Etiologic Link Between Chronic Pancreatitis and Pancreatic Cancer; A Unicentric Experience of Pancreatic Disease Institute of Wuhan Union Hospital of China

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Abstract: The aim of this study is to reveal the etiologic link that exists between pancreatic cancer and chronic pancreatitis through our unicentric experience. The clinical and cyto-pathological results of 300 patients were studied prospectively from January to December 2014 in the pancreatic center of Wuhan union hospital in china. Of the 300 pancreatic lesions patients, 196 were male and 104 female with a sex ratio of 1.8:1 ($p=0.001$). The factors assessed for the determination of etiologic link were the age, gender, the diameter of the lesion, the antecedents of disease (such as ulcer, cholecystectomy, smoking, alcohol abuse), the pancreatic lesion site, the diabetic link, the clinical presentations, the level of transaminases (GGT, ALP), peripheral blood analysis and cytopathological results of both PC and CP groups. According to the clinical data along with the respective results of the examinations, causal factors that link CP and PC are illustrated and it opens the pathway for further detailed studies as an investment for the future.

Keywords: Pancreatic Cancer, Chronic Pancreatitis, Etiologic Link, Unicentric Experience, Pancreatic Lesions

1. Introduction

Pancreatic cancer (PC) and chronic pancreatitis (CP) are the second and third cause of hospitalization in the pancreatic surgery department of Wuhan Union Hospital of China [1]. PC is a devastating disease and fourth, fifth and seventh leading cause of cancer-related death in the United States, European Union and China, respectively [2]. CP is defined as an inflammatory disease which is characterized by an irreversible conversion of pancreatic parenchyma to fibrous tissue [3]. In the Western world, its incidence has

been estimated to be 10/100,000 pa with rising morbidity among females. In 20–30% of cases of chronic pancreatitis and mass lesions in the pancreas may occur [3]. Several studies have demonstrated a strong link between inflammation and cancer [3]. Virchow was the first to ascertain this link in the 19th century. His hypothesis was thereafter endorsed by several epidemiological researches which acknowledged the etiologic link between CP and PC [4].

Highlighting the causal relationship between CP and PC is necessary since PC is a disease that has very poor

prognosis. The diagnosis of PC at an early stage is rare and the by the time it's discovered, it becomes resistance to therapies. Moreover, resection of tumor may not be possible in greater than 80% of PC patients due to metastasis, leading to a low five- year survival rate [5]. Furthermore, among the risk factors of PC such as obesity, alcohol, cigarettes smoking, diabetes, chronic pancreatitis and age, CP is the most prominent one [7]. Inflammation to become tumorous need an extended length of period thus inflammatory mediators has a great influence. These inflammatory mediators may cause change in gene expression which may induce activation of neoplastic pathways leading to cancer.

Moreover, during inflammatory response, an increase level of IL-1 (interleukins 1 receptor) in the brain and may cause breakdown of blood brain barrier. Furthermore IL-1 polymorphisms have been found to contribute to genetic susceptibility to some cancers. According to the literature, there are two distinct IL-1 receptors, IL-1R type 1 and IL-1R type II.

Type 1 receptor is primarily responsible for transmitting the inflammatory effects of interleukin-1 while the type 2 receptors act as a suppressor of IL-1 activity by competing for IL-1 binding. Thus IL-1 receptor represent an important counter-regulatory component of the inflammatory response.

In future studies gene array will demonstrate a prospective marker in relation to etiologic link. This article highlights the causal relationship between the two diseases with various factors and the potential markers of pancreatic lesions.

2. Materials and Methods

2.1. Patients

In Wuhan's pancreatic center of Union hospital, from January to December 2014, 300 patients were treated and included in our study. Among them, 266 cases were PC and 34 were CP. The sex ratio was 1.8: 1 ($P=0.001$) with 196 male and 104 female.

All the included cases in our study had done their routine blood examination, the transaminases test, tumors marker test and CT and MRI.

Patients with small-cell carcinoma, mucinous cystadenocarcinoma, islet cell, papillary cystic neoplasm, or no differentiates adenocarcinoma and biliary diseases were not eligible.

2.2. Assessment of Transaminases

GGT in serum was measured using the Szasz method [8], with γ -glutamyl-p-nitroanilide as substrate and glycylglycine as receptor. ALP activity was determined using the SMA 12/60 auto analyzer with p-Nitro phenyl phosphate. AST and ALT are assayed by the use of SMA 12/60 auto analyzer ultraviolet method. GGT was assayed within 48-60h after the serum sample was collected, and ALP, AST, ALT within 24h. However if they were not examined within 3 hrs. of collection, they were stored at 4°C [9].

2.3. Cytopathological Assessments

All cyto-pathological samples were processed as cell blocks and were interpreted by the same experienced cytopathologist. The specimens were considered satisfactory in the presence of several non-hemorrhagic small tissue filaments or even tissue core samples. The number of tissue needed to obtain a satisfactory specimen was documented. Briefly, once resected, the material was fixed in buffered formalin, underwent centrifugation, and was immersed in the liquid agarose. Once solidified, the agar cone with the cells in the top was embedded in paraffin to be handled as a routine tissue block. On reviewing the slides, cellularity, presence of loosely cohesive aggregates or single tumor or chronic cells, quality and quantity of cytoplasm, nuclear pleomorphism, chromatin patterns, nucleus to cytoplasm ratio and necrosis were systematically analyzed.

2.4. Clinical Assessment

The clinical data were collected using pre-established cards investigation. The following observations were made to highlight the etiologic bonds between the PC and CP:

1. Pain
2. Jaundice
3. Weight loss
4. Diameter of the masses
5. Antecedents of disease (Ulcer, cholecystectomy, smoking, and alcohol abuse)

During operations the macroscopic aspect of spleen was investigated and the peripheral blood, transaminases and tumor markers were analyzed before surgery.

2.5. Statistical Analysis

The statistical analysis was carried out using software SPSS version 21, and the figures using the software graph pad. Prism.v5.01. P value inferior at 0, 05 was regarded as statistically significant.

3. Results

The activity of the main transaminase among patient in chronic pancreatitis and pancreatic cancer. In pancreatic cancer, the GGT value ranged from 182 to 263 IU/L with a median value of 223 IU/L and the ALP ranged from 163 to 208 IU/L with a mean value of 186 IU/L.

In chronic pancreatitis, the GGT value ranged from 18 to 261 IU/L with a mean value of 140 IU/L and ALP value ranged from 70 to 248 IU/L with a mean value of 159 IU/L.

4. Discussion

4.1. From Inflammation to Cancer

Inflammation is the primary match that sets the fire of the robust stroma reaction surrounding PC cells. PC mass constitute of a stroma composed of fibroblasts, vessels and leukocytes. Leukocytes of the inflammatory cells are the

major actors engaged in initiating and sustaining the inflammation reaction. The leukocytes within the tumor stroma, as well as the cytokines and growth factors derived from the leukocytes, construct the complex extrinsic pathway which plays a core role in the tumor formation process [10].

Tumor-associated macrophages (TAMs) are the principal leukocyte subset driving amplification of the inflammatory response in the tumor milieu. They primarily belong to the myeloid cell lineage and are derived from myeloid progenitor cells. These precursor cells are located in the bone marrow and upon maturation the monocytes are released into the bloodstream. Thereafter, certain chemokines, e.g. CCL2 and CCL5 recruits TAMs into the tumor stroma, where they facilitate the invasive neoplastic state.

TAMs assist in the malignant behavior of the tumor cell by releasing cytokines, growth factors and matrix-degrading enzymes and a host of angiogenic factors. Lists of molecular alterations are involved in the TAM-PC connection. For example, administration of agonist CD40 antibody activates macrophages that in turn infiltrate tumor turning it into tumoricidal, and facilitate the depletion of tumor stroma [11]. TAMs may also secrete MIP3 α to increase the migration ability of PC cells by binding to the transmembrane receptor CCR6 [12]

A study showed that TAMs could convey pro-angiogenic effects to PC cells. Blocking the TIE2 ligand and angiogenic factor, angiopoietin-2, could impede the up regulation of TIE2 in TAMs and decrease tumor angiogenesis of PC [13]. Furthermore, TAMs help sustain the cancer stem cells, due to its chemo resistance, metastatic dissemination and the induction of immune suppression [14].

4.2. Demographic Data

From January to December 2014, 300 patients were treated at pancreatic center of Wuhan Union hospital in china. Out of 300 cases, 266 cases were PC and 34 were CP and the sex ratio in PC group was 1.98:1 and in CP group was 1.61:1 according to table 1 data, thus showing a male preponderance in both diseases compared to female (P=0.001, table 1). PC patients ranged from 14 to 84 years with a mean of 59 years and CP patients ranged from 24 to 68 years with a mean of 46 years. This shows that PC patients are 10 -15 years older than CP patients. The statistical analysis was significant with a P value of 0.001 (less than 0.05). The average diameter of the lesions was 3.6 $\pm$ 3.2 in PC group and 3.8 $\pm$ 3.3 in CP group as shown in table 1 and the most common lesions site was head of pancreas in both diseases. [1, 15]

Epidemiological report showed a parallel increase in both diseases in many countries. Niderau *et al* [16] found the prevalence of pancreatic cancer with CP to be 3.5 % and Lowenfel *et al* [17] showed a prevalence of 2.9%. This was in line with other calculations from 16 different studies published between 1960 and 1989 with an overall incidence of PC patients with CP to be 3 % with a range from 0.8% to 3 %) which is higher than expected, therefore showing some interrelationship between CP and PC [17, 19].

Table 1. Demographic data and clinical presentation of pancreatic lesion in PC and CP.

Parameters	Pancreatic cancer N=266	Chronic pancreatitis N=34	P value
Mea nage (range); years	59(14-84)	46(24-68)	0.001
Gender			
Male	174	22	0.001
Femele	92	12	
Meanlesionsize(range);cm	3.6+/-3.2	3.8+/-3.3	0.002
ClinicalPresentation	141	20	
Diabetes	141(53%)	20(58.82%)	
Abdominal pain	206(77.44%)	25(73.52%)	0.001
Weightloss	199(74.81%)	21(67.76%)	
jaundice	97(36.46%)	11(32.03%)	
Antecedents			
Ulcer	112(42.10%)	14(41.17%)	
Cholecystectomy	142(53.38%)	17(50%)	0.001
Smoking	180(67.66%)	22(64.70%)	
Alcoholdrinking	162(60.90%)	21(61.76%)	

This table shows that PC patients are 10 -15 years older than CP patients which correspond to the time needed for the inflammation to propagate into cancerous cells. The statistical analysis was significant with a P value of 0.001 (less than 0.05). The average diameter of the lesions was 3.6 $\pm$ 3.2 in PC group and 3.8 $\pm$ 3.3 in CP group (P=0.002).

The symptoms were found to be more common in PC patients with 77.4% cases of abdominal pain, 74.8% cases of weight loss and 36.5% cases of jaundice compared to 73.5%, 61.8% and 32.4% cases of CP patients with abdominal pain, weight loss and jaundice respectively (P=0.001). The data was of no significance in relation to the clinical presentation of both diseases.

In both PC and CP groups' almost same percentage of patients were observed to have hyperglycemia as a direct consequence of diabetes mellitus (P=0.001).

4.3. Clinical Symptoms

According to table 1, the symptoms were found to be more common in PC patients with 77.4% cases of abdominal pain, 74.8% cases of weight loss and 36.5% cases of jaundice compared to 73.5%, 61.8% and 32.4% cases of CP patients with abdominal pain, weight loss and jaundice respectively. The data was of no significance in relation to the clinical presentation of both diseases which was in line with the literature of Ardengh *et al* [20, 21].

From history, ulcer, cholecystectomy, smoking and alcohol drinking were found to be antecedents of the pancreatitis disease. Person who smoked had a higher percentage in both CP and PC as shown in the table 1 (P=0.001 less than 0.05). Our results were superimposable with majority of the meddicaleel literature [22].

Furthermore through this study, CA19-9, CEA, CYFRA21-1 and Ferritin are found to be the markers of both pancreatic cancer and chronic pancreatitis. However, other markers were also identified in different parts (table 2).

Our study along with the image proves that PC and CP are

more frequent in the body and tail of pancreas. (Table3) and (Figures A, B and C, D).

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Table 2. Furthermore through this study, CA19-9, CEA, CYFRA21-1 and Ferritin are found to be the markers of both pancreatic cancer and chronic pancreatitis. However, other markers were also identified in different parts.

Level of lesions	Pancreatic cancer N=266	Chronicpancreatitis N=34
Head	39(14.66%)	4(11.76%)
Head-neck	5(1.87%)	2(5.88%)
Neck	6(2.25%)	4(11.76)
Body	122(45.86%)	14(41.17%)
Tail	94(35.33%)	12(35.29%)

Table 3. Our study along with the image proves that PC and CP are more frequent in the body and tail of pancreas.

Tumor marker	PC	CP
CA19-9	138(51.87%)	17(50%)
CA125	74(27.81%)	8(23.52%)
CEA	63(23.68%)	8(23.52%)
Ferritin	139(52.25)	18(52.94%)
CA15-3	9(3.38%)	6(17.64%)
CA72-4	24(9.02%)	15(44.11%)
AFP	5(1.87%)	6(17.64%)
CYFRA21-1	55(20.67%)	9(26.47%)
NSE	60(22.55%)	12(35.29%)
PSA	2(0.75%)	0(0.00%)
SCC	20(7.51%)	5(14.70%)

4.4. Diabetes Mellitus

In both PC and CP groups' almost same percentage of patients were observed to have hyperglycemia as a direct consequence of diabetes mellitus (table 1). This is a common observation made by several publications in china [23]America [24]andEurope [25].

Normally pancreas is a mixed gland of exocrine and endocrine. Exocrine consist of acinar cell and duct cell secretions whereas endocrine pancreas are made up of Islets of Langerhans which contain beta-cells (one of the many) that secretes insulin.

Due to pancreatic lesions in exocrine part, acinar tissue loss and replacement by fibrosis occurs. Moreover, Islets become smaller than normal and may be isolated from their vascular surrounding due to fibrosis. Eventually endocrine insufficiency (diabetes mellitus) occurs with progressive destruction of gland.

4.5. Amino Transaminase

Alkaline phosphatase (ALP) is an enzyme found in large amount in bone liver and bile duct tissue. Normally, level of ALP in the blood, range from 44 to 147 IU/L. ALP has been

showed to be present in pancreatic duct epithelium, acini, islets and tumors.

Gamma glutamyl Transferase (GGT) is an enzyme found in cell membranes of many tissues mainly in the liver, kidney and pancreas. The reference range is 0- 51 IU/L. GGT is often measured in conjunction with ALP to determine whether ALP increase is due to liver or pancreatic disease [23].

In our center, an increase in ALP and GGT in PC and CP groups can be observed in figure 1A and 1B. High level of both ALP and GGT can be potential marker of pancreatic disease, especially in those patients with suspected for chronic pancreatitis or pancreatic cancer [26, 27].

Figure 1A and 1B. Shows the leukocyte levels compared to the normal range in PC and CP. NE (neutrophils), LY (lymphocytes), MO (monocytes), EO (eosinophils), BAS (basophils).

5. Conclusion

In summary, the etiologic factors that link PC and CP are as described: (1) the interactions of stromal -tumor result in a chaotic environment accompanied by loss of immune surveillance and repair response thereby developing a neoplastic events. (2) The peak age of PC patients has been observed to be 10-15 years older than CP, (table 1). (3) The lesion diameter was approximately the same in both diseases and the lesion site which was body and tail of pancreas was common (figures 2A,2B,2C,2D). (4) The body and tail of pancreas as a location has been showed by many publications [1, 13]. (5) The incidence of both diseases increased simultaneously in many countries [29, 32]. (6) Man was more affected in both groups than female with a sex ratio of

nearly 2:1($p=0.001$,table 1).Clinical symptoms were of no great value since they hardly differ in PC and CP. (7) Pancreatic insufficiency is a common factor in PC and CP, thus diabetes Mellitus is witnessed equally. (8) ALP and GGT are the enzymes that revealed to act as potential markers for pancreatic lesions. (9) Neutrophiles, lymphocytes were high in the pancreatic lesions patients but higher in chronic pancreatic patients than pancreatic canceras shown in figure 1A and 1B along with figure 3A and 3B. All these etiologic link factors and their respective results may act as

an indication in early recognition of pancreatic lesions therefore further detailed studies may prove to be helpful in future life.

A better understanding of the etiologic link between CP and PC would definitely lead to an earlier diagnosis and prevention of PC.This project can conclude that the causal relationship of PC and CP can be implicated by many factors and be used in the development of sophisticated screening procedures.

Figure 2A, 2B, and 2C, 2D. Show us, the most frequent localizations in the pancreatic cancer, and chronic pancreatitis. According to the results the body and the tail of the pancreas are the preferential sites PC and CP.

Figure 3A (CP) and 3B (PC). Provide a histopathological evidence to compare the high level of neutrophils in PC and CP. The neutrophils are marked with (NE).

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Conflict of Interest Statement

The authors declare that there is no conflict of interest with any financial organization or corporation or individual that can inappropriately influence this work.

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