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Insulin-secreting β-cell neoplasia in a 7-year-old female dog, case report and review

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Abstract: A 7-year-old female dog presented with intermittent episodes of urinary incontinence, tremors, intermittent episodes of pelvic limb weakness and collapse, and lethargy were noticed over a period of two months. Hypoglycaemia, secondary to an insulin-secreting β-cell tumour, was suspected on the basis of clinical signs, ultrasound and serum biochemistry. A laparotomy was then performed to remove the tumour mass. Post-surgical pancreatitis was a major complication. Histology revealed a malignant neuroendocrine neoplasia of the β-cells of the pancreas. This case review is reported to keep clinicians abreast of the canine insulinoma disorder and the complications surrounding its diagnosis and treatment.

Keywords: insulinoma; neoplasia; hypoglycaemia; diabetes; pancreas; beta cell; canine

1. Introduction

Insulinoma is a rare malignant neuroendocrine neoplasia of the β-cells of the canine pancreas (Madaram, Kayanuma, Shida, & Tsuchiya, 2009), yet it is recognized as the most common islet cell tumour of the endocrine pancreas (Elie & Zerbe, 1995). Often times the clinical picture of insulinoma is characterized by episodes of hypoglycaemia (low blood sugar) which induce syncope, weakness, seizures, ataxia and death. Treatment almost always requires surgery, which can be risky and not always effective. Average life expectancy ranges from 6 to 24 months after diagnosis. Canine insulinoma though a rare disease, it is the most common tumor of the endocrine pancreas (Elie & Zerbe, 1995). Often times the clinical picture of...
neuroglucopenia include seizures, ataxia and weakness, muscle atrophy, apparent blindness, appendicular hyporeflexia, behavioural changes and even coma (Elie & Zerbe, 1995). Thus clinicians may wrongfully diagnose it as diabetes. Differential diagnoses include cardiopulmonary disease, episodic haemorrhage, hypoglycaemia, hypoadrenocorticism, polymyositis, myasthenia gravis, orthopaedic or articular disease, and toxicosis and they must be considered (Goutal & Brugmann, 2012). Symptoms of insulinoma can vary from extreme behavioural abnormalities to mild seizures. In most cases a clear pattern is not seen. Diagnosis is, therefore, dependent on extensive laboratory tests and diagnostic imaging. Finding a very low blood glucose level and very high levels of insulin in the blood simultaneously may be a clear indication of insulinoma, diagnosis can be very elusive and dogs may require many blood glucose measurements after variable periods of fasting to document the low levels (Vallee, 2003). Though seizures can be caused by many other disorders but seizures caused by insulinoma are not different from those caused by epilepsy, brain tumours, etc. Often times the clinician may go on a wild goose chase in order to rule out some of these disorders either by laboratory tests or diagnostic imaging before insulinoma is suspected. Radiographs, ultrasound examination and magnetic resonance imaging (MRI) can be used to determine whether the metastatised stage of the tumour has occurred. Arriving at a definitive diagnosis, however, requires both surgery and histopathology. Therefore, Veterinarians should be aware of the behavioural signs, the clinical signs, physio-pathology, treatment options and prognosis of insulinoma or this metabolic disorder. Due to compensatory counter-regulatory mechanisms, clinical signs tend to be episodic and to last from a few seconds to a few minutes. An insulinoma is a functional adenocarcinoma of the β-cells of the endocrine pancreas. Insulinoma occurs most often in middle-aged to old dogs with an average age of nine years (Cohen, 2003; McDermott, Swainson, & Howard, 1999). The breeds most commonly affected are German Shepherds, Irish Setters, Boxers, Golden Retrievers and Terriers (Leifer, Peterson, & Matus, 1986). The prevalence of insulinomas in large breeds of dogs or canine species was also confirmed in a study where more than 72% of the dogs weighed more than 25 kg (Leifer et al., 1986). These carcinomas most commonly metastasize to regional lymph nodes and the liver in approximately 50% of the studied cases (Cohen, 2003; Leifer et al., 1986). This case review is reported to keep clinicians abreast of the canine insulinoma disorder and the complications surrounding its diagnosis and treatment. Furthermore, it explains one treatment option and the complications with the procedure. The following discussion compares and contrasts other findings with those of this case.

2. Case report
A seven-year-old female cross-bred dog was referred to Veterinary Clinic, Effurun, Delta State, Nigeria with complaint of urinary incontinence, tremors, intermittent episodes of pelvic limb weakness and collapse, and lethargy noticed over the past two months by the owner. After clinical examination, the dog was placed on routine antibiotics gentamycin 1 mg/kg with Diclofenac sodium 2 mg/kg for 5 days and oestrogen tablets 0.3 mg/kg/day for 1 week and then given three times a week for one month for treatment of urinary incontinence.

One month later the dog was brought back without any clinical signs of improvement and significant loss of body weight. The dog was panting and had a temperature of 38.6°C, mucous membranes were pinkish. The dog weighed 17 kg against 19 kg initial weight at first presentation. After clinical examination, the dog was placed on routine antibiotics gentamycin 1 mg/kg with Diclofenac sodium 2 mg/kg for 5 days and oestrogen tablets 0.3 mg/kg/day for 1 week and then given three times a week for one month for treatment of urinary incontinence.

The insulin level on this same day was found to be high (33.7 lU/mL; ref: 1–20 lU/mL). Insulin glucose ratio (IGR) (82.2 ref: <13.5) and adjusted insulin glucose ratio (AIGR) (306.4 ref: <30) (Table 1).

The dog was placed on gentamicin 4 mg/kg intra muscular (IM) injection for 5 days and oral multivitamin supplement was recommended. Two weeks later the dog was brought back for a follow-up. There was no significant improvement and this time there was marked anorexia, polyuria, and
polydipsia. A thoracic and abdominal radiograph and abdominal ultrasound scan was then carried out. Abdominal radiograph did not reveal any marked lesions but ultrasonography of the cranial abdominal region revealed an 8.5 mm × 14 mm hyperechoic elliptical lesion in the area of the right lobe of the pancreas (Figure 1). No other masses were evident in the abdomen. A laparotomy was then carried out.

3. Surgery
Pre-anaesthesia was achieved with atropine (0.05 mg/kg I.M) and xylazine (0.5 mg/kg I.M). Anaesthesia was induced with ketamine 10 mg/kg intravenously and maintained with 10 mg/kg ketamine IM. Dextrose saline (5%) was given intravenously at a rate of 5 ml/kg/hour throughout the surgery. Perioperative cefazolin at 22 mg/kg was also given intravenously. A standard approach for an exploratory laparotomy was performed. Examination of the pancreas revealed an adhesion between the caecum and the right lobe of the pancreas. The adhesion was separated by blunt dissection and about one-third of the distal right pancreatic lobe was resected using 3–0 nylon ligatures. The gastropancreatic lymph node was also found to be severely inflamed and necrotic, it was removed. A thumb-sized nodule (approximately 2 cm diameter) was also removed from the mid right pancreatic lobe along with the adjoining pancreatic tissues. The liver appeared normal. All suspected diseased tissues excised from the animal patient were persevered in 10% formalin and later sent for histopathological evaluation.

4. Post-surgical management
Postoperatively oral feeding was withheld for 48 h and the dog was monitored. There were vomiting and pyrexia, thus metoclopramide 0.2 mg/kg subcutaneous (S.C) injection and diclofenac sodium 2 mg/kg was administered. The dog recovered well from surgery. No clinical signs of pyrexia,

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**Table 1. Determination of IGR and AIGR from laboratory results**

| Results   | Normal range |
|-----------|--------------|
| Insulin   | 33.7 IU/mL   | 1–20 IU/mL    |
| Glucose   | 41 mg/dL     | 65–115 mg/dL  |
| IGR       | 82.2         | <13.5         |
| AIGR      | 306.4        | <30           |

\[
IGR = \frac{\text{Insulin}}{\text{Glucose}} \times 100
\]

\[
AIGR = \frac{\text{Insulin}}{\text{Glucose} - 30}
\]
vomiting and diarrhoea were noted 5 days after the surgery. The dog was discharged one week post-surgery.

Two weeks after surgery, the patient started vomiting and was brought back to the clinic. Complete blood cell count revealed leukocytosis and granulocytosis as well as anaemia and thrombocytosis. Vomiting was controlled by administering metochlopramide @ 0.2 mg/kg intravenously. A tentative diagnosis of pancreatitis was made. Vomiting persisted for four days oral feedings were stopped and the dog was put on 5% dextrose saline infusion. Three days later the dog died.

5. Histopathology
Histopathology on the resected pancreatic tissues revealed an exocrine pancreatic tissue with congested micro-capillaries (Figure 2). With sharp demarcation of the exocrine pancreatic tissue and areas of pleomorphic cells growth, separated by a delicate fibrous capsule. Also revealed the replacement of the normal gastropancreatic lymph node cells by nests of neoplastic cells arranged in packets along a fine fibrovascular stroma (Figure 3). The cells were large with clear eosinophilic cytoplasm and vesicular nuclei. Immuno-histochemical stains of the node showed the neoplastic cells stained diffusely for insulin. A diagnosis of metastatic insulinoma was then made and isolation of neoplastic cells similar to those found in the lymph node from the pancreas further confirmed the diagnosis.

Figure 2. Photomicrograph showing exocrine pancreatic tissue (EP) with congested microcapillaries (white arrows). Note the sharp demarcation of the exocrine pancreatic tissue and areas of pleomorphic cells growth (PM) by a delicate fibrous capsule (black arrows). H and E ×400.

Figure 3. Photomicrograph showing pancreatic lymphnode with areas of pleomorphic cells growth “possibly of the endocrine pancreas that produces insulin” (black arrows). Note the varying levels of fibrosis within the tissue (white arrows). H and E ×400.
6. Discussion

The most common pancreatic islet tumour is an islet cell carcinoma derived from insulin-secreting β-cells. These neoplasms are usually active hormonally and secrete insulin. Insulinomas are malignant neoplasms of the β-cells in the pancreas. The β-cells primarily secrete insulin, amongst other hormones. Apart from the primary function of regulating glucose levels throughout the body’s cells insulin produces a variety of effects in the body. Because insulinomas secrete excessive insulin there tends to be hypoglycaemia, which causes weakness and/or neurological problems (Cohen, 2003). Insulin-secreting tumours are usually diagnosed in middle-aged or older dogs, without sex predisposition. Large breed dogs, such as Irish setters, Boxers, German shepherds and Fox terriers are predisposed to insulinoma due to their size, although it may occur in any other breed (Leifer et al., 1986; Polton, White, Brearley, & Eastwood, 2007). The continued insulin secretion further exacerbates the low glucose levels by inhibiting gluconeogenesis and glycogenolysis (Nelson & Couto, 1998). As a result, the blood glucose level plummets until the body compensates.

The dog, in this case, was presented with intermittent signs characteristic of insulinomas. The behavioural changes and lethargy were due to the neuroglycopenic effects of low glucose on the brain (Leifer et al., 1986; Robben, van den Brom, Mol, van Haeften, & Rijnberk, 2006). The muscle tremors and intermittent hind limb paralysis were more related to the increased sympathetic tone in the central abdominal tumour (Iseri et al., 2007). Insulinomas often appear as round or lobular hypoechoic masses in ultrasound imaging. In this case, only a hyperechoic area in the right lobe of the pancreas was detected. Ultrasound can be especially helpful in localizing a neoplastic area. Ultrasound is of considerable value during surgery since insulinomas can be small and may only be detected through palpation of the affected pancreas. Surgical treatment involves attempts to remove all tumour tissue responsible for the insulinoma. This attempts to reduce the amount of insulin being secreted and a “cure” should not generally be expected except in very rare circumstances because the tumour being metastatic (Argyle & Saba, 2008; Cohen, 2003) will eventually grow back (Buishand, Kik, & Kirpensteijn, 2010; Buishand et al., 2012). Many dogs with insulinomas are quite old at the time of diagnosis and this understandably makes for the avoidance of surgery, particularly when the chances of a permanent cure are low (Withrow & MacEwen, 1996). This case, partial pancreatectomy was performed under general anaesthesia. Intravenous dextrose was also administered to prevent hypoglycemia. Partial pancreatectomy was performed on the affected pancreatic lobe and the tumour was removed. However, risks of surgery include post-operative pancreatitis which may become extremely serious or the development of diabetes. However the risk of both occurring is very low (Withrow & MacEwen, 1996). Diabetes can occur because, while the insulinoma is producing so much insulin the cells which should normally produce it in the pancreas “take a back seat” and cease production (Leifer et al., 1986; Ogilvie & Moore, 1995; Polton et al., 2007; Robben et al., 2006). Once the tumour is removed, these cells may take a while to generate new insulin or may have even wasted away entirely. Though this condition is only seen when a tumour that has been present for a very long time is removed. In this situation, daily insulin injections may need to be given either temporarily or occasionally for the rest of the dog’s life (Robben et al., 2006). This is something which needs to be considered before surgery. There is little that can be done to eliminate the risk of either of these problems and it is important that this risk is evaluated before deciding to perform surgery. Sometimes not all active tissue can be removed at surgery and medication is still needed (Cohen, 2003; Steiner & Bruyette, 1996).

Medical treatment will not cure the insulinoma but may lead to the signs being kept at bay for months depending on the severity. Medical treatment involves feeding small, frequent meals and the addition of oral medications (Cohen, 2003). The usual progression is that as the disease continues, medication helps less and higher doses of drugs are needed. Dogs receiving medical treatment...
usually start on a low dose of a corticosteroid like prednisolone which will often cause an increase in blood glucose levels but will also cause increased thirst, appetite and weight gain (Cohen, 2003; Vallee, 2003). Other drugs that may be added when prednisolone fails to control clinical signs include diazoxide and propranolol. Chemotherapy for insulinoma can be attempted but it comes with very high risks of kidney failure (Polton et al., 2007). It is usually not recommended for this reason. The antihormonal drug diazoxide may be used if the patient is unresponsive or intolerant to corticosteroids. Diazoxide acts by direct inhibition of insulin secretion, stimulating gluconeogenesis and glycogenolysis, and inhibiting tissue use of glucose (Cohen, 2003; Nelson & Couto, 1998; Polton et al., 2007; Robben et al., 2006). Other chemotherapeutic drugs that can be used include streptozotocin and alloxan which are cytotoxic to β-cells (Allen, Cornelius, & Mahaffey, 1998; Cohen, 2003; Nelson & Couto, 1998; Ogilvie & Moore, 1995). The nephrotoxicity of these drugs are severe and potentially irreversible thus confining their use to only severe refractory cases (Allen et al., 1998; Goutal & Brugmann, 2012; Lipowitz, Caywood, & Newton, 1996). Surgical exploration and removal of neoplastic tissue permit definitive diagnosis of the tumour, as well as a possible cure in dogs with a resectable mass. In animals where it is impossible to remove all neoplastic tissue, surgically debulking the tumour frequently results in an improvement of clinical signs by decreasing insulin secretion (Cohen, 2003; Vallee, 2003). Dogs that undergo surgery have significantly higher chances of survival compared to dogs treated with medical therapy alone (Cohen, 2003; Kintzer, 2012; McDermott et al., 1999). Although partial pancreatectomy is the treatment of choice, medical management of insulinomas can be used when surgery is not an option, if surgery fails to remove all the neoplastic cells, or if the tumour recurs. Even though surgery may offer the best prognosis, there is, however, a high frequency of postoperative complications, including pancreatitis, hyperglycaemia, and hypoglycaemia which was seen in this case. For this reason, medical management is an alternative to surgical removal of insulinomas. Frequent feedings of small, high protein, low carbohydrate meals and reduction of exercise may help to prevent hypoglycaemia (Cohen, 2003; McDermott et al., 1999). Hypoglycaemia and hyperinsulinism are hallmark signs of insulinoma but this must be differentiated from other tumour types such as epithelial liver tumour, symptomatically, considering the fact that these also cause hypoglycaemia. Hypoglycemia can be caused by non-insulinoma tumours in the retroperitoneum, thorax, or abdomen. Intra-abdominal tumours that may cause hypoglycemia include hepatocellular carcinoma, hepatoma, leiomyoma, leiomyosarcoma, melanoma, and hemangiosarcoma (Sakai, Asano, & Nakata, 2006).

The long-term prognosis for dogs with insulinoma is guarded at best, due to its metastatic nature. Dogs treated medically do not usually survive longer than 12 months from the onset of clinical signs (Cohen, 2003; Lipowitz et al., 1996; Nelson & Couto, 1998; Vallee, 2003). Dogs treated surgically may live up to 16 months from the time of surgery. The prognosis at the time of surgery is dependent on the presence or absence of metastatic lesions (Cohen, 2003; Vallee, 2003).

Histopathologic examination is needed to diagnose an islet cell tumour and evaluate for invasiveness. These tumours are often sharply demarcated from the adjacent parenchyma and are surrounded by a partial to complete thin fibrous capsule (Figure 2). Lobules are separated by fibrous trabeculae and are composed of polygonal cells in packets, nests, rows and, less often, form rosettes (Figure 2) and acini. Islet cell tumours are often minimally pleomorphic with low numbers of mitotic figures and; thus, malignancy is determined most often by evaluating for invasion through the fibrous capsule into the surrounding parenchyma, mesentery or vascular invasion.

The definitive diagnosis of insulinoma, in this case report, was accomplished by histopathology of the resected pancreatic lobe and gastropancreatic lymph node. The prognosis was guarded as metastasis to regional lymph nodes was present. The dog in this case died three weeks post-surgery even though recovery from surgery was good. Though, the dog’s glucose level returned to normal in the recovery period indicating that the tumour was successfully removed. Ten days after surgery, the dog became hyperglycaemic and symptomatic. This complication was anticipated as diabetes mellitus is known to occur after insulinoma removal (Cohen, 2003; Lamb, Simpson, Boswood, & Matthewman, 1995; Simpson, Stepnien, Elwood, Boswood, & Vaillant, 1995). The resulting diabetes is
believed to be caused by atrophy of the normal β-cells secondary to feedback inhibition by the high insulin levels produced by the tumour (Allen et al., 1998). The diabetic state may persist for days to months or it may be permanent. Also, pre-existing diabetes mellitus is not uncommon with insulinoma (Bryson, Snead, McMillan, MacDougall, & Allen, 2007). The patient also developed a delayed pancreatitis ten days after the surgery. The origin of this pancreatitis was quite unclear since pancreatitis secondary to surgery usually occurs in the first few days after surgery (Court, Dodman, & Norman, 1988; Simpson et al., 1995; Tobin, Nelson, Lucroy, Wooldridge, & Feldman, 1999). Episodes of pancreatitis can range from mild to severe, where patients may exhibit a plethora of signs from mild lethargy to multiple organ failure or death (Whittemore & Campbell, 2005). There is a possibility of the patient having subclinical pancreatitis which worsened with the surgery.

7. Conclusion
Recognition of the clinical presentation of insulinoma is critical in the management of the neoplasia and institution of appropriate therapy. Other diseases with clinical signs mimicking canine insulinoma must also be considered. Therefore, a thorough understanding of the disease is required in order to correctly diagnose the disease. However, insulinoma would always present with hyperinsulinaemia and hypoglycaemia it is a differential diagnosis that must be considered when dogs are presented with clinical signs of hypoglycaemia. The best chance of prolonged, survival is when surgical removal is performed. More so, the long-term prognosis after surgical resection of canine insulinoma is poor due to re-occurrence. Prior to surgery, it is important that diagnostic tests such as a CT scan be performed to determine the extent of the tumour. This can sometimes only be determined during surgery. In cases where surgical resection is not possible or not desired, palliative medical management can relieve clinical signs. It is important to make a decision about surgical intervention early. Major risks of surgery are pancreatitis and diabetes.

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