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CASE REPORT
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Necrolytic Migratory Erythema in a Cat with Glucagonoma Syndrome

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ABSTRACT

***Background*:** Glucagonomas are very rare neuroendocrine tumors of pancreatic endocrine islets alpha cells and they produced excessive amount of glucagon hormone. Necrolytic migratory erythema (NME) is a rare dermatosis that characterized by erosive, ulcerative and crusted lesions in different sites of the skin and the common cause of this situation related to glucagon secreted tumors. NME can occur commonly in man but some rare and recent reports available the occurrence of this situation in pet animals especially dogs. Both gross and histological findings in both human and animals are similar. This paper reports a NME case with glucagonoma and diabetes mellitus (DM) by clinical, histopathological and immunohistochemical examinations.

***Case*:** A 12-year-old, cat presented with complaints of skin lesions in neck region, hyperglycemia, weight loss and history of anorexia during the 2 months. Biochemical analysis results revealed high glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and creatinine levels but decreased blood urea nitrogen (BUN), total protein and potassium levels. After 2 weeks of anti-diabetic drug treatment, the blood glucose level became normal and skin lesions ameliorated but anorexia and weight loss continued. The cat exhibited general weakness and pain in abdominal area. Although the clinical sings ameliorated and skin lesions and serum biochemical findings returned the relatively normal levels compared the admission, the cat died after 2 weeks of treatment and necropsy performed. At necropsy, marked cachexia, loss of skin elasticity and decreased skin thickness were observed. During the examination of abdominal cavity of the cat, there was a mass 0.5x0.5 cm in diameter, hard and grayish color was diagnosed at the pancreas. In addition, numerous whitish foci were also present the pancreatic tissue. Additionally, enlargement and paleness were noticed at the liver. Hemorrhages were observed at the liver, stomach and gut. Histopathologically pancreatic mass composed of polygonal neoplastic cells supported by thin, fibrovascular stroma characteristic for neuroendocrine tumor. But type of the cells undistinguished by histopathology for that reason immunohistochemistry performed for to evaluated insulin and glucagon secreting cells. Immunohistochemical examination revealed that only small number of insulin secreting but numerous glucagon secreting cells in the tumoral tissue and the tumor diagnosed as glucagonoma. Marked decrease were also noticed in insulin secretin cells in pancreas and together with high serum glucose levels diabetes mellitus (DM) also diagnosed to the cat. Histopathological examination of the skin revealed that decreased skin thickness, alopecia, slight inflammatory reaction and necrosis of the spinous layer.

***Discussion*:** Glucagonomas are rare tumors of pancreas even in human, and the incidence of this tumor is very rare in cat. They are usually silent tumors and they generally caused by paraneoplastic phenomena than primary clinical symptoms. The most prominent features of the "glucagonoma syndrome" are NME and DM. In human NME is commonly diagnosed in patient with glucagonoma syndrome. Very rare NME reports available in cats and dogs. The present cat had obvious clinical symptoms and typical skin lesions for NME. This report includes the very characteristic case of NME in a cat due to glucagonoma and DM, closely resembling the glucagonoma syndrome occurred in humans. Possible cause of the liver damage was also related the DM characterized high serum glucose level. We thought that liver lesions were also supported the occurrence of characteristic skin lesions.

Keywords: necrolytic migratory erythema, cat, diabetes mellitus, pancreas.

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INTRODUCTION

Glucagonomas are very rare neuroendocrine tumors of endocrine part of pancreas. They may present together with paraneoplastic phenomena known as "glucagonoma syndrome". Characteristic clinical sign of this syndrome is a rash in skin known as necrolytic migratory erythema (NME) [8]. The glucagonoma syndrome is characterized by NME and diabetes mellitus (DM). The condition was firstly described in humans, where the internal lesion is most commonly a pancreatic, glucagon secreting neoplasia [7]. NME is rare dermatoses usually seen in older animals and generally associated with hepatopathy or glucagonoma [3]. The disease is typically diagnosed in older dogs, although there are very rare reports of it occurring in cats [5,13,16]. Signs of liver disease may also be present and DM often develops later in the disease process [18].

DM is a common disorder in dogs and cats, prevalence rate of this disease reported as ~0.4-1.2% [2]. Similarly in humans, the increasing frequency of predisposing factors such as obesity and physical inactivity are responsible for the increasing incidence of diabetes in domestic cats [12,14]. Other risk factors may be age, neutering and gender of the animal [9]. Clinical signs do not develop until hyperglycemia reaches a concentration that results in glycosuria, typically at blood glucose concentrations of 180-220 mg/dL in dogs and 220-270 mg/dl in cats [2]. The most common clinical symptoms of DM include polyphagia, polyuria, polydipsia, unkempt coat, muscle wasting, progressive weakness and loss or gain of weight [15]. The aim of this study was to report clinical and pathological findings of glucagonoma syndrome in a 12-year-old cat.

CASE

A 12-year-old female cat presented to the Veterinary Medical Teaching Hospital with cutaneous lesions of 2-month duration localized particularly at her neck (Figure 1a). According to the owner, she was healthy but in a period of 2 months lost weight and there was inappetite. Previously a private veterinarian had treated her lesions by antibiotic and antibacterial solution but treatment was unsuccessful. At admission, on physical examination, the cat was depressed but her body temperature, respiratory rate, heart rate were in normal ranges. But she had moderate dehydration and marked cachexia. In anamnesis owners stated frequent urination (polyuria) and drinking too much water (polydipsia) characteristic for DM.

Skin scrapes examinations were negative for parasites and fungi. A dermatophyte culture of hair was also negative. Urine and blood samples were collected for analysis. Serum biochemical analysis were performed with Idexx Vet-Test[1] equipment and reagents and MS9 blood counting equipment[2] was used for hematological analysis of the blood drawn in EDTA tubes[3]. For urine analysis Idexx VetLAB UA[1] equipment and URIPSIN 10 urine test strips were used. The serum was analyzed for glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total protein.

For treatment Diamicron[4] (30 mg, once daily), and a low carbohydrate, high protein diet was recommended. The cat was treated with clavulanic acid with amoxycillin[5] (Synulox Palatable Tablets) 12.5 mg/kg orally twice daily for her lesion in her neck. After 2 days' treatment with diamicron the biochemical analysis was repeated (second result). The cat slowly deteriorated with weight loss, progressive inactivity, and a worsening appetite. But the neck wound was healing. Therefore, it was decided to use insulin. For this reason, glargine[6] recommended at 0.5 U/kg dosages [11]. After insulin therapy, with two days of intervals, blood analyzes were performed 3 times again (third, fourth and fifth result) [Table 1]. The lesion in the neck of the cat was recovering gradually. Although in the last biochemical analysis blood glucose value was within the reference levels, other parameters were high and anorexia very progressed. After 2 weeks the cat died and presented to the department of pathology for necropsy.

At necropsy, the cat was cachectic, alopecia and healed areas were observed on skin around the neck (Figure 1b). Grossly numerous whitish foci and a 0.5x0.5 cm mass were seen at the surface of pancreas. Liver was enlarged and pale. Hemorrhages were observed at the liver, stomach and gut. Tissue samples were collected and fixed in 10% buffered formalin. Af-

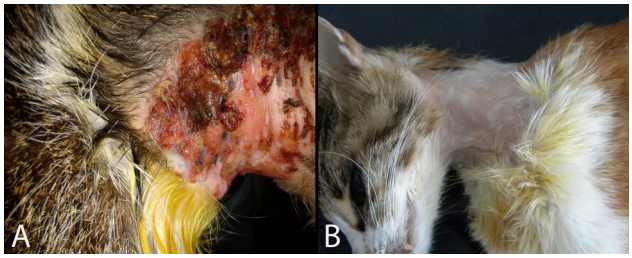

Figure 1. A- Gross appearance of the skin lesion of cat with in her neck at admission. B- Ameliorated neck lesions of the cat at necropsy.

Table 1. Serum biochemical analysis results in cat before and after treatment.

Parameter	First results	Second results	Third results	Fourth results	Fifth results	Reference levels
Glucose (mg/dL)	395	340	250	175	170	70-150
BUN (mg/dL)	18	18.3	19	19.3	19.4	20-65
Creatinine (mg/dL)	4.7	4.5	4.1	4.1	3.9	0.8-2.3
AST (U/L)	345	240	190	182	180	5-55
ALT (U/L)	425	320	194	179	160	28-76
ALP (U/L)	420	350	272	265	259	0-62
Total Protein (g/dL)	2.24	2.91	3.36	3.84	4.27	5.9-8.5
Potassium (mmol/L)	2.35	2.41	2.95	3.21	3.47	3.9-5.3

ter routine processing by an automatic tissue processor equipment (Leica ASP300S)[7], tissues were embedded in paraffin and sectioned to 5-µm thickness by a Leica RM2155 rotary microtome (Leica Microsystems)[7]. Tissue sections were stained with hematoxylin-eosin and examined microscopically. Afterward, pancreas samples were immunostained with insulin antiserum (Anti-insulin+ Proinsulin antibody [D6C4] ab8304)[8] and glucagon antiserum (Anti glucagon antibody, ab8055)[8] by streptavidin biotin technique. The sections were incubated with the primary antibodies for a period of 60 min, and immunohistochemistry was carried out using biotinylated secondary antibody and streptavidin-alkaline phosphatase conjugate. The antigens were demonstrated by using diaminobenzidine (DAB) as the chromogen.

There were no significant changes in blood hematological values. Results of a urinalysis were within normal limits, except for glucose (1050 mg/dL at admission), and pH values (5.05 at admission). Serum biochemistry analysis results at admission (first results) and during the treatment were shown in Table 1.

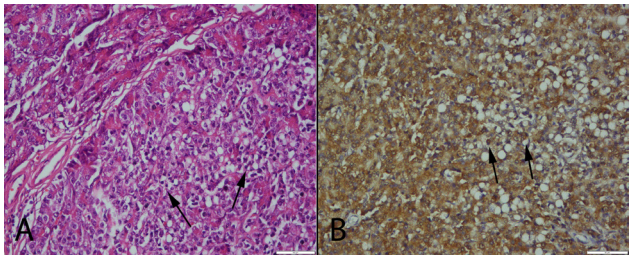

Figure 2. A- Histopathology of the tumoral mass surrounded by fine fibrous tissue at the pancreas and polygonal tumoral cells (arrows). [HE, Bar= 100 µm]. B- Strongly positive glucagon immunoreaction of the tumoral cells; Streptavidin biotin method. [Bar= 100 µm].

At the histopathological examination of pancreas, loss of the histology of endocrine part was diagnosed. No normal Langerhans islet was seen at the microscopical examination and degeneration and fibrosis were common in exocrine part of the organ. Inflammatory cell infiltrations were observed at the pancreas. A tumoral mass surrounded by fine fibrous tissue was observed at the histopathological examination of the pancreas. The tumoral mass composed of polygonal-polyhedral neoplastic cells formed small packets and nests supported by thin, fibrovascular stroma. Neoplastic cells had round to oval nuclei that contained moderate amounts of stippled chromatin, indistinct nucleolus and abundant eosinophilic cytoplasm. Anisocytosis, anisokaryosis and pleomophism were rare (Figure 2a). Histopathological review of the skin revealed vacuolization at the spinous layer and slight inflammatory reaction. In addition, chronic interstitial nephritis, severe degeneration and hemorrhages at the liver, and hemorrhages at meningeal vessels were observed.

The tumoral mass had strongly positive immunoreaction with glucagon antibody by immunohistochemistry (Figure 2b). Immunohistochemical examination of pancreas revealed that only small number of insulin secretes cells characteristic for DM.

DISCUSSION

Even in humans, glucagonomas are very rare tumors of endocrine pancreas. They are generally caused to paraneoplastic phenomena with marked lesions known as “glucagonoma syndrome”. The most prominent features of the glucagonoma syndrome are NME and DM. NME is generally diagnosed 70% of

patient with glucagonoma syndrome in human. NME is characterized with special skin rash usually occurring in the glucagonoma syndrome. Glucagonoma syndrome is due to a slow-growing cancerous tumor originated from the alpha cells of the pancreas [6,19]. NME has been rarely reported in cats and criteria for its diagnosis similar by the dogs [7]. The present cat had characteristic clinical findings and dermatohistopathology typical for NME. Necropsy revealed glucagonoma and immunohistochemistry supported the diagnosis. DM diagnosed by biochemical analysis of the blood and urine. DM supported by immunohistochemistry and characterized by decreased insulin secreted cells. Characteristic skin lesions attributed to the glucagonoma syndrome in this case. Although lesions generally localized on extremities in animal NME cases, skin rashes occurred on neck region in this report firstly.

The diagnosis of NME can be challenging, both clinically and histolopathologically. Clinically, the skin eruption is characterized by a pattern of spontaneous remissions and exacerbations. The typical lesions are intensely erythematous, well-demarcated plaques [17]. Although the exact pathogenesis of NME remains unclear it is thought to be due to hypoaminoacidemia or other nutritional deficiencies invoked by hyperglucagonemia [1,4]. Similar characteristic clinical and pathological symptoms were observed in this cat. But no spontaneous remission was observed, amelioration on skin lesions were occurred after antidiabetic treatment.

Histologically, the hallmark of NME is necrosis of the upper spinous layer (hence the term "necrolytic") [10]. Although the characteristic histopathology the skin scraps were examined for mites, fungi and bacteria in this case. Amelioration was observed but marked decreased in thickness of the skin were diagnosed in this case after 2 weeks treatment.

The diagnosis of diabetes is based on the presence of appropriate clinical signs and persistent hyperglycemia and glycosuria. Treatment options are similar to those for human diabetics and include insulin injections (usually administered twice a day at 12 h intervals), dietary modifications, correction of obesity, exercise in dogs, and oral hypoglycemic medications in cats [2]. In this case antidiabetic treatment decreased the blood biochemical parameters but due to glucagonoma and multiple organ failure the cat died.

The key features of the "glucagonoma syndrome" are NME and DM. In human NME is the most specific feature of the syndrome, and is the presenting symptom in most of the patients [6,19]. Similarly, in this cat, glucagonoma and DM were diagnosed as a cause of NME. Because of the NME is based on the secondary effects of glucagon, skin lesions should examine for endocrinopathies in cats. The diagnosis of NME might have a great importance, since it might be a valuable sign for the early detection of glucagonoma in cat.

MANUFACTURERS

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Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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