A Case Report of Localized Pancreatic Amyloidosis in Diabetes Mellitus

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In 1901, Opie[1] reported that the degenerative change of the islets of Langerhans in the diabetic pancreas was hyalinosis. But, thereafter some other investigators, such as Gomori,[2] Ahronheim[3] and Arey,[4] pointed out that the change was not hyaline degeneration but chiefly due to the deposit of amyloid-like substance. Recently, many investigators[5,7,8,10] gave special attention to amyloid degeneration of the islets of Langerhans and examined its nature using the new histochemical staining and technique. And they emphasized that amyloid degeneration was clearly demonstrated in considerable rate of the cases diagnosed as hyaline degeneration by ordinary staining procedures.

In this paper, the author reported an autopsy case of pancreatic amyloidosis with particular reference to the results of histochemical stainings and polarization microscopic study.

Case ; 74 aged male (no occupation).

Clinical diagnosis ; Diabetes mellitus and Malignant tumor.

Family history ; Noncontributory.

Personal history ; Suspicious of liver cirrhosis (in 1957).

Present illness ; In 1960, the patient was diagnosed as diabetes mellitus at Medical Clinic of Yamaguchi University. Thereafter, he accepted out-patient treatment, injection of insulin, every two days. He complained of abdominal fullness, pain of the right hypochondriac region and dysorexia on March 30, 1964. He was admitted to Medical Clinic of Yamaguchi University on April 1. After admission, he was treated with insulin and accepted various other treatments. For a while, he was in good condition. But, ascites rapidly appeared at the end of April. Gradually, he became cachectic and died on June 9, 1964.

Laboratory examination ; Glucose tolerance test showed continuously high rate (table 1). Blood sugar also was the same result showing abnormally high rate (table 2). On urinary examination, sugar was obviously positive. The patient was diagnosed as diabetes mellitus. However, he had no complication for diabetes mellitus. Paper electrophoresis of serum protein showed increased α_1-globulin, β-globulin (table 3). Volume of ascites was 4700ml in April, and 4500ml at the end of the disease. Ascites was yellowish and translucent. Cytological examina-

tion of the ascites showed no malignant tumor cell.

Table 1: Glucose tolerance test.

	31/III	13/IV
Fasting	240 mg/dl	247 mg/dl
1 hr.		525 mg/dl
2 hr.	448 mg/dl	568 mg/dl
3 hr.	350 mg/dl	508 mg/dl

Table 2: Systematic Blood Chemistry.

	1/IV	30/IV	19/V	26/V	29/V
Hemoglobin (g/dl)	14. 1	13. 1	clot	12. 9	
Serum protein (g/dl)	6. 9	6. 9	6. 2	6. 3	6. 0
Blood sugar (mg/dl)	216	164	500	312	
Alb. Glob. ratio	1. 09	0. 6	0. 77	0. 58	0. 82
Hematocrit (%)	41. 2	37. 6		38. 1	
M. C. C. (%)	34. 1	34. 8		33. 9	
Icteric index	5	5	7		5
C. C. F. T.	0	0	1	2	0
Albumin (g/dl)	3. 6	2. 6	2. 7	2. 3	2. 7
Globulin (g/dl)	3. 3	4. 3	3. 5	4. 0	3. 3
Cholinesterase (ΔpH)	0. 45	0. 41	0. 6		0. 45
Alk. Phosphatase (u.)	2. 7	3. 0	2. 3		2. 6
Cholesterol (mg/dl)	269	217	192		214
Phenol. turb. t. (u.)	14	15	13		13
N. P. N. (mg/dl)	31	31	38		40
Urea N (mg/dl)	16	16	23		25
G. P. T. (u)	8. 5	2. 4	2. 0		22.

Table 3: Paper Electrophoresis of Serum protein.

Albumin	41. 6%
α_1-Globulin	7. 8%
α_2-Globulin	14. 8%
β -Globulin	13. 2%
γ -Globulin	23. 2%
Total Protein	6. 0 g/dl
A/G Ratio	0. 74

Autopsy findings; There was thumb-sized, round tumor at the cardiac region of the stomach. Numerous soy-bean-sized metastatic tubercles were recognized

in the peritoneum. Many lymph-nodes of the mesenterium and omentum were slightly swollen. Ascites 6000 ml. From above mentioned finding, it was diagnosed as gastric cancer with peritonitis carcinomatosa. As to others, focal pneumonia was noted in both lungs. No abnormal change was macroscopically recognized in the pancreas. However, the both kidneys showed senile contracted kidney.

Microscopic findings ; Tumor at the cardia was adenocarcinoma and its metastases were observed in the peritoneum and lymph nodes. The lungs showed severe bronchopneumonia. The pancreas showed typical diabetic pancreas. Observing the islets of Langerhans in this case, staining reaction of the islets was not similar to hyaline degeneration commonly observed in other organs even with H-E stain. Therfore, various stainings were performed to clarify whether this change was hyaline degeneration or not. Moreover, to make the diagnosis more precisely, examination by means of poralization microscope was done, and consequently degenerative change of the islets of the pancreas seen in this case was diagnosed as amyloid degeneration.

MATERIAL AND METHOD

The head and tail of the pancreas were investigated with various staining methods and polarization microscope in detail. The specimen observed were previously fixed with formalin at the time of autopsy. As control cases, the liver which previously diagnosed as amyloid-liver was observed. Hyaline degeneration of the central artery of the spleen and normal pancreas was prepared as control.

Staining methods employed were as follow ;
Hematoxylin-eosin, PAS, van Gieson, Congo-red, van Gieson-Congo-red, Alcian-blue, Toluidine-blue and Gentiane-violet stain.

Table 4 : Staining reaction for amyloid.

	Case	Liver Amyloid	Hyalin	Control
H. E.	light pink	light pink	light red	—
P. A. S.	light red	light red	crimson	—
van Gieson	yellowish brown	yellowish brown	reddish brown	—
Congo-red	orange	orange	light orange	—
van Gieson-Congo red	light orange	orange	light orange	—
Alcian-blue	light blue	light blue	light purple	—
Toluidine-blue	light gray	light gray	reddish purple	—
Gentian-Violet	crimson	crimson	light red	—
Dichroic-birefringence	+	+	—	—

RESULTS

Table 4 presented the results of the staining reaction and polarized-light reaction for every specimen. Microscopic appearance of the islets in this case was homogeneous and amorphous. The amorphous substance was recognized not only in the islets of the Langerhans but in the wall of blood vessel of the interstitial tissue in the pancreas, too. As to this substance, no difference between the head and the tail of the pancreas could be recognized. On polarization microscopic examination, this substance showed the change in color from green to yellow by rotation of the stage, showing dichroic birefringence.

COMMENT

The author proved that amorphous material seen in the islets was amyloid substance, because this material showed the same staining reaction and polarized microscopic finding as amyloid liver, and this material was quitely differentiated from hyaline degeneration of the spleen. To assure the diagnosis more exactly, electron microscopic study will be necessary. But such ultramicroscopic examination had not been done. All staining reaction revealed the difference between hyaline and amyloid degeneration. Hyalin did not show double birefringence by polarization microscope. Nakagawa[11] emphasized that there were three types in amyloid ; pre-amyloid, typical-amyloid, and post-amyloid, and it was difficult to differentiate pre-amyloid from undeveloped hyaline degeneration, because two substances show almost the same staining reaction and also the same findings with polarization microscope. But, this case showed completely dichroic birefringence and differentiation between amyloid and hyaline degeration was definitely revealed with staining reaction. The author, however, could not decide the pathogenesis of it.[6] Many investigators[2~5] reported that amyloid was found relatively in high rate in the diabetic pancreas, which was commonly regarded as hyaline degeneration of the Langerhans' islets. Recently, it is reported that material of hyalin-like degeneration in diabetes mellitus is amyloidosis.[9] But it was not decided in this case whether amyloid degeneration was associated with diabetes mellitus or diabetes mellitus was induced by amyloid degeneration.

In 1901, Opie,[1] reported hyalinosis of the islets of the Langerhans in diabetes mellitus. Thereafter many investigators have recognized that in some cases the change of the Langerhans-islets in diabetes mellitus was amyloid degeneration, as the staining methods have been improved[4,8,10] and polarization microscope have commonly been used. At the same time, the problem whether treatment of diabetes mellitus has relation to amyloid degeneration has occurred. In general, insulin has been used for treatment of diabetes mellitus as protamine zinc insulin since 1935.

The author had doubt if the antibody produced against insulin might react with injected insulin[12] and antigen-antibody complex might have induced amyloid deposit the islets of the diabetic patients receiving insulin treatment of long duration. There was no amyloid deposit in other organs in this case, and amyloid deposit was only localized at the pancreas. As was demonstrated in this case, Ehrlich and Ratner[9] emphasized that pancreatic amyloidosis was localized-amyloidosis and not present in other organs. Localized amyloidosis of the pancreas was reported by many investigators but such case is rarely found in Japan. In future, the author will clarify deposited substance, and will decide experimentally if insulin-treatment has any relation to amyloid deposit in the islets of Langerhans.

SUMMARY

1. Amyloidosis of the pancreas in a 74-year-old diabetic patient associated with adenocarcinoma at the cardia of the stomach is reported.
2. Amyloidosis of the pancreas is localized-amyloidosis.
3. Localized pancreatic amyloidosis is rare in Japan.

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Explanation of Figures

Fig. 1. Amyloid in the islet stained with H. E. shows light pink color. × 100

Fig. 2. Amyloid in the islet stained with P. A. S. shows light red color. × 400

Fig. 3. Amyloid in the islet stained with van Gieson obviously shows yellowish brown color. × 400

Fig. 4. Amyloid in the islet stained with congo red reveals orange color. × 400

Fig. 5. Amyloid in the islet doubly stained with van Gieson and congo red shows light orange color. × 100

Fig. 6. Amyloid in the islet stained with alcian blue shows light blue color. × 100

Fig. 7. Amyloid in the islet stained with toluidine blue reveals light gray color. × 100

Fig. 8. Metachromatic change of amyloid in the islet stained with gentian violet shows crimson color. × 400

Fig. 9. Polarization microscopic picture of amyloid in the islet stained with congo red demonstrates green and yellow refraction. × 400

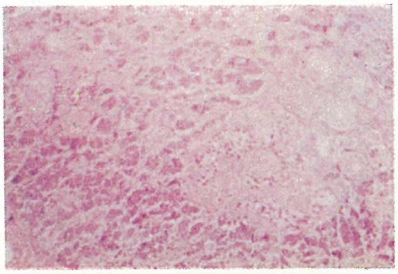


Fig. 1.

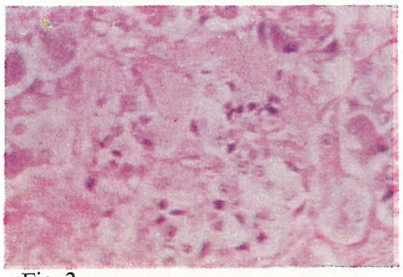
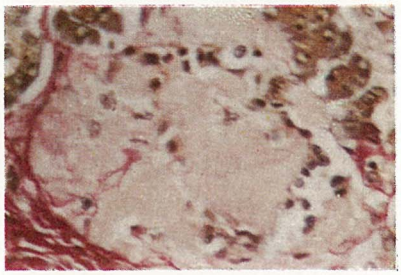


Fig. 2.



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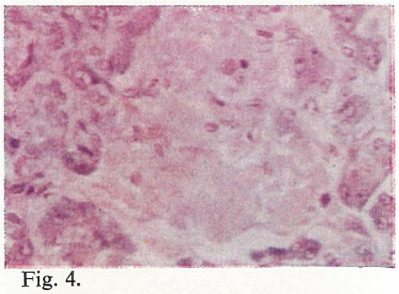


Fig. 4.

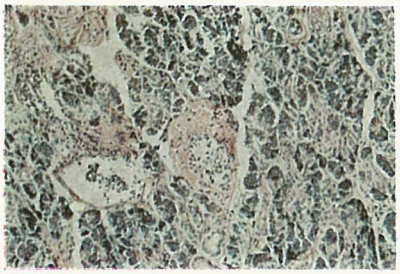
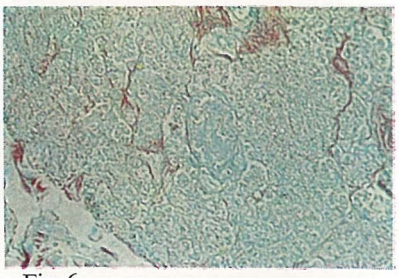


Fig. 5.



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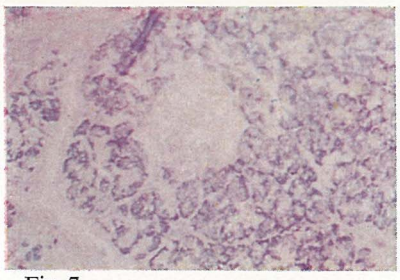

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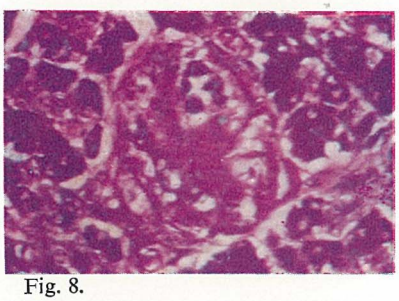

Fig. 8.

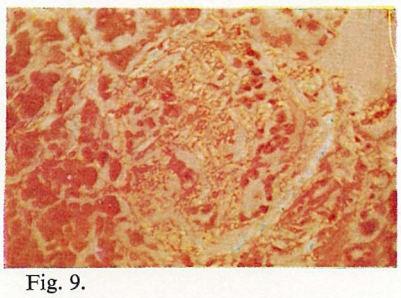

Fig. 9.