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Age-related pathological changes in the pancreas

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1. ABSTRACT

Pancreas has a complex histology and is characterized by a combination of endocrine and exocrine cells. Pancreas undergoes various pathological changes with aging characterized by increased fatty replacement, fibrosis, lymphoplasmacytic infiltration, amyloid deposition, a decreased weight as well as development of intra-epithelial neoplastic changes. These age-related alterations lead to diabetes mellitus and can predispose the individual to pancreatic ductal adenocarcinoma. In this review, we summarize age-related morphological and pathological changes of aging in pancreas.

2. INTRODUCTION

The pancreas is located deep in the retro-peritoneum and has a complex histology, which is characterized by the unusual combination of endocrine and exocrine cells in the same organ (1). Acinar cells make up about 85% of the pancreas, are arranged in acini or round nests, and possess zymogen granules. Acinar cells synthesize and secrete digestive enzymes; therefore, acinar cells can be labeled for lipase, amylase, trypsin, chymotrypsin, and elastase by immunohistochemistry. Each acinar compartment connects to the pancreatic duct system. The centro-acinar cells represent the most peripheral duct system and partially cover the apical surface of the acinar cells. The intercalated ducts are found downstream of the centro-acinar cells. These converge and form the intralobular ducts and interlobular ducts, which, in turn, eventually drain into the main pancreatic duct. The pancreatic exocrine system is considered an origin of pancreatic ductal adenocarcinoma (PDAC).

Endocrine cells represent only 2% of the overall mass of the pancreatic gland and form about 10^5–10^6 islets. At least four different endocrine cells are recognized: glucagon-producing α-cells, insulin-producing β-cells, somatostatin-producing δ-cells, and pancreatic polypeptide-producing PP-cells. Of these, β-cells make up 60–80% of the islet cell population, and dysfunction of β-cells can cause diabetes mellitus (DM). Development of islets is complete several days after birth, and β-cells cannot proliferate and differentiate in the adult. The low regenerative ability of β-cells may affect the occurrence of DM (2).

Morbidity and mortality of both PDAC and DM are increasing worldwide, and both diseases are closely associated with age-related changes in the pancreas. In this review, we focus on age-related pathological changes of the pancreas.

3. AGE-RELATED MORPHOLOGICAL CHANGES IN THE PANCREAS

Aging is a process that starts at birth and involves development, maturation, and senescence with both physiological and pathological aging processes involved. Physiological aging is a normal process that causes a decrease in organ function in

Table 1. Age related morphological alterations of the pancreas

General changes
• Decrease of pancreatic weight
• Atrophy, lobulocentric atrophy
• Fatty liplacement, fatty infiltration
• Fibrosis
• Lymphoplasmacytic infiltration
Exocrine system changes
• Duct ectasia
• Metaplasia
• Acinar to ductal metaplasia
• Squamous metaplasia
• Goblet metaplasia
• Oncocytic metaplasia
• Pancreatic intraepithelial neoplasia
Endocrine system changes
• Decrease of endocrine cells
• Decrease of β-cells
• Ductulo-insular structure
• Amyloid deposition

all individuals. Pathological aging is a stimulation of aging, and includes factors such as malnutrition, genetic factors, and some diseases, that can lead to pathological conditions in certain individuals. Aging induces various types of change, for example functional, morphological, psychological, and social changes. These changes are interrelated. Organ weights decrease in the elderly (3), and this correlates with functional and morphological changes in each organ. The weight of the pancreas increases until the age of 30–40 years, after which, pancreas weight gradually decreases (4). The likelihood of developing various pancreatic diseases or dysfunction increases as the pancreas decreases in weight in the elderly. Also, a variety of histological changes in the pancreas are associated with advanced age (1), which are described in Table 1.

The incidence of fatty replacement, also known as lipomatosis, increases with advancing age. The relationship between increasing age and pancreatic fatty replacement is not well understood. There is a possibility that there may be a relationship with arteriosclerosis and reduced blood circulation. Fatty replacement may be the end stage of a gradual loss of exocrine tissue. The degree of fatty replacement varies both within the pancreas and between individuals. Islets are usually spared from the atrophic process and persist as singletons or clusters in the expanding adipose tissue. Despite the loss of pancreatic parenchyma, the weight of a lipomatous pancreas is usually increased, hence the term “lipomatous pseudohypertrophy.” Lipomatosis is also associated with obesity, DM, chronic pancreatitis, pancreatic duct obstruction, severe atherosclerosis, and cystic fibrosis. Fatty replacement in patients with PDAC has been reported after neoadjuvant chemoradiotherapy (5).

Mild focal or segmental duct ectasia of the main pancreatic duct or branch ducts can also be part of age-related pancreatic changes. Dilatation of the main pancreatic duct to over 4 mm in diameter has been found in 16% of patients at autopsy (6). Duct ectasia often associates with a mild degree of periductal fibrosis. Low-grade pancreatic intraepithelial neoplasias (PanINs) are often seen in the elderly (7). In addition, autopsy studies show that elderly patients often harbor metaplastic changes in the pancreas, such as acinar to ductal metaplasia, squamous metaplasia, goblet metaplasia, and oncocytic metaplasia.

Lobulocentric atrophy is a combination of changes, including atrophy of acinar parenchyma, fibrosis, and acinar to ductal metaplasia. The degree of change can vary from partial acinar atrophy, with a small focus of acinar to ductal metaplasia, to nearly complete acinar atrophy, with the replacement of most of the affected lobule by acinar to ductal metaplasia, fibrosis, and clustered islets. Acinar dilatation and

prominence of centro-acinar cells and intercalated ducts may also be part of the spectrum of age-related changes. Lobulocentric atrophy is often associated with PanIN (8).

Lymphoplasmacytic infiltration and fibrosis in the interlobular septa are often seen in the autopsied elderly (7). This change is named as chronic interstitial pancreatitis, and post mortem studies of patients with uremia, chronic inflammatory bowel diseases, cachexia, malnutrition, or extensive exhaustion for any reason, demonstrate a high frequency of mild inflammatory changes in the pancreas. The degree of change is usually mild, asymptomatic, and subclinical. Alcohol consumption, duct obstruction, and DM can enhance inflammation and fibrosis.

Islet endocrine cells play a key role in blood sugar control, and islet function usually declines according to age. There is a gradual and marginal decline in volume densities of islets and loss of both β- and non β-cells with aging. The mass of these components increase during maturation and slowly decrease after the age of forty (9). Ductulo-insular structures consist of both the duct and the islet, and associate with pancreatitis and islet hyperplasia. Amyloid deposition in the islet and vascular walls is also associated with advancing age.

None of these changes are specific to advancing age, and similar alterations may be seen in association with various conditions and factors, including uremia, pancreatitis, duct obstruction for any reason, PDAC, DM, excessive alcohol consumption, or smoking.

5. AGE-RELATED DISORDERS OF THE PANCREAS

5.1. Neoplastic lesions

PDAC is a malignant epithelial neoplasm arising in the pancreas, which exhibits glandular differentiation and does not contain a predominant component of another type of neoplasia. PDAC accounts for 85–90% of all pancreatic neoplasms. Due to its poor prognosis (10), PDAC is one of the few cancers for which the incidence nearly equals the mortality rate. It is the 7th leading cancer-related cause of death in the world, and the 5th leading cancer-related cause of death in Japan (11). Age is an important risk factor for PDAC (12) and affects mainly the middle-aged to elderly. Diagnosis of PDAC is uncommon before the age of 40 (13) and extremely uncommon before the age of 20.

Studies from autopsies and surgically resected materials, as well as recent molecular studies, have shown that the development of PDAC occurs at least in part through the intraepithelial proliferation/dysplasia-cancer sequence (14). The vast majority of PDACs are likely to arise from PanIN. Recent reports have proposed that the centro-acinar compartment might be an origin of precursor lesions, and PanINs and atypical flat epithelium might arise in tubular complexes as a result of acinar-ductal transformation (15). Among these, high-grade PanIN is considered an immediate precursor to PDAC.

In our analysis using autopsied samples, most primary tumors were PDAC (193 cases, 2.3.%, mean patient age; 78.1. years) with a peak incidence at 50–59 years (16). PDAC in elderly patients tends to progress asymptomatically, but once symptoms develop, the mortality rate is higher in elderly patients compared with younger patients. High-grade PanIN/carcinoma *in situ* was found in 4% of examined cases, while PanIN-1 and PanIN-2 were present in 77% and 28% of cases, respectively (7). We found that high-grade PanIN lesions were more likely to be found in older patients and in those with DM.

Multiple studies suggest that PanIN lesions are associated with fibrosis, lobular atrophy, and fatty replacement of the pancreas (8, 17). Low-grade PanIN may occur in both normal and diseased pancreata. Their frequency correlates with age: low-grade PanINs are rare in patients younger than 40 years but increase in frequency after 40 years of age. Low-grade PanINs are often seen in chronic pancreatitis and in the background of pancreata with PDAC or other neoplasms. In contrast, high-grade PanINs are rare in the normal pancreas but may occasionally be found in chronic pancreatitis and in the background of pancreata with PDAC. However, hereditary chronic pancreatitis patients and familial PDAC patients often harbor all grades of PanIN even at a younger age (18).

It is very challenging to detect high-grade PanIN even now. We need to develop effective diagnostic methods including pathological diagnosis, imaging, or blood markers to improve the diagnosis of PDAC.

5.2. Diabetes mellitus

DM is a group of chronic metabolic diseases in which there are high blood sugar levels. DM is a result of insufficient production of insulin by the pancreas or the inability of the body to respond properly to the insulin produced. If untreated, DM can cause many complications including cardiovascular disease, stroke, chronic kidney failure, foot ulcers, and eye damage. Type 1 DM results from the failure of the pancreas to produce enough insulin. Type 2 DM begins with insulin resistance, and as the disease progresses, a lack of insulin may develop. Usually, children and young adults suffer from type 1 DM, and the middle-aged and elderly suffer from type 2 DM. However, slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM), a subtype

of type 1 diabetes (19), is generally diagnosed in patients aged between 30 and 50 years as well as in the elderly. Trends suggest the morbidity rate of DM will continue to rise. Approximately 400 million people have DM worldwide, with type 2 DM making up about 90% of these cases; therefore, we focus on type 2 DM.

Methods for the diagnosis and treatment of DM have been developed. Genetic factors may have a big influence on DM (20). However, histopathological diagnosis of DM is still challenging. Most pancreata of type 2 DM do not show any specific morphological alterations. It has been reported that the pancreas of a type 2 DM individual shows lipomatosis, fibrosis, inflammation, islet hyperplasia, islet swelling, and islet hyalinosis; however, these alterations are often seen in normal pancreata, especially in the elderly.

Islet amyloidosis seems to be the only specific finding of type 2 DM, but only severe type 2 DM patients and elderly patients harbor islet amyloidosis (21). Islet amyloidosis can be detected by polarized microscope, where it shows as apple green in color, and by a positive stain results for amylin protein by immunohistochemistry. Electron microscopy reveals irregular thin fibers without branches and is a definite diagnosis of amyloid fibers. Islet amyloidosis is found in 10% of type 2 DM patients aged 50–60, 30% of 60–70 years and in over 50% of patients aged over 70 years (22). Approximately 4–23% of non-DM patients also show islet amyloidosis, and it may associate with advancing age and a usually mild degree of amyloid deposition. Severe amyloid deposition causes a decrease in the number of endocrine cells and islets.

Amylin peptide forms amyloid in the islet. Amylin is secreted with insulin; therefore, individuals with type 2 DM show hyper-secretion of insulin and amylin peptide deposits in the islet. Islet amyloidosis reflects hyper-secretion of insulin. Amylin may inhibit insulin secretion and have cytotoxic effects on β-cells (22).

Alterations in islet size and β-cell density in type 2 DM is still controversial. Some reports indicate that the pancreas of type 2 DM patients shows a decrease in islet size and β-cell density, as compared with non-diabetic patients (23). The distribution of islet and endocrine cells is different in each area of the pancreas. In addition, there may be many differences between mild and severe DM as well as early and late DM. Therefore, it is difficult to analyze morphological changes of the islet.

5.3. Inflammatory diseases

Acute and chronic pancreatitis exhibit characteristic morphological features, but there is also a degree of overlap. At autopsy, acute and chronic pancreatitis are often seen, and most cases are subclinical. Acute pancreatitis at autopsy is often associated with hypocirculation, termed shock-related pancreatitis (24). Systemic infection, certain drugs, obstruction, and neoplasms may cause acute pancreatitis. Morphologically, mild acute pancreatitis shows edema and neutrophil infiltration in interlobular septa. In addition to these findings, there is focal necrosis and hemorrhage in the interlobular septa and acinar parenchyma of early severe acute pancreatitis. Extensive necrosis and fat necrosis are seen in severe acute pancreatitis. Infection may occur, and this is associated with a significant mortality rate. The most important thing is that severe acute pancreatitis is fatal but is often subclinical because of the absence of characteristic clinical features; therefore, it is important to identify acute pancreatitis accurately at autopsy.

Chronic pancreatitis is a progressive inflammatory disease of the pancreas that leads to irreversible morphological changes. The process occurs slowly over many years and may be associated with recurrent episodes of acute exacerbation. Autopsied elderly patients often harbor mild inflammatory changes and fibrosis, and these changes are associated with advancing age as well as alcohol consumption. Mild chronic pancreatitis shows fibrosis in the interlobular septa. Advanced chronic pancreatitis is associated with marked inter- and intralobular fibrosis and duct dilatation with protein plugs and calculus. Chronic pancreatitis also shows various types of metaplastic, regenerative, and neoplastic changes, including squamous metaplasia, acinar to ductal metaplasia, ductulo-insular structure, and PanINs. Chronic pancreatitis is a risk factor for PDAC. Recently, new types of chronic pancreatitis have been characterized, such as autoimmune pancreatitis. Therefore, morphological diagnosis of chronic pancreatitis is becoming more important.

6. CONCLUSION

There are various types of age-related changes and diseases of the pancreas. Both DM and PDAC are leading causes of death worldwide, and they are associated with advancing age. Further analysis of morphological changes of the elderly pancreas may provide us with useful information in order to develop diagnostic tools and treatments for age-related pancreatic diseases.

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