

# Histopathologic aspects of pancreatic islet cell tumor in a dog

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## Abstract

A 12-year-old 4.3 kg intact female Terrier presented with a history of lethargy, anorexia and melena for one month. The animal was dull and depressed. Dermatologic examination revealed some focal erythematous, crusty and papulopustular lesions over the ventral abdomen. Ultrasonographic evaluation displayed abnormal parenchymal pattern of liver which -was noticed in the cranial part of the abdomen -with diffuse hepatic involvement with irregular, hypoechoic and heterogeneous ill-defined areas [a honey- comb-like echotexture]. Lateral thoracocervical radiograph showed numerous well-defined, small lytic lesions [polyostotic punched-out lesions] in the dorsal spinous process of axis bone in C2-C5 and pelvis that were likely metastatic lesions. In spite of hospitalization and treatment, the dog died after 2 weeks and necropsy was performed. At postmortem examination, a 5-cm mass was observed in pancreas adjacent to duodenal loops which was finally diagnosed as a pancreatic tumor. Abnormal laboratory findings included elevated blood urea nitrogen, creatinine, cholesterol, total bilirubin, aspartate aminotransferase,

alkaline phosphatase, gamma-glutamyltranspeptidase and calcium. Histopathological examination of the affected pancreas, revealed neoplastic cells which were arranged mainly as solid nests or clusters and the amounts of the tumor stroma among the cellular clusters or individual neoplastic cells were scant. According to immunohistochemical study which was positive for chromogranine A, the condition was diagnosed as pancreatic islet cell tumor.

Although rare, pancreatic islet tumors should be included in the differential diagnosis of abdominal discomforts, pancreatic inflammation and hepatopathies. Final diagnosis of the tumor is achieved by combining imaging techniques and advanced histopathologic evaluations.

**Key words:** Tumor, Pancreatic islet cell tumor, Histopathology, Immunohistochemistry, Dog

**Abbreviations:**

**C2-C5:** Cervical vertebrae

**GI:** Gastrointestinal

**Introduction**

Pancreatic endocrine tumors have been reported in various species including humans, dogs, cats and ferrets [1]. In order to diagnose the pancreatic endocrine tumors, pathologist should confirm the neuroendocrine nature of the tumor cells. These tumors have various microscopic results, and immunohistochemical staining with different kinds of markers like chromogranin A, synaptophysin and neuron-specific enolase, can usually confirm the neuroendocrine origin [2]. It can be difficult to accurately evaluate the degree of malignancy of pancreatic endocrine tumors but other features of the tumors, including local invasion and metastases to lymph nodes and distant organs, are helpful to explain their malignant nature [3]. There are different commonly

recognized pancreatic endocrine tumors like gastrinomas, insulinomas, glucagonomas and somatostatinomas. Although these different types of pancreatic endocrine tumors share some clinical features and histological aspects, they differ in their pathogenesis, hormonal syndromes produced, many aspects of biological behavior and most importantly, in their response to chemotherapy and/or molecular targeted therapies. Here, we presented the histopathological appearance of a pancreatic islet cell tumor in an old Terrier dog. To the best of our knowledge, this is the first report of pancreatic tumor in Iran.

### **Case report**

A 12-year-old female Terrier dog weighing 4.3 Kg was presented to the Ferdowsi University of Mashhad Veterinary Teaching Hospital with a history of lethargy, anorexia and melena for approximately one month. On physical examination, the animal was dull and depressed with a normal body condition score. Dermatologic examination revealed some focal erythematous, crusty and papulopustular lesions over the ventral view of the abdomen. Differential diagnoses included endocrinopathies and malignancies. Complete blood count showed 1 % nucleated red blood cell and lymphopenia (520; Reference 1000-4800). Serum biochemistry revealed elevated blood urea nitrogen (88; Reference 10-28), creatinine (3.19; Reference 0.5-1.5), cholesterol (286; Reference 135-270), total bilirubin (0.43; Reference 0.1-0.4), aspartate aminotransferase (471; Reference 23-66), alkaline phosphatase (6470; Reference 20-156), gamma-glutamyltranspeptidase (45.5; Reference 1.2-6.4) and calcium (12.40; Reference 9-11.3). Other parameters, including C-reactive protein, were within normal ranges (Table 1).

Diagnostic imaging evaluations consisted of ultrasonography and radiology. Abdominal ultrasonography was performed with a 7.5 MHz linear transducer (Mindray, 6600 vet, China). Abnormal parenchymal pattern of liver was noticed in the cranial part of abdomen (Figure 1a).

Diffuse hepatic involvement with irregular, hypoechoic and heterogeneous ill-defined areas (a honey- comb-like echotexture) were observed that may be due to metastatic lesions or primary neoplasia. Lateral thoracocervical radiograph showed numerous well-defined, small lytic lesions (polyostotic punched-out lesions) in the dorsal spinous process of axis bone in C2-C5 and pelvis that is likely metastatic lesions (Figure 1b).



Figure 1: (a) Sagittal images of liver ultrasonography showed diffuse hepatic involvement with irregular, hypoechoic and heterogeneous ill-defined areas. (b)

Lateral cervical radiograph showed numerous well-defined, small lytic lesions [punched-out lesions] in the dorsal spinous process of C2.

Characteristic ultrasound features of evenly distributed hypoechoic nodular pattern, reflecting the neoplastic cells in the liver, which were consistent with the typical honeycomb pattern of superficial necrolytic dermatitis. Pancreatic mass was not detected by ultrasonography but later at necropsy a mass was detected.

In spite of hospitalization and supportive treatment, the dog died after 2 weeks and necropsy was performed. At postmortem examination of the case, a 5-cm mass was observed in pancreas adjacent to duodenal loops which was finally diagnosed as pancreatic tumor. Liver was diffusely pale and had rounded margins and hepatomegaly was another prominent finding. Histopathological samples were taken from the liver and the suspected unknown mass in the pancreas and then, then fixed in 10% formalin before being embedded in paraffin. Some sections of the mass were used for immunohistochemical study for chromogranin A detection [4]. Histopathological examination of the liver revealed severe and diffuse vacuolar change of hepatocytes. Most of the affected hepatocytes had clear and swollen cytoplasm (Figure 2a). In the affected pancreas, neoplastic cells were arranged mainly as solid nests or clusters and the amounts of the tumor stroma among the cellular clusters or individual neoplastic cells were scant. Prominent and hyalinized collagenous connective tissue was observed between neoplastic region and normal exocrine acini, and also in some parts of the tumor that formed a few separated microscopic areas within the tumor. Immunohistochemical study showed that the neoplastic cells were positive for chromogranine A (Figure 2b-2d). Based on postmortem, histopathological and immunohistochemical findings, the condition was diagnosed as pancreatic islet cell tumor.

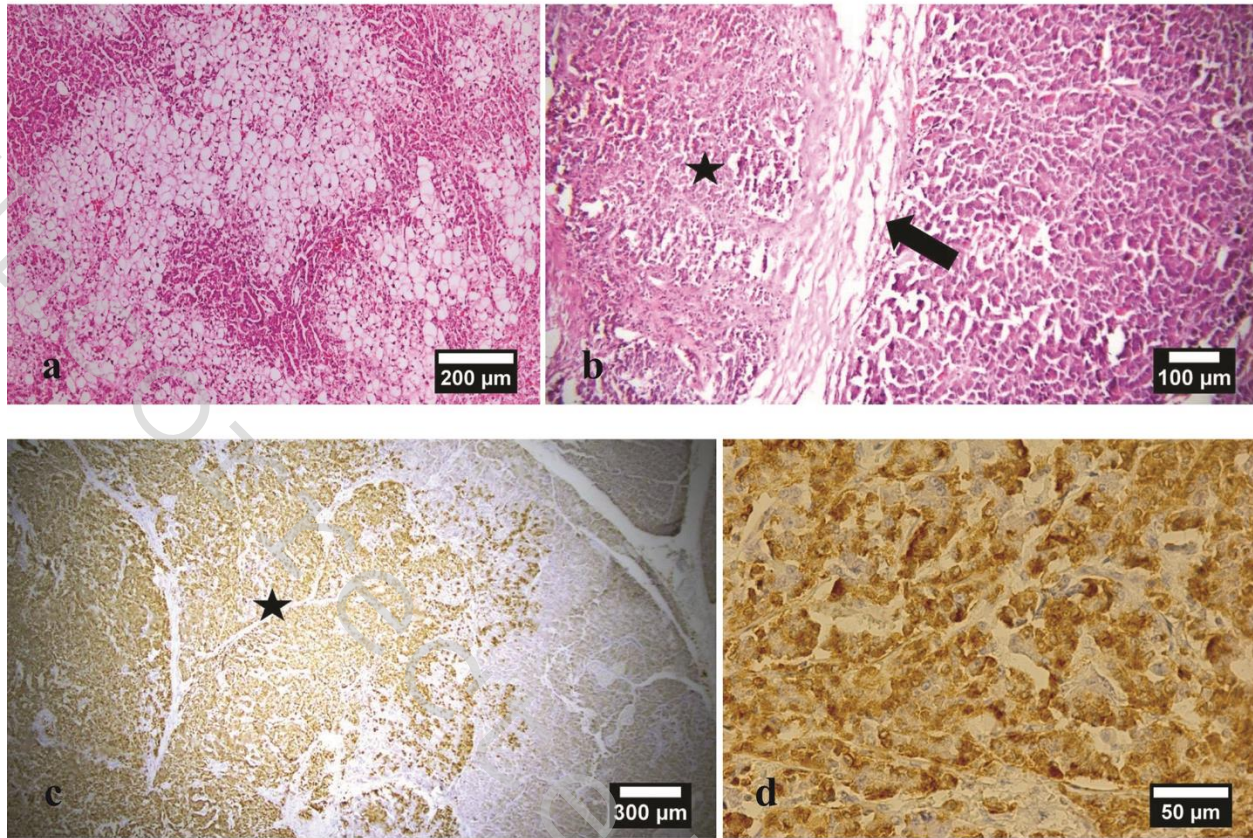


Figure 2: (a) Severe vacuolar change of the hepatocytes in the affected case. (b) The neoplastic region [asterisk] is separated from the exocrine pancreatic tissue by a connective tissue capsule. (c) Immunohistochemical staining is positive for chromogranine A in the neoplastic area [asterisk]. (d) Higher magnification of the positive neoplastic cells for chromogranine A.

## Discussion

The islet cell tumors are immunohistochemically reactive for multiple hormones and can secrete different kinds of hormones including insulin, glucagon, somatostatin, pancreatic polypeptide, and gastrin, either singly or in combination [5].

Our case was a dog who was presented with concurrent skin lesions, hepatic failure and lytic bone involvement. The skin lesions are caused by degeneration of keratinocytes, resulting in epidermal edema and necrosis [6]. The precise mechanism underlying the development of skin disease in islet cell tumors remains unknown, but one of the proposed mechanisms is the occurrence of hypoaminoacidaemia, which may induce keratinocyte necrosis through epidermal protein deficiency [7]. Unfortunately, we were not able to take skin biopsy sample during the examination and necropsy of delayed diagnosis of the tumor (missing data). Although not confirmed histopathologically, the presentation of the skin lesions in the present case resemble typical skin lesions of superficial necrolytic dermatitis [6, 8].

With pancreatic tumors, the signs can be vague or nonspecific (10); signs may include loss of appetite, vomiting, watery diarrhea, lethargy, pain in the abdomen and weight loss. If the tumor has metastasized such as the bones, the clinician may notice lameness. Most of affected dogs also have a non-regenerative anemia, mild hyperglycemia, increased serum liver enzyme activities and a honeycomb-appearing liver on abdominal ultrasonography. [6, 8]. The dog presented here had a history of lethargy, anorexia and melena for approximately one month. These unremarkable signs might be due to concurrent pancreatitis, inflammation of GI tract and/or cholangiohepatitis.

Laboratory abnormalities observed in the present case indicate severe hepatocellular dysfunction. A wide variety of reasons, including, for instance, metastasis of pancreatic tumor, concurrent GI disease and/or cholangiohepatitis reported as reasons for these abnormal findings.

Bone lesions in the present case, might be due to metastatic invasion of tumor, which was not confirmed histopathologically. Skeletal metastases including both osteolytic and osteoblastic

lesions have been described. In people a prevalence range of 5 to 20 percent of these lesions has been reported [9]. Most patient have widely metastatic disease at the time of diagnosis.

As emphasized in the present study, immunohistochemistry has become an essential ancillary examination for the identification and classification of this kinds of tumors. In the present case, the neoplastic cells were positive for chromogranin A, which is specific to endocrine cells.

Chromogranin A, due to its primary expression throughout the neuroendocrine system, is a widely accepted biomarker for the assessment of neuro-endocrine tumors [11].

Many authors believe that the prognosis of islet cell tumors is grave, although surgical removal of a pancreatic tumor may be curative in the unlikely scenario that metastasis has not occurred [11]. Clinicians should be aware of the uncommon early manifestations of islet cell tumors. Early diagnosis allows complete surgical removal of the neoplasm and provides the only chance of a cure. Additional case studies are needed to further characterize the cytomorphologic features and clinical presentation of pancreatic islet cell tumor in dogs.

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Table 1: Hematological and biochemical findings of the patient.

Table1: Haematological findings

Hematologic findings	patient	Reference values <sup>a</sup>
Hematocrit (%)	39	36-60
Hemoglobin (g/dl)	12.2	12.1-20.3
Red Blood Cell ( $\times 10^6/\mu\text{l}$ )	6.3	4.8-9.3
MCV (fl)	63	58-79
MCH (pg)	28	19-28
MCHC (g/dl)	37	30-38
Platelets( $\times 10^3/\mu\text{l}$ )	225	170-400
White blood cells ( $\times 10^3/\mu\text{l}$ )	11050	6.02-16.02
Mature neutrophils ( $\times 10^3/\mu\text{l}$ )	9750	2060-10600
Bnad neutrophils ( $\times 10^3/\mu\text{l}$ )	0	0-300
Lymphocytes( $\times 10^3/\mu\text{l}$ )	<b>550</b>	690-4500
Monocytes ( $\times 10^3/\mu\text{l}$ )	100	0-840
Eosinophils ( $\times 10^3/\mu\text{l}$ )	650	0-1200
Basophils ( $\times 10^3/\mu\text{l}$ )	0	0-150
James K. Klaassen, Reference Values in Veterinary Medicine LABORATORY MEDICINE VOLUME 30, NUMBER 3 MARCH 1999		

Table2: Serum biochemistry results

Biochemistry findings	patient	Reference values <sup>a</sup>
Total protein (g/dl)	<b>7.5</b>	5-7.4
Albumin (g/dl)	3.1	2.7-4.4
BUN (mg/dl)	<b>88</b>	4-27
Creatinine (mg/dl)	<b>3.19</b>	0.5-1.6
Glucose (mg/dl)	135	70-138
Cholestrol (mg/dl)	286	92-328
Bilirubin Total (mg/dl)	<b>0.43</b>	0.1-0.3
Alkaline phosphatase (IU/L)	<b>6470</b>	5-131
Alanine aminotransferase (IU/L)	<b>156</b>	12-118
Aspartate aminotransferase (IU/L)	<b>471</b>	15-66
Gamma-glutamyltranspeptidase	<b>45.5</b>	1.2-6.4
Calcium	<b>12.4</b>	9-11.3
Creatinine kinase (IU/L)	78	59-895

## شرح هیستوپاتولوژیک یک مورد تومور یاخته‌های جزایر درون ریز پانکراس در یک قلاده سگ

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یک قلاده سگ تریر 12 ساله ماده عقیم با وزن 4.3 کیلوگرم با شکایت تظاهرات جلدی روی شکم، بی حالی، بی اشتها، کاهش وزن و ملنا در یک ماه گذشته، به بیمارستان آموزشی ما ارجاع داده شد. در معاینه فیزیکی، حیوان بی حال، افسرده و دارای نمره توده بدنی طبیعی بود. در ارزیابی درماتولوژیک جراحات جلدی اریتماتوز، دلمه ای و پاپولوپوستولار روی شکم بیمار دیده شدند. بررسی اولتراسونوگرافی نشان دهنده الگوی پارانشیمی غیرطبیعی کبد به صورت نواحی نامنظم هایپو اکوژن و هتروژن پر از هوا بود. در رادیوگرافی جانبی، شمار زیادی ضایعات پلی اُستوتیک پانچی در زائده خاری مهره های گردنی شماره 2 تا 5 و در لگن مشاهده شد که احتمالاً ضایعات متاستاتیک بوده‌اند. به رغم درمان، بیمار زنده نماند و نکرپسی انجام شد. در کالبد گشایی، یک توده 5 سانتی متری در پانکراس در کنار لوپ‌های دوازدهه مشاهده شد که نهایتاً تومور پانکراس تشخیص داده شد. یافته‌های آزمایشگاهی غیرطبیعی عبارت بودند از افزایش اوره، کراتینین، کلسترول، بیلی روبین تام، آنزیم‌های کبدی، گاما گلو تامیل ترانسفراز و کلسیم. اندازه کبد بزرگ شده و به طور وسیع رنگ پریده با لبه های گرد بود. بررسی هیستوپاتولوژیک کبد نشان دهنده تغییرات واکوئلار وسیع هپاتوسیت‌ها بود. در پانکراس در گیر، سلول های توموری بیشتر بصورت توده های سلولی توپور آرایش پیدا کرده بودند و مقدار استرومای تومور در بین توده های یاخته های توموری و یاخته های منفرد بسیار کم بود. بافت همبند کلاژنه هیالینه و مشخص بین ناحیه توموری و آسینی های طبیعی بخش برون ریز و همچنین در برخی بخش های تومور مشاهده شد که تعدادی کانون میکروسکوپی مجزا در داخل تومور تشکیل داده بود. ارزیابی ایمونوهیستوشیمی نشان داد که یاخته‌های سرطانی برای رنگ کروموگرانین A مثبت هستند. بر مبنای یافته‌های کالبد گشایی، هیستوپاتولوژی و ایمونوهیستوشیمی، عارضه بیمار، تومور یاخته‌های بخش درون ریز پانکراس تشخیص داده شد. گرچه این نوع تومور نادر است ولی لازم است در فهرست تشخیص‌های افتراقی مشکلات ناحیه شکم، التهاب پانکراس و مشکلات کبدی جای گیرد. تشخیص نهایی نوع تومور با بهره گیری از روش های پیشرفته تصویر برداری و ارزیابی هیستوپاتولوژیک صورت می‌گیرد.

**واژگان کلیدی:** تومور، تومور پانکراس، هیستوپاتولوژی، ایمونوهیستوشیمی، سگ