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Scientific Report

Concurrent diabetes mellitus and lymphoma in a German shepherd dog

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Summary

Concurrent disorders with diabetes mellitus is one of the most challenging subject. Our knowledge of the most common concurrent disorders in diabetic dogs may be useful in diagnosis of these disorders and better treatment of diabetic dogs. In this study diabetes mellitus was diagnosed in a 7-year-old male German shepherd dog, based on clinical and laboratory findings. Following the diagnosis of diabetes mellitus, insulin therapy was started and blood glucose concentration reached to the accepted level. Eleven months later the dog was presented again with acute episodes of collapse and hypoglycaemia. The owner noted that there was no change in the animal's routine insulin treatment programme and the dog had received his daily insulin injections. Further ancillary diagnostic tests were refused by the owner and the animal was humanely euthanized. Histopathological diagnosis was correlated with lymphoma. The association between diabetes mellitus and lymphoma has been reported in human medicine but the similar clinical condition has not been reported in veterinary literature.

Key words: Diabetes mellitus, Dog, Lymphoma

Introduction

Diabetes mellitus results from impaired glucose utilization, increased gluconeogenesis, and increased hepatic glycogenolysis. The decrease in peripheral glucose utilization leads to accumulation of glucose in serum, followed by osmotic diuresis. Osmotic diuresis drives polydipsia and inadequate intake of fluids results in dehydration (Greco, 1996). Lymphoma is the most common neoplastic condition of the canine haemolymphatic system (Dobson and Gorman, 1993). The prevalence of lymphoma in canines is approximately 13 to 30 cases per 100 000 dogs (Gavazza *et al*., 2001; Fan and Kitchell, 2002) which accounts for approximately 8.5 to 9% of all canine tumours (Dobson *et al*., 2001). This report describes a case of diabetes mellitus in a male German shepherd dog which subsequently developed lymphoma. To the best of our knowledge, this is the first report of concurrent diabetes mellitus and lymphoma in the veterinary literature.

Case history

A 7-year-old male German shepherd dog was presented to the Veterinary Medical Teaching Hospital of Islamic Azad University of Karaj with the history of anorexia, vomiting, polyuria, and polydipsia. Lethargy, dehydration and Kussmaul respiration were evident during the clinical examination. Obesity was evident in association with other physical findings during the clinical observations. Systemic antibiotics had been administrated before referring the animal to the hospital but it

seems to be ineffective and clinical condition of the animal had not been improved. On presentation, the haemogram was normal. Serum biochemical analysis demonstrated severe hyperglycaemia (Table 1). A tentative diagnosis of diabetes mellitus was made based on hyperglycaemia and presence of glucoseuria and ketonuria on urinalysis.

In order to correct the animal's hydration status, sodium chloride 0.9% was administrated intravenously. To confirm the provisional diagnosis of diabetes mellitus, serum glucose level and the results of urinalysis were evaluated in the following day after 12 h of fasting. The same laboratory results were achieved in the next examination: regular crystalline insulin was started initially at the dose of 0.2 U/kg and followed by 0.1 U/kg every one hour. During this time blood glucose was monitored hourly in conjunction with insulin injections. After 6 doses of insulin injections, serum glucose concentration reached to the accepted glycaemic level (Table 1). The animal then received regular insulin every 8 h. Two days following the first visit, the dog's condition was stabilized, intravenous serum therapy was stopped but blood glucose concentration was variable.

The owner was advised to inject NPH insulin (0.1 U/kg) subcutaneously every 12 h. To facilitate the subcutaneous insulin injections and in order to decline the risk of inappropriate drug administration, two small areas in both sides of the thoracic skin were clipped, and injection of insulin through these hairless locations was recommended. Special dietary comments and regular exercises were explained to the owner to control the blood glucose level. The complete blood count and blood glucose level were evaluated monthly. Other essential clinical examinations and special comments had done. Eleven months later, the animal was presented to the clinic with generalized lymphomegaly, acute collapse, severe lethargy and loss of consciousness. The owner noted that there was no change in the animal's routine insulin treatment programme and the dog had received his daily insulin injections. The client informed us that three episodes of acute collapse and loss of consciousness were observed during the past days. Serum glucose concentration was significantly declined. Complete blood count showed a remarkable eosinophilia. The results of serum biochemical analysis revealed azotaemia and elevated hepatic enzymes levels. The owner refused further investigation and diagnostic approaches so the animal was euthanized. Necropsy was performed and samples of the kidneys, liver, lymph nodes and other organs were submitted for histopathological examination. Pathological study revealed infiltration of neoplastic lymphocytes in many organs, including the kidneys, liver and lymph nodes. In the kidneys the normal architecture had been replaced heavily by a diffuse sheet infiltrate of closely packed small round cells, fairly uniform in size and shape. They resembled mature small lymphocytes, most of them had scant to moderate, slightly eosinophilic cytoplasm and a small round deeply basophilic nucleus (Fig. 1). The liver showed diffuse infiltration with small lymphocytes. Neoplastic cells were present in sinusoids throughout the liver, and distinct aggregates were found both in portal tracts, where they surrounded the vessels and bile ducts and the peripheral part of the central veins (Fig. 2).

Discussion

Over the years, several clinical syndromes have been described in association with diabetes mellitus. World opinion has focused somewhat on the two

Table 1: Serum biochemical and hematological findings in the presented case

Parameter	Day 1	Following administration of 6 dose of regular insulin	Day 2	During monthly examinations	11 months After first visit	Reference range
BUN	14	-	-	12-18	50	10-25 mg/dl
ALT	43	-	-	32-47	300	<100 IU/L
ALP	27	-	-	23-40	270	<200 IU/L
Glucose	560	230	220-270	200-280	44	60-120mg/dl
Eosinophils	70	-	-	0-100	3800	<1300/microlitter

- Not determined

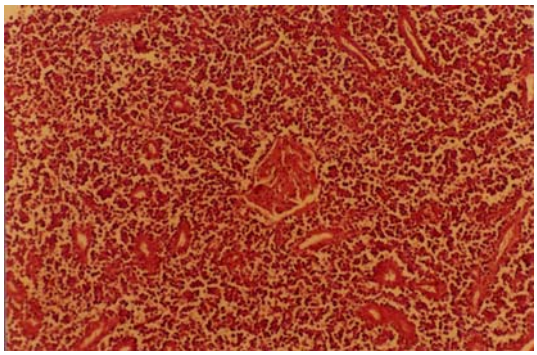

Fig. 1: kidney: the diffuse and heavy infiltration of lymphocytes which deface the normal structure of kidney (H&E, ×100)

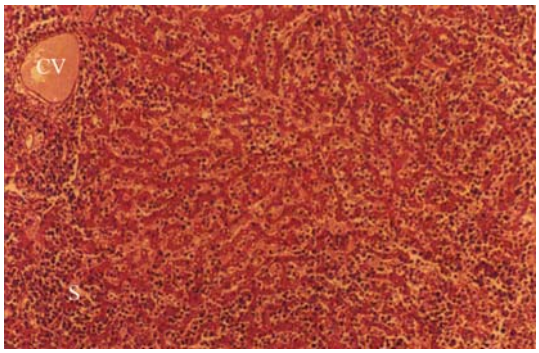

Fig. 2: liver: the centrilobular zone around the central vein (C.V) and sinusoidal spaces (S) invaded by neoplastic cells (H&E, ×100)

main types of diabetes mellitus. Type 1, insulin dependent diabetes mellitus, results from pancreatic inadequacy as a result of a variety of insults such as autoimmune attack, toxic damage, etc. Insulin administration is at the core of the therapeutic approach. Type 2, non-insulin-dependent diabetes mellitus, results from reduced responsiveness of the target tissue to insulin and therefore, an insulin resistance syndrome is described (Morrison *et al*., 2006). Virtually all dogs with diabetes mellitus have insulin-dependent diabetes mellitus at the time of diagnosis (Nelson and Couto, 2003). The incidence of diabetes mellitus is similar in the dog and cat, with a reported frequency varying from 1 in 100 to 1 in 500 (Panciera, 1990). In the referred dog, blood glucose level measured about 560 mg/dl at the initial presentation. Hyperglycaemia will occur if blood glucose concentration becomes greater than 130 mg/dl, although the clinical signs of hyperglycaemia do not develop until the renal tubular threshold for the resorption of glucose exceeds 180 to 220 mg/dl (Nelson and Couto, 2003).

This animal was overweight because it had been kept in a small yard and had no chance of doing a normal physical exercise during the day. Numerous studies demonstrated that obesity in companion animals may be predisposed them to orthopedic disease, diabetes mellitus, abnormalities in circulating lipid profiles and cardiorespiratory disease (German, 2006). The reported dog was a male Germen shepherded dog. Some studies have indicated that the incidence of lymphomas in male dogs is higher than females, but there is no significant breed predisposition to lymphomas (Dobson and Gorman, 1993). Lymphosarcoma, a common canine haematopoietic neoplasm, occurs in multicentric, alimentary, mediastinal, and extranodal forms (Lowe, 2004). Animals with multicentric lymphoma were presented with a solitary or generalized lymphadenopathy which may be accompanied with hepatospenomegaly, involvement of bone marrow or other organs (Morris and Dobson, 2001). Most cases of lymphoma are middle-age animals with an average age of 6-7 years (Morris and Dobson, 2001). In contrast, the majority of dogs with diabetes mellitus are 4- to 14-year-old at the time of diagnosis, with a peak prevalence at 7 to 9 years of age. The age of the dog presented in this report was similar to the mean age reported for the affected animals with these two clinical diseases. In this case, concurrent with diagnosis of lymphoma, the results of serum glucose concentration were indicated obvious hypoglycaemia. This finding was extremely unusual in a case suffering from diabetes mellitus. The history revealed that there was no obvious change in the dose and interval of insulin administration in this dog. Hypoglycaemia has been reported in association with hepatic tumours. Potential mechanisms of hypoglycaemia include excessive utilization of glucose by the tumour, release of insulin-like factors or other substances such as somatostatin from the tumour and secondary hepatic parenchimal destruction with impaired glycogenolysis or gluconeogensis (Johnson, 2000). According to the results of complete blood count, eosinophilia was the main

haematological finding in this case. Eosinophilia defined when absolute eosinophil count was greater than 1.3×10^9 /l in the dog. Hypereosinophilia could be a paraneoplastic syndrome in association with tumours (Grodecki, 2000). The association between hypereosinophilia and lymphoma is well established in human patients, in whom production of IL-5 by neoplastic cells has been demonstrated. Hypereosinophilia has been reported with intestinal lymphoma in cats and horses. There is only one report of hypereosinophilic paraneoplastic syndrome in dogs with lymphoma (Marchetti *et al*., 2005).

Concurrent disorders with diabetes mellitus is one of the most challenging subject. In human patients with diabetes mellitus, an increased incidence of vascular, glomerular, and ocular complications is associated with inadequate glycaemic control. The most frequently observed disorders among dogs with diabetes mellitus are urinary tract infections, dermatitis, otitis, acute pancreatitis, neoplasia and hypothyroidism (Hess *et al*., 2000). Therefore, the authors suggest that it is important to consider additional diagnostic tests in dogs with diabetes mellitus to explore possible concurrent diseases in these patients. In this case hepatic lymphoma and insulin therapy resulted in dramatic reduction in blood glucose level, severe hypoglycaemia and collapse. These effects could be misunderstood with improper setting of insulin dose by clinicians, and in an absence of awareness about this mechanism, management of diabetic dogs is much difficult and even impossible.

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