

## Spontaneous insulinoma in a male SHR rat

Je-kyung Seong, Young-min Yun, Yang-seok Oh\*

Department of Laboratory Animal Medicine, Medical Research Center,  
College of Medicine, Yonsei University, Seoul 120-742, Korea  
Experimental Animal Center, College of Medicine,  
Hallym University\*, Chunchon 200-701, Korea

(Received Jun 2, 1999)

Spontaneous pancreatic islet tumors, especially insulinoma have been reported in several laboratory rodents<sup>1-5</sup> and domestic animals<sup>6-15</sup>. But only few case reports of spontaneous insulinoma has been reported in SHR (Spontaneously hyper-tensive rat) rats. In this report, we describe the clinical, histological and immunohistochemical features of insulinoma in a male SHR.

The animal was a 14-month-old mated male SHR. This rat was maintained under conventional conditions in Experimental Animal Center, College of Medicine, Hallym University (Chunchon, Korea). The rat was fed a commercial diet (Shincheon Co., KOREA) including 20% protein and water *ad libitum*. The humidity (60%), temperature ( $24 \pm 2^\circ\text{C}$ ) and light (12D/12L) of animal rooms were controlled constantly. Blood glucose concentrations were detected by glucose-oxidase method when animal was autopsied. Plasma insulin level was measured by radioimmunoassay method using commercial RIA kit (<sup>125</sup>I-rat insulin kit, Incsta Co., USA). The pancreas of male SHR was examined histopathologically and immunohistochemically. Pancreas and the other organs were removed and then fixed in 10% neutral buffered formalin. Tissues were processed routinely and embedded in paraplast. Paraffin sections were stained with

hematoxylin & eosin. The paraffin sections of pancreas were additionally immunostained with polyclonal primary antibodies against insulin (guinea pig anti-porcine insulin, Dako Co., USA) and glucagon (rabbit anti-glucagon, Dako Co., USA) according to the avidin-biotin complex methods using commercial kit (Vectastain Elite ABC kit, Vector Co., USA). Antibodies were diluted 1 : 200 by commercial reagents diluents (Biogenex Co., USA). Sections were colored with the substrate solution of 0.3% diaminobenzidine tetrahydrochloride (Sigma Co., USA). Sections were counterstained with Mayer's hematoxylin. Positive and negative controls were prepared in normal SHR and WKY rats.

Plasma concentration of insulin of tumor-bearing animal was markedly elevated (12.5ng/ml) compared to that of SHR ( $1.89 \pm 0.29\text{ng/ml}$ ,  $n = 30$ ). Non-fasting blood glucose level of tumor-bearing animal was slightly higher (182mg/dl) than normal SHR ( $108 \pm 9.4\text{mg/dl}$ ,  $n = 30$ ). Histopathological findings revealed marked enlargements of pancreatic islets stained pale with hematoxylin and eosin (Fig 1). The other organs such as liver, kidney, spleen, lymph node, intestines and heart did not show any abnormalities. Tumor cells in pancreas were not shown encapsulated (Fig 1). Most of tumors cells in this SHR have distinct nucleolus (Fig 2).

---

Address reprint requests to Dr. Je-kyung Seong, Department of Laboratory Animal Medicine, Medical Research Center, College of Medicine, Yonsei University, Seoul 120-742, Republic of Korea.

Tumor cells were stained strongly positive for insulin. Insulin granules were mostly oriented toward the peripheral margins of the tumor cells (Fig 3). In same islets, glucagon positive cells were not observed frequently (Fig 4).

Pancreatic islet cell tumors have been described in various animal species<sup>6-15</sup>, but are not common in laboratory rodents<sup>1-3</sup>. In general, insulinomas are accompanied with hypoglycemia and neurologic dysfunction associated with peripheral nerve metabolism<sup>6,7,9,11-13</sup>. In our case, however, no specific neurologic signs were noted. Also this animal showed different features of insulinoma compared with another case. But in this case, animal revealed slightly high level of blood glucose with hyperinsulinemia. However immunohisto-

chemical and histological appearances in our results provided that insulinoma in a SHR rats was similar to those of previous reports in other species<sup>2-15</sup>. SHR rat is well known as an useful animal model for human essential hypertension. This rat strain has also been proposed as a model for the study of insulin resistance in hypertension<sup>16</sup>. High blood glucose level with hyperinsulinemia observed in our case may be related with susceptibility of insulin resistance in SHR rat<sup>16</sup>. These findings might stimulate the research of relationship of insulin resistance and hypertension in SHR rat.

**Acknowledgements :** This work was supported by the fund(N81560) of Ministry of Science and Technology, Korea.

### Legends for figures

**Fig 1.** Photomicrograph of the pancreas from a SHR rat with insulinoma.

Note well-demarcated and expansive neoplastic mass (I) in the pancreas. Hematoxylin and eosin,  $\times 30$ .

**Fig 2.** Higher magnification of Figure 1.

Note centrally placed distinct nucleolus (arrow) of tumor cells. Hematoxylin and eosin,  $\times 400$ .

**Fig 3.** Photomicrograph of the immunohistochemical findings of pancreas in a SHR rat.

Islets stained strongly positive for insulin (arrow). Insulin granules are intracytoplasmic and oriented toward the peripheral margins of tumor cells. ABC methods,  $\times 200$

**Fig 4.** Photomicrograph of the immunohistochemical findings of pancreas in a SHR rat.

Glucagon positive cells (arrow) are not frequent in the neoplastic pancreatic islets. ABC methods,  $\times 200$ .



## References

1. Roe FJC, Roberts JDB. Pathology of tumors in laboratory animals, Vol. I. IARC Scientific Publ., New York, 1973.
2. Cardesa AA, Bullon-Ramirea, Levitt MH. Pathology of tumors in laboratory animals. Vol. II. IARC Scientific Publ., New York, 1979.
3. Mohr U, Renzik G. Pathology of tumors in laboratory animals. Vol. III. IARC Scientific Publ., New York, 1982.
4. Like AA, Steinke J, Jones KE, *et al.* Pancreatic studies in mice with spontaneous diabetes mellitus. *Am J Pathol*, 46:621-644, 1965.
5. Stromberg PC, Wilson F, Capen CC. Immunocytochemical demonstration of insulin in spontaneous pancreatic islet cell tumors of Fischer rats. *Vet Pathol*, 20: 291-297, 1983.
6. Capen CC. Tumors in domestic animals. pp. 48-90, Univ. Calif. Press, California, 1990.
7. Braund KG, Steiss JE, Amling KA, *et al.* Insulinoma and subclinical peripheral neuropathy in two dogs. *J Vet Intern Med*, 1(2):86-90, 1987.
8. O'Brien TD, Hayden DW, O'Leary TP, *et al.* Canine pancreatic endocrine tumors: immunohistochemical analysis of hormone content and amyloid. *Vet Pathol*, 24(4):308-314, 1987.
9. Leifer CE, Peterson ME, Matus RE. Insulin-secreting tumor: diagnosis and medical and surgical management in 55 dogs. *JAVMA*, 188:60-4, 1986.
10. Dahlgren RR, Emerick FM. Pancreatic beta cell carcinoma with renal metastasis in a dog. *JAVMA*, 187: 425-426, 1985.
11. Shahar R, Rousseaux C, Steiss J. Peripheral polyneuropathy in a dog with functional islet B-cell tumor and widespread metastasis. *JAVMA*, 187(2):175-177, 1985.
12. Fix AS, Harms CA. Immunohistochemistry of pancreatic endocrine tumors in three domestic ferrets (*Mustela putorius furo*). *Vet Pathol*, 27:199-201, 1990.
13. Jergens AE, Shaw DP. Hyperinsulinism and Hypoglycemia associated with pancreatic islet cell tumor in a ferret. *JAVMA*, 194:269-71, 1989.
14. Luttgen PJ, Stort RW, Rogers KS, *et al.* Insulinoma in a ferret. *JAVMA*, 189(8):920-1, 1986.
15. Kaufman J, Foodman MS. Pancreatic beta cell tumor in a ferret. *JAVMA*, 185:998-1000, 1984.
16. Hulman S, Falkner B, Freyvogel N. Insulin resistance in the conscious spontaneously hypertensive rat: Euglycemic hyperinsulinemic clamp study. *Metabolism*, 42:14-18, 1993.