Anonymous 2000).

Recently, it was shown that in healthy dogs famotidine, pantoprazole and omeprazole significantly suppressed gastric acid secretion but ranitidine did not (Bersenas et al 2005), and of the drugs tested only omeprazole approached the potential therapeutic efficacy for acid-related disease when assessed using criteria for human patients. One study (Quatrini et al 2005) of 18 patients, all of which had relapsing peptic ulcers, showed that surgically curing gastrinoma or appropriately inhibiting gastric acid hypersecretion (initially with histamine type-2-receptor antagonists then later with omeprazole) in ZES patients prevented death and favoured long-term survival, regardless of gastrin levels and the size or number of tumours.

Long-acting somatostatin analogues such as octreotide have been shown to be effective in controlling symptoms in both human (Vinik et al 1988; Gaztambide and Vazquez 1999; Ricci et al 2000; Saijo et al 2003) and veterinary (Lothrop 1989; Altschul et al 1997) patients with metastatic gastrinoma. These drugs reduce hyperacidity by acting directly on the tumour cells, causing reduction of gastrin secretion, and indirectly by binding to high-affinity cell-surface somatostatin receptors on gastric parietal cells, thus reducing gastric acid secretion (Altschul et al 1997). The addition of alpha-interferon to the somatostatin analogue octreotide showed promise in one study, and produced anti-proliferative efficacy in a group of patients with advanced metastatic disease that was unresponsive to treatment with octreotide alone (Frank et al 1999). Somatostatin analogues are not considered by some to be the therapeutic principle of first choice (Arnold et al 1994) for human gastrinomas. For control of acid hypersecretion, the proton pump inhibitors such as omeprazole are considered superior to all former and present alternatives (Arnold 1990; Arnold et al 2000; Konturek et al 2002).

In conclusion, the case described here reports a typical case of canine gastrinoma. Despite the grave prognosis, proton pump inhibitors such as omeprazole appeared to significantly reduce morbidity and may well extend life expectancy. Although further studies are required to validate its efficacy, proton pump inhibitors are likely to be beneficial in cases of gastrinoma, either as a pre-surgical treatment to reduce morbidity or, in the case of non-operable disease, for effective palliation of clinical symptoms.

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