CASE REPORT

Cryohypophysectomy used in the treatment of a case of feline acromegaly

A 10-year-old female spayed cat was diagnosed with acromegaly secondary to a pituitary tumour. At the time of diagnosis, the cat had insulin-resistant diabetes mellitus and its insulin-like growth factor-I levels were elevated. Clinical signs included polyuria, polydipsia and weight gain. Persistent hyperglycaemia and glucosuria were identified, and fructosamine levels remained elevated. Magnetic resonance imaging of the brain showed a pituitary tumour. Transsphenoidal cryohypophysectomy was used to treat the pituitary tumour. Postoperatively, the serum insulin-like growth factor-I levels decreased and the diabetes mellitus was controlled with routine levels of insulin. To the authors' knowledge, this is the second reported case of acromegaly treated with cryohypophysectomy, and the first that reports a favourable long-term outcome. Cryohypophysectomy may be a safe and effective treatment for cats with a pituitary mass resulting in acromegaly.

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INTRODUCTION

Insulin resistance in diabetic cats occurs when serum hyperglycaemia persists despite an adequate insulin dosage, often in excess of 1·5 iu/kg (Feldman and Nelson 2004). Insulin-resistant feline diabetics often have a serum glucose level exceeding 16 mmol/l during a 24-hour glucose curve and fructosamine levels greater than 500 µmol/l (Feldman and Nelson 2004).

Feline acromegaly results from an increase in growth hormone production secondary to a functional somatotrophic pituitary adenoma. Most cats with acromegaly have concurrent and poorly regulated diabetes mellitus (Peterson and others 1990, Feldman and Nelson 2004). Once regarded to be an uncommon condition, acromegaly is an increasingly recognised cause of insulin resistance in cats. Recent reports suggest that acromegaly is underdiagnosed in cats (Berg and others 2007, Niessen and others 2007a). Definitive therapeutic options for treating feline acromegaly are limited and the most commonly reported treatment option is radiotherapy (Kaser-Hotz and others 2002, Brearley and others 2006, Mayer and others 2006). Radiation therapy is an effective treatment modality for feline acromegaly, with a reported median survival time of 72·3 weeks and a 2-year survival of 50 per cent (Brearley and others 2006). Reported adverse effects in cases of feline acromegaly treated with radiation are uncommon, but include transient neurological signs, transient dermatitis, alopecia, cataract formation and vision and hearing impairment (Kaser-Hotz and others 2002, Brearley and others 2006, Mayer and others 2006). Medical management of feline acromegaly with somatostatin analogue or dopamine agonist therapy has not been effective in reducing growth hormone levels or improving clinical signs (Peterson and others 1990, Abraham and others 2002).

CASE HISTORY

An 11-year-old, spayed, female domestic shorthair cat was referred for evaluation of persistent hyperglycaemia despite insulin therapy. The cat had been diagnosed with diabetes mellitus five months before referral. The diagnosis of diabetes mellitus was made after several months of weight loss, polyuria and polydipsia and was based on persistently elevated serum glucose and fructosamine levels as well as concurrent glucosuria.

Despite therapy with 0·5 iu/kg of lente pork insulin (Caninsulin; Intervet) injected subcutaneously every 12 hours, the cat remained polyuric and polydipsic. Persistent hyperglycaemia was evident on glucose curves (Fig 1) and the cat's bodyweight increased from 6·5 to 7·6 kg over six months. Therapy was changed to a long-acting human insulin analogue, glargine (Lantus; Sanofi-Aventis), initially administered at a dose of 0·5 iu/kg subcutaneously every 12 hours. The dose and frequency of

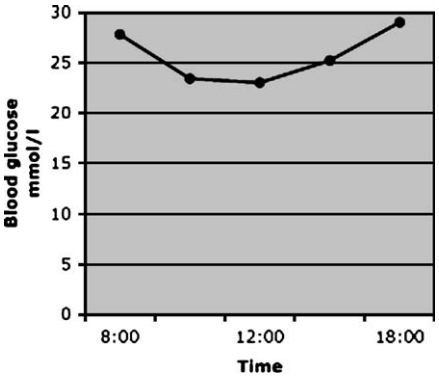

FIG 1. Ten-hour glucose curve: meal and 0·5 iu/kg lente pork insulin given at 8:00 hours

glargine was increased to 0·7 iu/kg administered every eight hours, but the cat remained hyperglycaemic on a 24-hour glucose curve (Fig 2). The serum fructosamine level was 515 µmol/l (reference range for well-controlled diabetic cats 350 to 400 µmol/l) and glucosuria persisted. There were no other abnormalities identified on a serum biochemical profile or urinalysis. Haematological parameters were normal and a urine culture was negative for bacterial growth. The cat tested negative for feline leukaemia and feline immunodeficiency virus. The total thyroid hormone level was 29 nmol/l (reference range 13 to 55 nmol/l). A low-dose dexamethasone suppression test (LDDST) was performed by administering 0·1 mg/kg dexamethasone subcutaneously (Feldman and Nelson 2004). The resting cortisol level was 24 nmol/l (reference range 15 to 97 nmol/l) with cortisol levels of less than 10 nmol/l at two, four and eight hours post-dexamethasone (reference range

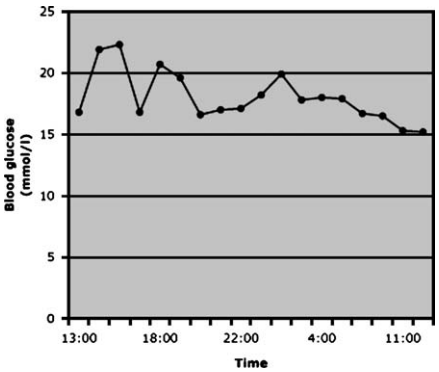

FIG 2. Twenty-four-hour glucose curve: meals and 0·7 iu/kg glargine insulin given at 16:00, 22:00 and 7:00 hours

<22 nmol/l). Results of the LDDST were not consistent with hyperadrenocorticism (Feldman and Nelson 2000). Serum insulin-like growth factor-1 (IGF-I) level was measured using a radioimmunoassay validated for use in human beings (Diagnostic Center for Population and Animal Health, Michigan State University, Michigan, USA). The IGF-I level was 192 nmol/l (reference range 5 to 70 nmol/l).

Thoracic radiographs showed a mild bronchointerstitial pattern. An abdominal ultrasound was normal and echocardiography showed no cardiac abnormalities. Magnetic resonance imaging (MRI) of the brain was performed under general anaesthesia with a 1·5 T scanner. Images were acquired in T1 (pre- and post-contrast) and T2 in dorsal, sagittal and transverse planes. A focal mass identified in the region of the pituitary gland and was isointense to adjacent grey matter. Tumour invasion beyond the sella turcica or compression of adjacent brain tissue was not evident. The mass enhanced heterogeneously after administration of the contrast agent gadodiamide (Omniscan; GE Healthcare Canada) and measured 5 mm in diameter (Fig 3). The mass identified with MRI was consistent with a pituitary adenoma.

Transsphenoidal cryohypophysectomy was performed via a mid-line incision through the soft palate under general anaesthesia. The dural covering of the pituitary was incised after exposure and a small pituitary biopsy was obtained. A triple, 30-second penetration freeze was performed with a liquid nitrogen cooled cryoprobe. Cytological analysis of the pituitary mass was consistent with either nodular hyperplasia or adenoma of the pituitary. A predominance of acidophilic cells was described, with presence of chromophobe cells.

Upon recovery from surgery, the cat was treated with intravenous injections of 0·1 mg/kg dexamethasone every 12 hours for three days to help counter postoperative inflammation and a reduced dose of 0·3 iu/kg glargine was administered via subcutaneous injections every 12 hours. At a dose of 13·3 mg/kg, amoxicillin-clavulanic acid (Clavamox; Pfizer), given orally every 12 hours was prescribed for 14 days. Prophylactic supplementation with 0·01 mg/kg of levothyroxine (Syn-

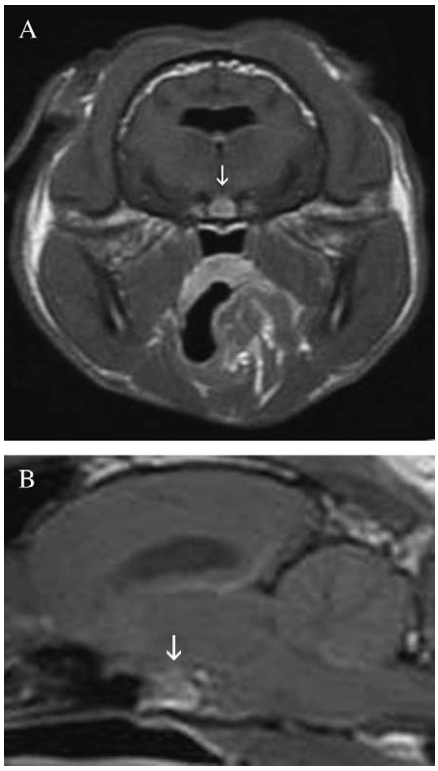

FIG 3. Transverse (A) and sagittal (B) T1-weighted magnetic resonance images of the brain following intravenous injection of gadodiamide contrast. A 5 mm diameter, contrast-enhancing mass (arrow) is present in the area of the pituitary

throid; Abbott Laboratories Ltd) was administered orally every 12 hours. Thyroid supplementation was tapered and discontinued four weeks postoperatively. Moderate hyperglycaemia (blood glucose ranged from 12·1 to 18·4 mmol/l) was detected during four days of hospitalisation after surgery. Serum IGF-I levels 72 hours after surgery were 162 nmol/l.

The cat was re-evaluated eight weeks after surgery. Then the serum IGF-I level was 172 nmol/l. An eight-hour glucose curve performed at home by the owner showed adequate glycaemic control when the cat was treated with subcutaneous injections of 0·6 iu/kg of glargine every 12 hours, with a peak blood glucose level of 15·9 mmol/l and a nadir of 7·3 mmol/l. A recheck total thyroid hormone level was normal (25 nmol/l; reference range: 13 to 55 nmol/l). Six months after surgery, a serum fructosamine level was 416 µmol/l. Eighteen months after surgery, a glucose curve showed a peak blood glucose level of 14·2 mmol/l and a nadir of 6·5

mmol/l. The cat does not display clinical signs of diabetes mellitus and no clinical signs of acromegaly, such as weight gain or enlargement of facial features are noted. The cat's owners remain very satisfied with the outcome of the procedure and the cat's quality of life.

DISCUSSION

Acromegaly is an increasingly recognised feline endocrinopathy, characterised by chronic excessive secretion of growth hormone (Feldman and Nelson 2004, Berg and others 2007, Niessen and others 2007a). Excessive growth hormone levels in circulation cause both anabolic and catabolic effects in the body. Anabolic effects are mediated through IGF-I and cause increased bone and soft tissue growth. Catabolic effects include lipolysis and breakdown of carbohydrates leading to hyperglycaemia and insulin antagonism (Peterson and others 1990, Feldman and Nelson 2004). Acromegaly typically affects older, male cats (Feldman and Nelson 2004). Clinical signs reflect concurrent diabetes mellitus and often include polyuria, polydipsia and polyphagia. Weight loss is variable and many cats display weight gain if the anabolic effects of growth hormone dominate. Physical examination findings can include prognathia inferior, abdominal organomegaly and thickening of the oropharyngeal soft tissues leading to respiratory stridor. Hypertrophic cardiomyopathy, degenerative arthropathy and/or renal insufficiency may develop as a consequence of chronic excessive growth hormone (Peterson and others 1990, Feldman and Nelson 2004). Neurological signs, such as stupor, anorexia and seizures, may develop as a result of pituitary tumour expansion (Peterson and others 1990, Feldman and Nelson 2000). Clinical findings in the reported case included polyuria, polydipsia and weight gain. Cardiac, renal, neurological and musculoskeletal changes were not identified in this cat.

The most common aetiology of acromegaly in the cat is pituitary neoplasia (Peterson and others 1990, Elliott and others 2000, Norman and Mooney 2000, Feldman and Nelson 2004). Computed tomography or magnetic resonance imaging (MRI) of the brain is often used to establish a diagnosis of acromegaly in cats (Elliott and others 2000). In recent years, a feline growth hormone assay has not been widely available. Serum IGF-I levels were measured to estimate the previous 24 hours of growth hormone secretion and have been elevated in acromegalic cats (Nelson and Lewis 1990, Abrams-Ogg and others 1993, Feldman and Nelson 2000, Norman and Mooney 2000, Berg and others 2007, Niessen and others 2007a). An IGF-I concentration greater than 100 nmol/l in a cat is considered consistent with acromegaly (Feldman and Nelson 2004). Serum IGF-I concentration has a sensitivity and specificity of 84 and 92 per cent, respectively, for the diagnosis of feline acromegaly (Berg and others 2007).

An ovid growth hormone radioimmunoassay has recently been validated for use in cats. The assay identified significantly higher growth hormone levels in acromegalic cats compared with non-diabetic, non-acromegalic cats (Niessen and others 2007b). Most reports of growth hormone evaluation in acromegalic cats have identified elevated growth hormone levels (Peterson and others 1990, Norman and Mooney 2000, Niessen and others 2007b). Concurrent evaluation of serum growth hormone and IGF-I levels may increase the utility of these diagnostic tests (Norman and Mooney 2000, Niessen and others 2007a).

The most commonly reported treatment for feline acromegaly is irradiation of the underlying pituitary mass (Peterson and others 1990, Goossens and others 1998, Kaser-Hotz and others 2002, Brearley and others 2006, Mayer and others 2006). One report of three acromegalic cats treated with cobalt 60 irradiation resulted in a reduction of insulin requirements for all three cats. However, improvement was transient and clinical signs returned in six and nine months for two of the affected cats. None of the three cats experienced any adverse effects associated with irradiation (Goossens and others 1998). One of two acromegalic cats treated with linear accelerator radiotherapy died from possible hypoglycaemia eight months after treatment, while the other died of causes unrelated to acromegaly or radiation therapy 5·5 months after treatment (Kaser-Hotz and others 2002). In a third report, one of two cats treated with cobalt 60 irradiation, the tumour decreased in size by more than 50 per cent within two months of therapy, but insulin resistance recurred six months after therapy (Peterson and others 1990).

Cryohypophysectomy has been reported as treatment for a pituitary mass in one acromegalic cat (Abrams-Ogg and others 1993). Plasma IGF-I levels before surgery were 2181 iu/l (reference range 170 to 438 iu/l). The procedure resulted in resolution of the clinical signs associated with diabetes mellitus and normal IGF-I levels 15 months after surgery. The cat experienced complications related to hypoglycaemia and a possible adverse drug reaction two months postoperatively after an abrupt resolution of insulin-resistant diabetes and was euthanased 15 months after surgery because of behaviour changes related to this complication (Abrams-Ogg and others 1993, 2002).

Medical therapy does not appear to be effective in the treatment of feline acromegaly. Treatment of one acromegalic cat with L-deprenyl, a dopamine agonist, did not result in improvement of clinical signs (Abraham and others 2002). Four cats treated with the somatostatin analogue octreotide showed no decline in growth hormone levels (Peterson and others 1990).

IGF-I levels in the reported case decreased slightly following surgery, but remained above the reference range despite resolution of insulin resistance. A reported case of feline acromegaly treated with radiation therapy showed persistent elevation of IGF-I after treatment despite resolution of diabetes mellitus (Littler and others 2007). A previously reported case of feline acromegaly treated with cryohypophysectomy documented a marked increase in IGF-I levels from 2181 u/l (reference range 170 to 438 u/l) in the preoperative period to 6212 u/l two months after surgery. Six months after surgery, the IGF-I level declined to 893 u/l. While IGF-I levels were slightly decreased in the patient in the current report one month postoperatively, IGF-I levels were not measured beyond this point. Other cases of feline acromegaly treated with radiation therapy document a decline in growth hormone concentration after treatment (Peterson

and others 1990, Goossens and others 1998). Growth hormone concentration declined in one acromegalic cat undergoing radiation therapy while IGF-I levels remained elevated post-treatment (Niessen and others 2007a). The reported decline in insulin resistance in cats with acromegaly two to 10 months after radiation therapy is suggestive of a decrease in growth hormone secretion (Peterson and others 1990, Goossens and others 1998, Kaser-Hotz and others 2002, Mayer and others 2006, Brearley and others 2006).

Growth hormone and IGF-I levels in human beings with acromegaly have a variable response after treatment with radiation therapy or surgery. Normalization of growth hormone levels despite continued elevation IGF-I levels occurs was reported to occur after radiation therapy in the vast majority of patients in one study (Barkan and others 1997). However, a more recent study using a larger number of subjects and more uniform treatment guidelines showed that growth hormone and IGF-I levels declined in parallel, with over 60 per cent of patients showing a normal IGF-I level 10 years after radiation therapy (Jenkins and others 2006). Postoperative evaluation of human patients demonstrates a discrepancy in the time between normalisation of growth hormone and IGF-I levels. One report shows that growth hormone levels decline reliably within one week of surgery, while IGF-I levels are more variable within a three-month period after surgery (Feelders and others 2005).

The elevation in IGF-I may partly be explained by chronic insulin therapy used in this cat. Recently studies have demonstrated elevations of IGF-I in diabetic cats not suspected to have acromegaly (Lewitt and others 2000, Starkey and others 2004, Niessen and others 2007a**).** Elevated IGF-I levels were identified in diabetic cats treated long term (that is 14 months or longer) with insulin therapy (Starkey and others 2004). However, Berg and others (2007) failed to identify a strong correlation between IGF-I concentration and length of insulin treatment in diabetic cats. Additionally, significantly higher IGF-I levels were documented in cats with acromegaly compared with variably controlled diabetic cats (Berg and others 2007, Niessen and others 2007a). Therefore, duration of insulin therapy alone is unlikely to be the only factor causing increased serum IGF-I concentration in the cats in the report by Starkey and others (2004). The discrepancy in growth hormone and IGF-I levels observed after radiation therapy and the persistence of an elevated IGF-I level in this patient may be reflective of a lower concentration of growth hormone than previously thought required to sustain an elevated IGF-I level. The relationship between growth hormone and IGF-I levels may be indirect, or IGF-I may be influenced by a number of other factors. Age, gender, pregnancy, nutritional status and disease states, such as renal and hepatic insufficiency can influence IGF-I levels in human beings, but the effects of these parameters on IGF-I levels in cats is unknown (Brabant and Wallaschofski 2007).

Objectives for the treatment of acromegaly in human beings include the reduction of growth hormone and IGF-I levels. Normalization of IGF-I and growth hormone levels in human beings treated for acromegaly reduces risk of mortality (Holdaway and others 2004). One cat with continued elevation of IGF-I after radiation therapy maintained a large body size and ravenous appetite, suggesting that acromegaly was persistent (Littler and others 2007). Unfortunately, the IGF-1 level in this reported case was not measured in the long-term postoperative period. Further investigation of the long-term effects of cryohypophysectomy on growth hormone and IGF-I levels and prognosis in cats is needed.

As pituitary adenomas are generally slow growing, short-term prognosis for feline acromegaly may be good (Peterson and others 1990, Norman and Mooney 2000, Brearley and others 2006). Long-term prognosis for feline acromegaly is considered poor, because of the lack of consistent definitive treatment (Feldman and Nelson 2000). In a report of five acromegalic cats treated with gradually increasing doses of insulin, good control of clinical signs of diabetes mellitus was described in three cats for two to six months. The mean dose of insulin required was 23·5 iu per day (Norman and Mooney 2000).

The cat in this report had rapid resolution of clinical signs associated with poorly controlled diabetes mellitus postoperatively. No postoperative complications were noted and the cat is alive at the time of publication, 18 months after surgery. While the IGF-I levels decreased only slightly, no clinical signs of progressive acromegaly were observed postoperatively and the diabetes mellitus could be controlled with routine levels of insulin. Cryohypophysectomy may be a safe and effective treatment for cats with a pituitary mass resulting in acromegaly.

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