Chronic Pancreatitis in *Macaca* Monkeys

Minoru TSUCHITANI, and Isao NARAMA

Hamamatsu Seigiken Research Laboratory, Co., 95-10 Aoicho, Hamamatsu 433, Japan

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ABSTRACT. Chronic pancreatitis in 18 wild-caught *Macaca* monkeys was studied histologically. Pancreatic lesions were divided into three groups, diffuse, multifocal and focal, according to each condition of extent and distribution of lesions. Diffuse, multifocal and focal types of pancreatitis were detected in 10, 4 and 4 cases, respectively. Histological features in all 18 cases showed varied extent and distribution with inflammatory cell infiltration which consisted primarily of lymphocytes and plasmacytes and, interlobular and intralobular fibrosis. In spite of relatively slight polymorphonuclear leukocytes, small necrotic foci or areas with many polymorphonuclear leukocytes were occasionally observed. Similar property between multifocal chronic pancreatitis and diffuse chronic pancreatitis suggested that focal acute pancreatitis could advance to multifocal chronic pancreatitis and finally to diffuse chronic pancreatitis.—**KEY WORDS:** chronic pancreatitis, *Macaca* monkey.

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Disease in the pancreas is uncommon in nonhuman primates as well as various species of domestic animals [11, 16]. Acute and chronic pancreatitis encountered in dogs and cats is the most common pancreatic disorder [1, 9, 15, 16]. In nonhuman primates, the pancreatic disease reported most frequently is diabetes mellitus associated with insular amyloidosis [7, 11]. In comparison, a few cases of inflammatory disease of the pancreas in monkeys have been reported [3, 8, 14]. McClure and Chandler reported 18 cases of diffuse, acute or chronic pancreatitis and 10 cases of focal chronic pancreatitis by histologic survey [11]. They described that pancreatitis occur practically in nonhuman primates at considerable frequency in spite of a small number of reports. Etiologic factors of pancreatitis of monkeys have not been clarified except those of adenovirus infection in acute pancreatitis [4, 5, 12], and *Moloney torulosus* (Trichostrangylidae) infection in chronic pancreatitis [2]. The present report describes the histopathological features of chronic pancreatitis observed in wild-caught *Macaca* monkeys imported to Japan from Malaysia, Indone-

sia, and India for laboratory use during the period from 1973 to 1981.

MATERIALS AND METHODS

Total 2849 *Macaca* monkeys captured in Malaysia, Indonesia, and India were transported to Japan for laboratory use during the period from 1973 to 1981. Of this group, 364 monkeys were killed or died of various diseases during the quarantine period, and chronic pancreatitis were detected in 17 cynomolgus (*Macaca fascicularis*) and 1 rhesus (*Macaca mulatta*) monkeys. The species, country of origin, sex and age of these monkeys are shown in Table 1. Their ages were estimated by dentition.

All the animals were necropsied, and the pancreas and other tissue specimens for microscopy were fixed in 10% formalin, embedded in paraffin wax after routine processing and sectioned at 5 μ m. Sections were stained with haematoxylin and eosin (HE). For investigating the distribution of inflammatory lesions, sections were taken from several parts of the pancreas, except 6 cases in which the entire pancreas had not

been preserved adequately.

RESULTS

The type of pancreatic inflammatory lesions, clinical signs and principal lesions found in other organs are summarized in Table 1.

Clinical signs in the affected monkeys showed varied degrees of diarrhea and respiratory disease. Responsible lesions for most of those signs were confirmed histologically as enterocolitis or colitis and pneumonia. Gradual weight loss was observed in three cases. There was no sex difference in the incidence of chronic pancreatitis.

Only a few of the 10 monkeys with a diffuse type of pancreatitis showed gross alterations in the pancreas. Lesions observed assumed increased firmness, or

slightly diminished size without discoloration. No pancreas of the other cases showed such a remarkable change.

Pancreatic inflammatory lesions were divided into three types, diffuse, multifocal or focal, according to the extent and distribution of lesions. Diffuse chronic pancreatitis which involved more than one third of the pancreatic parenchyma was detected in 10 monkeys. The histological findings of these 10 monkeys consisted mainly of various degrees of fibrosis with lymphoplasmocytic infiltration, destruction and loss of exocrine tissue. The inter- and intralobular fibrosis was observed consistently in these 10 monkeys, while the severity of the lesions varied between individual cases, and within the same case. Frequently, the size of lobule was irregularly reduced as the result of subdivision of the lobules by fibrous septa or infiltration in the lobules by fibrous tissues

Table 1 Data of 18 monkeys with chronic pancreatitis

Case number	species	Country of origin	Sex	Age (yr)	Pancreatic lesion	Clinical signs	Other principal lesions
1	M. fascicularis	Malaysia	F	5	diffuse	watery diarrhea	chronic interstitial nephritis, colitis
2	M. fascicularis	Malaysia	F	4-5	diffuse	loose stool	.....
3	M. fascicularis	Malaysia	F	4-5	diffuse	loose stool	chronic interstitial nephritis, gastric ulcer, colitis
4	M. fascicularis	Malaysia	F	>5	diffuse	weight loss	chronic interstitial nephritis, colitis
5	M. fascicularis	Malaysia	F	>5	focal	loose stool, nasal discharge, cough, weight loss	enterocolitis, bronchopneumonia
6	M. mulatta	India	F	?	diffuse	.....	colitis
7	M. fascicularis	Malaysia	M	>6	multifocal	nasal discharge	colitis, bronchopneumonia
8	M. fascicularis	Malaysia	F	>6	diffuse	.....	.....
9	M. fascicularis	Malaysia	M	>6	focal	watery diarrhea, nasal discharge	giant cell pneumonia
10	M. fascicularis	Malaysia	F	5-6	multifocal	loose stool	disseminated intravascular coagulation
11	M. fascicularis	Indonesia	F	>6	focal	loose stool, weight loss	colitis
12	M. fascicularis	Indonesia	M	>6	focal	watery diarrhea	colitis
13	M. fascicularis	Malaysia	M	>6	diffuse	loose stool	cardiac ischemia, enterocolitis
14	M. fascicularis	Malaysia	M	>6	diffuse	loose stool	.....
15	M. fascicularis	Indonesia	M	>6	multifocal	watery diarrhea	chronic interstitial nephritis, colitis, steatitis
16	M. fascicularis	Indonesia	M	>6	diffuse	cough	bronchopneumonia, steatitis
17	M. fascicularis	Indonesia	F	>6	multifocal	loose stool, cough	lobar pneumonia
18	M. fascicularis	Indonesia	M	>6	diffuse	watery diarrhea	chronic interstitial nephritis

Fig. 1. Diffused lesion of chronic pancreatitis. Subdivision of the lobules by fibrous septa and infiltration in the lobules by fibrous tissues are evident. HE. $\times 60$.

(Fig. 1). The number of lymphoplasmocyte was not related to the severity of fibrosis. One case with relatively intense lymphoplasmocytic infiltration was accompanied by rather mild fibrosis. Small number of polymorphonuclear leukocytes were scattered concurrently with mononuclear leukocytes in some cases. Acinar cells frequently diminished in size and were destroyed, resulting in loss of acinar architecture (Fig. 2). The degree of parenchymal loss corresponded to the severity of fibrosis in general. In some monkeys, the normal architecture of the pancreas was completely destroyed and replaced by extensive fibrous tissue composed of dense collagen fibers and small numbers of cellular components. Occasionally, small necrotic foci or areas with many polymorphonuclear leukocytes were observed in interlobular connective tissue or degenerative parenchyma (Fig. 3). Some exocrine tissue preserved in the fibrotic

Fig. 2. Severe fibrosis and some lymphoplasmocytic infiltration in pancreatic lobules. Normal parenchymal architecture was destroyed. HE. $\times 390$.

Fig. 3. Necrotic area with polymorphonuclear leukocyte infiltration. Note the edematous loosening of interlobular connective tissue and fibrinous exudation. HE. $\times 120$.

Fig. 4. Protein plugs (arrows) in intralobular ducts and dilated acinar lumina. HE. $\times 260$.

lesions showed dilatation of the acinar lumen and proliferation of small ducts. Protein plugs and/or cell debris were seen in some dilated acinar lumina or intralobular ducts (Fig. 4).

In two cases, inflammatory lesions were predominant around the interlobular main duct showing branching and hyperplasia (Fig. 5). Periductal lesions consisted of marked fibrosis accompanied with varied degrees of infiltration of polymorphonuclear cells, lymphocytes, plasmocytes and macrophages. Interlobular main ducts showed dilatation, branching, and mucous metaplasia of the epithelial cells in some cases. Unidentified trematodes were found in the dilated main duct of 1 case.

Focal or multifocal chronic pancreatitis was detected in 4 cases each. Focal lesions ranged in size from very small, limited within one lobule, to large, with extension

to several lobules. Histological changes of focal and multifocal chronic pancreatitis were essentially identical with that of the diffuse type. In 3 cases with multifocal pancreatitis, the severity of the fibrosis and the number of inflammatory cells varied from focus to focus. Dilatation, branching and mucous metaplasia of epithelial cells of interlobular ducts were detected in 1 focal and 3 multifocal cases.

The endocrine pancreas was usually normal. In 1 case with diffuse pancreatitis, large hyperplastic islets were found in fibrous tissue which completely replaced the exocrine pancreas.

DISCUSSION

Histological features of pancreatic lesion in the present case were interlobular and intralobular fibrosis of varied extent, infiltration of lymphocytes, plasmocytes and

Fig. 5. Periductal inflammatory lesion. Fibrosis and cellular infiltration are predominant around the interlobular main duct. Branching (arrow) of main duct are also evident. HE. $\times 50$.

few polymorphonuclear leukocytes, and occasional necrotic foci in the exocrine tissue. The lesion was diagnosed as chronic pancreatitis based on the presence of fibrosis and the absence of acute inflammatory changes such as hemorrhage, conspicuous infiltration of polymorphonuclear leukocytes and widespread edema with exudation of fibrin. However, occasional necrotic foci and lymphoplasmocytic infiltration also suggested that this lesion was progressive in nature. Similar property between multifocal chronic pancreatitis and diffuse chronic pancreatitis suggests that repeated focal acute pancreatitis may advance to multifocal chronic pancreatitis and finally to diffuse chronic pancreatitis.

Although the cause of the repeating destructive actions on exocrine tissue is still unknown, occlusion of pancreatic ducts is suspected to be one important factor in

pancreatic disease. Experimental obstruction of pancreatic ducts has been shown to induce pancreatitis in rhesus monkeys [6]. Fibrosis, resulting in duct obstruction, may follow an inflammatory process in other lobules [10]. Inflammation of the main duct seen in present two cases and parasitic obstruction in one case also might result in stasis of pancreatic secretions.

It is also possible that acute diffuse pancreatitis was the initial change which resulted in chronic diffuse pancreatitis. Although several cases of acute diffuse pancreatitis caused by adenoviral infection have been described [4, 5, 12], it is difficult to consider that diffuse chronic pancreatitis of our cases resulted from acute adenoviral pancreatitis. Because adenoviral pancreatitis seemed to be fatal in many cases [4, 5, 12] and no viral inclusions were detected in our cases.

Afro-Asian (tropical) pancreatitis is one of the frequent types of chronic pancreatitis in humans [10]. This occurs in developing tropical countries and is associated with a high infection rate in childhood with low-protein diet. This indicates that the recurrent infections and protein calorie malnutrition are associated with stasis of pancreatic secretions and the resultant chronic pancreatitis [13]. The monkeys under study originated in a wild habitat, being probably influenced by recurrent infection and malnutrition until they were kept in our animal room. Therefore, these factors may be important for considering the etiopathogenesis of chronic pancreatitis in monkeys as indicated in human cases.

McClure and Chandler [11] reported 105 cases with inflammatory changes of pancreas out of randomly selected 1000 monkeys, but only 28 cases were diagnosed as diffuse or focal pancreatitis. The incidence of chronic inflammatory lesions of the pancreas in our monkeys was 0.6% of all stock animals, but was 5% for the animals that

were either killed or died of spontaneous diseases during the quarantine period. The true incidence of chronic pancreatitis in our monkey population is unclear, because autopsy and histological examination have not been conducted on the clinically healthy animals, and chronic pancreatitis is rarely detectable by clinical signs or laboratory determinations [8].

In the present case, clinical signs attributable to pancreatic disease may have been masked by the presence of severe gastrointestinal or respiratory symptoms. Gradual weight loss in three cases was the only clinical sign that might be attributable to the pancreatic lesions. Therefore, the pancreatic lesions were found in the result of the diagnostic histological examination. Such a silent clinical course seems to be a reason why only a few workers have paid attention to this disease in monkeys.

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要 約

マカカ属のサルにみられた慢性膵炎：土谷 稔・奈良間 功(株)生物科学技術研究所——18頭のマカカ属のサルにおける慢性膵炎を病理組織学的に検索した。膵病変はその拡がりや分布状態から瀰漫性、多巣状性、巣状性に分けられ、それぞれ10例、4例、4例に認められた。いずれの型においても、主な組織学的変化はリンパ球・形質細胞を主体とした炎性細胞浸潤と小葉間および小葉内線維化であり、さまざまな拡がりを示した。好中球浸潤は比較的軽度であったが、ときに多数の好中球浸潤を伴う小壊死巣が認められた。多巣状性病変と瀰漫性病変の個々の炎症性反応は極めて類似の性格を持つことから、巣状急性膵炎から多巣状慢性膵炎へ移行し、最終的に瀰漫性慢性膵炎像が形成されたと思われる。