Etiology of Fat Replacement of the Pancreas

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SUMMARY: During the past 14 years, 104 patients received operations for chronic pancreatitis, in the 2nd Department of Surgery, Nagasaki University School of Medicine, in which, there were two cases of lipomatosis of the tail of the pancreas. Angiographical diagnosis revealed the complete devisualization of that area in the phase of the pancreatic parenchyma. It was suggested that reduction of the blood flow into the pancreas brought these pathological changes.

Destruction of pancreatic tissues, stricture of the pancreatic duct and fibrosis of the pancreatic parenchyma are well-known as histological findings of chronic pancreatitis, although proliferation of fat tissues in the pancreas is another inevitable finding of chronic pancreatitis. In order to clarify the relationship between arterial circulation and fat replacement of the pancreas, the author carried out the experiments, such as, the arterial ligation, venous ligation, and ligation of both the artery of the pancreas and the pancreatic duct of the canine, respectively. In the arterial ligation group, proliferation of the fatty tissues was observed around 4 weeks after ligation. These experiments showed that disturbance of the blood flow in the pancreatic arteries mainly related to proliferation of fat tissues in the pancreas.

INTRODUCTION

An interest in diagnosis and treatment of diseases of the pancreas has been growing in recent years along with the progress in diagnostic techniques. However, there are cases misdiagnosed as pancreatic tumor due to localized fat replacement of the pancreas or due to localized chronic pancreatitis, and it is difficult to distinguish these cases from carcinoma by the various imaging diagnostic techniques such as ultrasound (U. S.), endoscopic retrograde pancreatography (E. R. P.), computed tomography (C. T.) or angiography (Angio), etc. During the past 14 years, 123 cases of chronic pancreatitis were admitted at the 2nd Department of Surgery, Nagasaki University School of Medicine, 104 patients of which underwent laparotomy (Table 1). Among these

| Table 1. Therapies of 123 patients with chronic pancreatitis (1970-1983) |
|-----------------|-----------------|
| CONSERVATIVE THERAPY | 19              |
| LAPAROTOMY    | 104             |
| Pancreatectomy | 20              |
| Pancreaticojejunalostomy | 22        |
| (Partington’s operation) | 21       |
| (Duval’s operation) | 1              |
| Pancreatoduodenectomy | 5          |
| (Distal Pancreatoduodenectomy) | 15    |
| Biliary operation | 37             |
| Nardi’s operation | 6              |
| Cyst-jejunalostomy | 3           |
| Others         | 16              |
| TOTAL          | 123             |
104 patients the preoperative diagnosis was made by suspected pancreatic cancer in 13 cases. The operative findings in 2 cases revealed the area of the fibrosis and of the lipomatosis at the tail of the pancreas, and the feeding arteries of which changed into sclerosis. It was suggested that reduction of the blood flow into the pancreas brought these pathological changes.

Destruction of pancreatic tissues, stricture of the pancreatic duct and fibrosis of the pancreatic parenchyma are well-known as histological findings of chronic pancreatitis. Although proliferation of fat tissues in the pancreas is another inevitable finding of chronic pancreatitis, there has been very little study concerning this change. The author carried out an investigation in order to elucidate the cause of fat replacement of pancreas.

**CLINICAL INVESTIGATION**

During the past 14 years in our department, 104 patients received operations for chronic pancreatitis, among which 20 included pancreatectomy. Pancreatic fibrosis and proliferation of fat tissues were observed in all of the histological specimens, and two cases were found to have localized fat replacement (Table 2). The chief complaint in these two cases was upper abdominal pain with back pain. The patients were middle-aged, average stature, and non-obese. The history showed that Case 1 had received cholecystectomy for gallstone 10 years previously. In case 2, laboratory findings revealed a mild disorder of exocrine pancreatic function. 50gr. OGGT revealed glucose tolerance disorders in both cases. ERP disclosed diffuse dilatation of the main pancreatic duct in the head of the pancreas and severe stenosis of the duct in the body of the pancreas in Case 1, and tapering of the main pancreatic duct in the body of the pancreas in Case 2. The duct in the tail of the pancreas was completely invisible in both cases (Figure 1). Angiography revealed encasement of the transverse pancreatic artery near the body of the pancreas in Case 1, and marked meandering of the splenic artery and encasement of the great pancreatic artery in Case 2. In the phase of the pancreatic parenchyma in both cases, it revealed the complete devisualization of the tail of the

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MPD; Main Pancreatic Duct
pancreas (Figure 2).

Distal pancreatectomy was performed in both cases. Magnifying glass findings revealed that the respected specimens were differentiated into two parts: one was an area showing histological feature of the chronic pancreatitis with a combination of fibrosis and normal pancreatic tissues; the other was fat replacement. Light microscopy revealed atrophy, degeneration and disappearance of the acinar cells, infiltration of lymphoid cells, and fibrosis in the fibrotic areas. Langerhans islands were scattered in the areas replaced by fat tissues. The arteriosclerotic changes were found in its area. In none of the specimens did the histological findings reveal malignancy (Figure 3). It was suggested that fat replacement of the pancreas might be results of disturbance of arterial circulation of the pancreas. Therefore, the author performed the following experimental investigation.

EXPERIMENTAL INVESTIGATION

MATERIAL AND METHODS

The canine pancreas has a left and right lobe. The former is nourished from the branch of the splenic and left gastric artery, while the latter is nourished from the branch of the duodenal and superior mesenteric artery. They are endarteries, therefore the areas of arterial supply are well-demarcated, and they are useful in the investigation of the relationship between the pancreatic tissue and its blood supply. In the present study, young adult mongrel dogs both sexes weighing 8-12Kg. were used. Laparotomy was performed under 25-50 mg/kg. Numbutal venous anesthesia, and the dogs were divided into 4 groups, that is, one group receiving ligation of the arteries supplying the pancreas, one undergoing venous ligation, one lymphatic ligation, and another one ligation of both artery and pancreatic duct, respectively.
In the arterial ligation group, the superior and inferior pancreatoduodenal arteries, which supply the right lobe of the pancreas, were ligated with hemoclip just before they enter the pancreatic parenchyma (Figure 4). Similarly, the veins in the venous ligation group were ligated just where they flow out from the pancreas. Lymphatic ligation was carried out as follows. One day prior to operation the dogs were given a high fat diet, so that at laparotomy the lymphatic ducts might turn white and stand out on the pancreatic capsule. The entire lymphatic system on the right lobe of the pancreas was then ligated with 5-0 nylon sutures. Subsequently, the dogs were sacrificed 3 days, 1 week, 4 weeks and 8 weeks after operation, and at each time, the histological features of the pancreatic specimens were investigated. The unaffected left lobe of the same dogs was used as control. Hematoxylin-Eosin stain, Elastica-Van Gieson Stain, Aldehyde-Fuchsin stain and Oil Red stain were used in the histological studies. The tissue blood flow in the arterial ligation group was measured by the hydrogen gas clearance method before ligation, immediately after ligation, 4 weeks and 8 weeks after ligation and immediately before sacrificing.

RESULTS

—The arterial ligation group—
1) Three days after ligation (Figure 5)
The lobule structure was destroyed, the acinar cells showed degeneration and necrosis, nuclear fragments were scattered, and only a few acinar cells remained intact around the lobules, furthermore, interlobular edema was evident. These changes became more marked in the lobules near the pancreatic capsule and at the peripheral area of the right lobe.

2) One week after ligation (Figure 6)
The appearance of granular tissues composed mainly of fibroblasts was observed in the degenerated and necrotic lobules, while fat cells were observed in the necrotic lobules near the pancreatic capsule. These fat cells were irregular in size and immature. Degenerated and atrophied Langerhans islets and necrotic foci of acinar cells were observed in fat tissues.
In the central portion of the pancreatic parenchyma, that is, the area surrounding the main pancreatic duct, more or less normal tissues were observed.

Fig. 6. 1 week after the arterial ligation (H-E stain)
Fat cells are visible beneath the pancreatic capsule. Below these area, there were degenerative and necrotic tissues.

3) Four weeks after ligation (Figure 7)
The proliferation of fat tissues spread from the periferal area of the right lobe toward the left lobe and from the pancreatic capsule toward the main pancreatic duct. Degenerated and atrophied Langerhans islets, acinar cells and small pancreatic ducts were still evident in the fatty tissues. Also, the necrotic foci in the lobules still remained at this period. There were some fibrotic changes in the interlobular space, but it was still unclear when compared with the left lobe. The fat cells were relatively regular in size, and seemed almost matured. Fibroblasts were present in necrotic foci within the lobules near the main pancreatic duct.

4) Eight weeks after ligation (Figure 8, 9)
By this time, the border between healthy lobules and the pancreatic tissues replaced by fat tissues had became well demarcated (Figure 8).

Fig. 7. 4 week after the arterial ligation (H-E stain)
Fat tissues with scattered small pancreatic ducts and islets were evident. At the left normal pancreatic tissue, and in one part necrotic foci were observed.

Fig. 8. 8 week after the arterial ligation (H-E stain)
Pancreatic ducts and Langerhans islets were evident in the fat tissues. The border between the lobules and the fat tissues was well demarcated.

Fig. 9. 8 week after the arterial ligation (Oil Red stain)
The interlobular edema which had been observed commonly 3 days and 1 week after
ligation, completely disappeared. Figure 9 shows the Oil Red stain at this point. Atrophied pancreatic ducts and degenerated lobules were evident in the fat tissues.

— The venous ligation, lymphatic ligation, and arterial and pancreatic duct ligation group —

In the both venous and lymphatic ligation groups, from the beginning, findings indicating congestion of blood and the lymph were observed.

In the arterial and pancreatic duct ligation group, the proliferation and irregular dilatation of small pancreatic ducts were observed, and there were marked destructive, degenerative and fibrotic changes around the main pancreatic duct. The remaining acinar cells were scattered about among the fibrotic tissues. On the pancreatic parenchyma beneath the capsule, it was confirmed that fat replacement was occurring simultaneously.

— Blood flow of the pancreatic tissues in the arterial ligation group —

The pancreatic tissue blood flow before and after ligation in the arterial ligation group was measured before ligation, 30 minutes, 4 weeks and 8 weeks after ligation by hydrogen gas clearance test.

The average value was 25.1/min/100g before ligation, and it decreased to 6.9 ml/min/100g 30 minutes after ligation, a further decrease to 4.6 ml/min/100g 4 weeks after ligation and a final decrease to 4.2 ml/min/100g 8 weeks after ligation.

DISCUSSION

Various factors, such as interruption of the pancreatic blood flow, or lymphatic flow, or obstruction of the pancreatic duct, are said to have some relation to the etiology of pancreatitis.

Panum\(^2\), in experiments on the study of the effect of disturbance of the blood supply on the pancreas, reported the appearance of localized hemorrhagic pancreatitis after injection of a tiny drop of wax into the canine pancreatic artery. Popper et al.\(^3\) ligated the main pancreatic duct in the dog and injected Secretin intravenously, at which time edematous pancreatitis occurred but did not escalate to necrotic pancreatitis. However, the pancreas becasme necrotic when they stopped the flow of the gastroduodenal artery for 15 minutes. They concluded that a disorder in blood supply to the pancreas, in addition to congestion of pancreatic juice, induced the development of the necrotic pancreatitis.

Peffer et al.\(^4\) injected microsphere of synthetic resin into the pancreatic artery of the dog and observed the tissues of the pancreatic parenchyma over a long period. They noticed marked necrosis and proliferation of fibrotic tissue in the parenchyma, closely resembling chronic pancreatitis, and suggested that microcirculation disturbance is involved in the occurrence of chronic pancreatitis.

On the basis of abundant histological investigations concerning acute pancreatitis, Hayashi\(^5\) stated that if the course of development of necrotic foci in lobules of acute pancreatitis was investigated, changing of immature fibrotic cells to fat cells was observed in the pancreatic tissues, which was unlike the scarring in other organs. In various reports\(^6\) concerning fat replacement of the pancreas, obstruction of the main pancreatic duct was revealed by imaging diagnostic technique and the peripheral pancreas was replaced by fat cells.

Also, the experimental results of Walters\(^7\) suggested that the degeneration and necrosis of acinar cells caused by obstruction of the pancreatic duct inevitably lead to the formation of fatty tissues. This is contradicted, however, by the experiment of White\(^8\) in which ligation of the main pancreatic duct of the dog never brought about fat replacement but fibrotic change in the pancreas. The histological findings of the two clinical cases of fat replacement experienced in this study showed typical features of chronic pancreatitis such as, fibrotic change in the pancreatic tissues, inflammatory cell infiltration, proliferation of small pancreatic ducts, and changes in lobular structure, and there were definite findings of sclerosis of the arteries supplying the pancreas. Also, Langerhans islands were scattered in the fat tissues, which had a well demarcated border,
and angiography performed before operation revealed the absence of a parenchymal image of the tail of the pancreas. The above findings suggested that the lesion might be caused by ischemic changes in the pancreas. From the present experiment when the arteries supplying the pancreas were ligated and the blood supplying to the pancreatic parenchyma reduced to below 20% of the normal flow, the necrotic tissue of the pancreas changed to fat tissues about 4 weeks after operation. Therefore, disturbances of the arterial blood flow to the pancreas may involve fat replacement of that organ.

Concerning the histopathology of the pancreas in portal hypertension, it was stated that chronic hyperemia of the pancreas caused fibrotic change in that organ\textsuperscript{141}. It was also stated that congestion of the lymphatic system caused fibrotic change around the pancreatic duct and in the pancreatic interlobular space\textsuperscript{15}. In the present study, no proliferation of fat tissues in the pancreas was observed in either the venous ligation group or the lymphatic ligation group.

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