Chronic Pancreatitis: Relation to Acute Pancreatitis and Pancreatic Cancer

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Summary

The relationship between chronic pancreatitis (CP) and other pancreatic diseases, such as acute pancreatitis (AP) and pancreatic cancer (PK), remains a fairly debated question. The progression from alcoholic AP to CP is controversial, and some long-term epidemiological studies suggest that alcoholic CP might be the result of recurrent alcoholic AP (necrosis-fibrosis sequence) and a subgroup of alcoholics may present recurrent AP without progression to CP. Other predisposing factors (genetic, nutritional, environmental) seems to be important in inducing different outcomes of pancreatic damage due to alcohol. However, recurrent episodes of AP are clearly involved in pathophysiology of CP in patients with hereditary pancreatitis. A relationship between CP and subsequent PK development has long been suspected, but we actually don't know whether this association is direct or is the result of confounding factors, such as alcohol intake or cigarette smoking. Many issues should be considered as indicators of a causal association, and several of them are not fulfilled Nonetheless, epidemiological studies (case-control or cohort studies) showed that the risk of PK is increased in patients with CP; the risk is significantly higher in tropical calcifying CP and hereditary pancreatitis. Studies on growth factors, oncogenes, tumor-suppressor genes, and angiogenesis suggest that the sequence PC – KP is plausible from the biological standpoint.

Index terms: Chronic pancreatitis, acute pancreatitis, pancreatic cancer, hereditary pancreatitis, tropical pancreatitis, idiopathic pancreatitis.

Introduction

Though recent years have witnessed important development in the knowledge of the pathogenesis and natural history of chronic pancreatitis (1-10), many features still remain unclear. In particular, the relation of chronic pancreatitis (CP) to other pancreatic diseases, such as acute pancreatitis (AP) and pancreatic cancer (PK), is a fairly debated question. The aim of this article is to review the recent understanding on this topic.

Relation of chronic pancreatitis to acute pancreatitis

CP is not a single disease but a clinical syndrome due to various causes, resulting from severe fibrotic changes in the pancreas and evolving over a period of several years into end-stage disease (4, 5, 7). In clinical practice, first-onset AP as well as advanced CP can be diagnosed with a high accuracy. Between these two extremes, a precise classification of pancreatitis is quite difficult for various reasons, including the unavailability of routine means to assess histology, still considered the diagnostic gold standard of early stage (9). Over the last 40 years a major controversy has existed as to whether AP and CP are separate entities or a continuous spectrum of the same disease. Biliary pancreatitis virtually never progresses to CP (with the exception of patients who develop obstructive CP as a consequence of Oddi's sphincter pathology or residual scars of pancreatic ducts (11)), whereas the progression of alcoholic AP to CP is debated (12). With respect to natural history of CP, some important issues have to considered (9). Firstly, acute pancreatic necrosis occurs in only 10-12% of patients with CP (13) and only 5-10% of chronic alcoholics develop clinical AP, which suggests that

Riassunto

PANCREATITE CRONICA: RAPPORTO CON PANCREATITE ACUTA E CANCRO DEL PANCREAS

Il rapporto fra pancreatite cronica (PC) ed altre malattie pancreatiche, quali la pancreatite acuta (PA) ed il cancro del pancreas (PK), è a tutt'oggi oggetto di discussione. Rimane controversa la possibilità di progressione da PA alcolica a PC; alcuni studi epidemiologici a lungo termine suggeriscono che la PC alcolica potrebbe essere il risultato di attacchi ricorrenti di PA alcool-indotta (sequenza necrosi → fibrosi), laddove un sottogruppo di etilisti possono presentare PA ricorrenti senza mai manifestare segni e sintomi di una PC. Altri fattori predisponenti (genetici, nutrizionali, ambientali) sembrano essere importanti nell'indurre differenti evoluzioni del danno pancreatico alcool-correlato. D'altra parte, nei pazienti affetti da pancreatite ereditaria, episodi ricorrenti di

PA sono chiaramente implicati nel determinismo di un danno pancreatico cronico. Da molto tempo è stato postulato un rapporto fra una condizione preesistente di PC e il successivo sviluppo di un PK, ma allo stato attuale noi non sappiamo se questa associazione è diretta o è il risultato di fattori confondenti quali l'assunzione etilica o il fumo di sigaretta. Nel definire una stretta associazione causale vi è necessità che molti parametri vengano soddisfatti, e tutto ciò non è verificato nella interrelazione PC-PK. Ciò nondimeno, diversi studi epidemiologici (caso-controllo o di coorte) hanno mostrato che il rischio di PK è aumentato nei pazienti con PC, essendo significativamente in incremento nella PC calcifica tropicale e nella pancreatite ereditaria. Dal punto di vista biologico, studi recenti sui fattori di crescita, sugli oncogeni, sui geni tumor-suppressor e sulla angiogenesi suggeriscono che la sequenza PC → PK appare plausibile.
Parole chiave: Pancreatite cronica, pancreatite acuta, tumore del pancreas, pancreatite ereditaria, pancreatite tropicale, pancreatite idiopatica.

other predisposing factors (e.g., genetic, nutritional, environmental) are important in inducing alcoholic AP, which may then progress to CP. Secondly, there is evidence that the progression of acute to CP in alcoholics is closely related to the incidence and severity of acute attack. Amman and Muellhaupt (14) reported in a prospective long-term (30 years) study a yearly incidence of acute attacks significantly higher in alcoholic calcific and non-calcific CP than alcoholic "non-progressive" CP. The latter group of patients showed a lower disease severity, as expressed by the number of total and cephalic pseudocysts. These findings together with other morphological features coming from a long-term studies of the same authors (12, 15) strongly suggest that a) alcoholic CP might be the result of recurrent alcoholic AP (*necrosis-fibrosis* hypothesis (4)), and b) a subgroup of alcoholics may present recurrent AP without progression to CP; in other words, alcoholic AP does exist as a *distinct* nosological entity (15, 16) – Figure 1 –. The so-called "necrosis-fibrosis" sequence is based on the concept that severe alcoholic AP is associated with necrosis around and within the pancreas and subsequent postnecrotic "bridging" fibrosis which may distort the pancreatic duct system and lead to inflammation spreading and acinar destruction (4).

With respect to the relationship "alcoholism – AP – CP", other pathogenetic mechanisms have been advocated (2, 5, 16-18). Briefly, these are: 1) abnormalities of lithostatine function with the formation of protein precipitates and calculi in the ducts, leading to duct obstruction; 2) a primary role for acinar cell dysfunction as a result of alcohol toxicity; 3) an oxidative stress mechanism; and 4) a primary role for ductal stenosis, independent of the etiology of the disease. It should be noted that all these mechanisms are not mutually exclusive and could contribute to an episode of AP that triggers off the necrosis-fibrosis sequence (19).

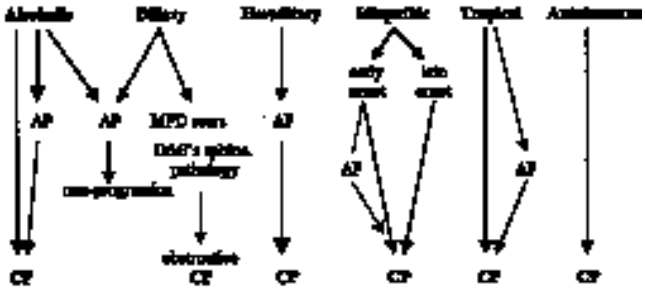

Fig. 1: relationship between acute pancreatitis (AP) and chronic pancreatitis (CP) with respect of the prominent etiological categories. Solid arrows indicate typical evolution (or non-progression); broken arrows indicate debated or unknown evolution; MPD = main pancreatic duct.

Other opinions contrast with the "autonomy" of alcoholic AP (2, 6, 17) and postulate that clinical acute episodes occur regularly on the basis of pre-existent (clinically latent) CP, but this statement has not been substantiated by unequivocal (morphological and evolutive) findings (12).

New insights into relation between CP and AP has recently derived from the studies on hereditary pancreatitis (20). Surgical biopsies of chronic hereditary pancreatitis are indistinguishable from alcoholic CP; since there is only one gene mutation in this autosomal dominant disease, and since the key gene is trypsinogen, the CP in these families with hereditary pancreatitis almost certainly arises from recurrent AP (8). The mutant gene is cationic trypsinogen and unbalanced activation of trypsin within the acinar cells plays a central role in the pathophysiology of chronic hereditary pancreatitis. Recurrent clinical episodes of AP as well as frequent episodes of localised pancreatitis involving a limited number of lobules (that falls below the threshold of the clinically accepted criteria of typical pain and significantly elevated serum pancreatic enzyme levels) develop during the patient's life and finally lead to overt CP. This does not exclude the importance of ductal pathology, with stenosis and/or protein plugs precipitation, in disease progression. So, hereditary pancreatitis could represent a good strict relationship model between CP and AP.

Relation of chronic pancreatitis to pancreatic cancer

Little is known of the etiology of exocrine PK and, over the past years, many epidemiologic studies have been performed to detect specific risk factors. Occupational and chemical exposure, dietary factors, diabetes, and smoking have been considered, but, except for the latter, there was only weak evidence of the importance of these risk factors (21-27). A relationship between CP and subsequent cancer development has long been suspected (23-26, 31, 35-37) and this relation is of considerable interest. If patients with CP are at increased risk for KP, is it because CP predisposes to PK or do both conditions share common etiologies?. A number of problems are involved

in exploring this relationship. One important problem is to determine whether this association is direct or is a result of confounding, i.e., is due to another factor that is related both to PC and to PK. For example, it would be appropriate to investigate whether the relationship between alcoholic PC and PK is due to a direct carcinogenetic effect of CP or whether there are other factors, such as alcohol or cigarette smoking (CP patients are usually heavy smokers), that may be related to the occurrence of PK. Alcohol abuse *per se* may influence the risk of PK and heavy alcohol intake may be a risk factor (38). Other issues are indicators of the likelihood of a causal association between CP and PK and should be carefully considered (Tab. I). In addition, results of autoptic studies in patients who die from PK and who present at same time histologic features of CP should not be contemplated as proof of causal association because in most cases CP is secondary to obstructive changes from the cancer itself (22).

From the biological standpoint, is the association between CP and PK or the sequence PC → KP plausible? – Figure 2 –. Molecular analysis on an mRNA level revealed an increased expression of growth factors (such as transforming growth factors α and β, fibroblast growth factor, epidermal growth factor) in pancreatic tissue of CP,

Tab. I – RELATIONSHIP BETWEEN CHRONIC PANCREATITIS (CP) AND PANCREATIC CANCER (KP): INDICATORS OF A CASUAL ASSOCIATION

Indicators of a causal association	*comment*
Strength of the association	expressed by the magnitude of the relative risk; in one study (23) the cumulative risk of PK at 10 and 20 years after the diagnosis of PC was 1.8 and 4.0, respectively (see text)
Temporal relationship	exposure must precede the onset of the disease; satisfied in most studies
Specificity of the association	not satisfied; extrapancreatic carcinomas (respiratory and upper gastrointestinal tract) have been reported in CP with varying incidence, reaching from 3.9% to 12.5% (ref # 6, 17, 29-31); risk ascribed to the increased consumption of tobacco and alcohol
Relationship demonstrated in more than one study	reproducibility of the association: satisfied; ref # 23-26
Association biologically plausible	satisfied; involvement in both diseases of oncogenes, tumor suppressor genes, growth factors; hyperplasia → dysplasia sequence plausible

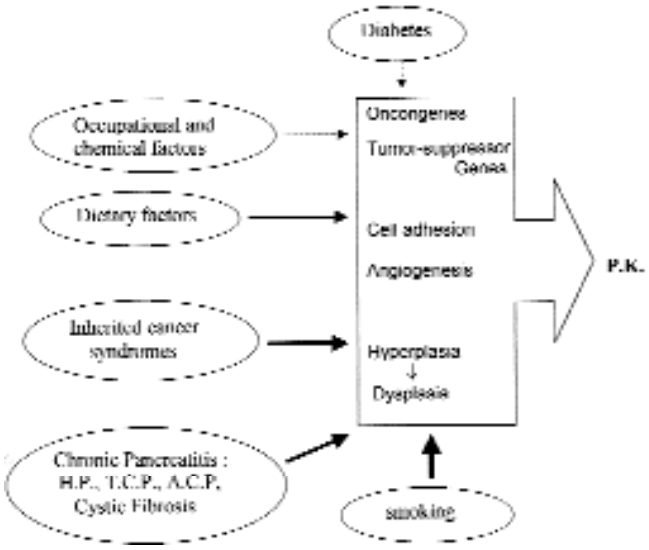

Fig. 2: etiological spectrum of pancreatic cancer (PK); H.P. = hereditary pancreatitis; T.C.P. = tropical calcifying pancreatitis; A.C.P. = alcoholic chronic pancreatitis.

which are known to be over-expressed in PK (39, 40). Extracellular-matrix molecules as well as c-erb-B-2 oncogene are frequently over-expressed both in PK and CP (41). All these findings suggest a dysregulation of a number of genes in CP, resulting in altered mRNA levels, over-expression of growth factors and their receptors, which may be responsible of the onset of the hyperplasia → dysplasia sequence (42). In addition, enhanced angiogenesis and over-expression of vascular endothelial growth factor were recently described both in CP and KP (43). A hyperplasia → dysplasia → carcinoma sequence seems to be likely, as it is now generally accepted that pancreatic carcinogenesis is a multistep process, including activation of protooncogene(s) and inactivation of tumor-suppressor genes (39, 44).

There are some problems with epidemiological data which are based on retrospective studies on registered information, particularly owing to the small number of cases examined, the lack of appropriate control groups, and the apparent difficulties in distinguishing a primary from secondary (obstructive) CP (21). In several case-control studies, CP has been linked to PK (1, 26, 32-35) with a population attributable risk ranging from 1.5% to 5% of PK cases. In the study of Fernandez et al. (26) adjustment for the major recognised risk factor for PK (tobacco smoking) and for CP (alcohol drinking) was performed: the association CP – PK was somewhat reduced after allowance for these factors and partly explained by such covariates (relative risk = 3.9). But, this may present some degree of over-adjustment if, for instance, alcohol is causally linked to CP, which in turn is causally related to PK.

Two large cohort studies (23, 37) faced the question of possible increased risk of KP in patients with CP (one study [37] is the expansion of a previous cohort study of

the same group [36]). Lowenfels et al. (23) have published the results of a multicenter historical cohort study of 2015 patients with CP recruited from clinical centers in six countries (Denmark, Germany, Italy, Sweden, Switzerland, USA), showing that the risk of PK was significantly increased. Restricting the analysis to the subjects with a minimum of 5 years of follow up, the standardised incidence ratio was 14.4 (95% confidence interval [C.I.], 8.5 - 22.8). In the Cox proportional hazards model, only increasing age at the diagnosis of CP was a significant predictor of subsequent development of PK; compared to the subjects less than 40 years old, the risk ratio was 3.1 (95% C.I., 1.1 – 8.6) and 9.7 (95% C.I., 2.7 - 35.1) for middle-aged and older subjects, respectively. The risk of developing cancer after CP was unrelated to type of pancreatitis (approximately 75% of CP were considered to be alcoholic in type) and was the same for males as for females. The cumulative risk of PK increased steadily over time: at 10 years the overall risk was 1.8% (95% C.I., 1.0 – 2.6) and at 20 years had increased to 4.0% (95% C.I., 2.0 – 5.0). Karlson et al. (37) have reported the results of a prospective large size population-based cohort study including 29350 patients with a discharge diagnosis of pancreatitis from 1965 to 1983 in the Swedish Inpatient Register. Various sub-cohorts were identified: a) patients with one episode of unspecified pancreatitis; b) patients with one episode of AP; c) patients with recurrent pancreatitis; d) patients with CP (n = 7328). After exclusion of cancer occurring in the first year, there were excess risks for PK in all sub-cohorts; although patients with unspecified or CP had a sevenfold increased risk, the excess was mainly confined to the early years and receded to twofold after a decade of follow up. This finding is in accordance with the results of Bansal et al. (25), but clearly in contrast with the results reported by Lowenfels et al. (23). A persistent excess risk for PK after 10 years was restricted to patients associated alcohol abuse (standardised incidence ratio 3.8; 95% C.I., 1.5 – 7.9). The authors concluded that CP is not causally associated with a long-term risk of PK and alcohol consumption and smoking contribute to some of the patterns of risk observed (37).

An increased risk of KP was also reported in some more rare forms of CP. In tropical calcifying pancreatitis a fivefold relative risk was observed (24). With respect of hereditary pancreatitis, an international epidemiological study (45) showed a striking increased risk of PK with an estimated risk to 70 years age of 40%. A paternal inheritance pattern increases the probability of developing KP to approximately 75% at age of 70 years. Since hereditary pancreatitis is not caused by an altered oncogene or tumor-suppressor gene, the current interpretation is that the high risk of PK reflects the *long duration of* CP and may be therefore an extension of increased cancer risk in patients with CP from other causes. Increased mutation rate of cystic fibrosis transmembrane conductance regulator (CFTR) gene was recently reported in 13% of CP (46) and in 37% of idiopathic pancreatitis (47). In patients with cystic fibrosis an excess of PK and intestinal cancers (without evidence of an increased risk of any other tumors) have been observed (31, 48). The differential risk of cancer in various organs may partly be explained by the level of CFTR expression and by varying sensitivities of individual organs. Another possible explanation (31) is that the excess risk of PK and intestinal cancer is related to the persistent malabsorption with deficiencies of the antioxidants selenium and vitamin E, which may offer some protection from cancer.

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