Chronic Pancreatitis: Relationship to Acute Pancreatitis and Pancreatic Cancer

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Relationship Between Chronic and Acute Pancreatitis

The aetiology of pancreatitis is still partly uncharted territory, and whether it originates in the acinar cells or from a disease of the pancreatic ducts continues to be a debatable issue [1]. For this reason, it still proves impossible to establish a definite relationship between acute (AP) and chronic pancreatitis (CP), in that the basic question as to whether or not these are two distinct diseases in physiopathological terms has still to be answered. In recent years, however, substantial progress has been made and important insights have been gained, particularly with regard to certain types of pancreatitis.

Taking clinical observations as our starting point in this review, we sometimes see that major acute exacerbation occurs in the course of CP taking the form of severe AP. In a very limited number of cases, moreover, CP manifests itself initially as a severe episode of AP. It has long been recognized that severe acute exacerbation is part of the clinical picture of CP [2]. In our experience, roughly 18% (153/853 cases) of CP sufferers have experienced an episode of severe acute pancreatitis in the course of the disease; fewer than half of these patients (70/853 = 8.2%) experienced such episodes at the onset of CP. Only 8 (9%) of the patients with severe AP at the onset of CP were easily identifiable as chronic cases, presenting, for instance, intraductal calcifications. The real problem, then, arises when the episode of AP of non-

biliary origin occurs without any Wirsung duct abnormalities suggestive of CP. In this situation, even today, the correct diagnosis can often be achieved only as a result of follow-up of the patient.

In the literature, the relationship between an episode of AP and the existence of CP has been the subject of several studies over the years which have sought to postulate possible pathogenetic mechanisms.

The first hypothesis is that the AP episode, if associated with a high alcohol intake, is very often, in actual fact, the first manifestation of CP; as we have already said, the pancreas sometimes presents typical morphological characteristics such as Wirsung duct abnormalities or calcifications [3-5].

There is a second hypothesis. Whereas restoration of integrity is the norm in cases of edematous AP [6], healing in necrotizing AP may be imperfect with the formation of scars which give rise to stenosis, for example, of the main duct, thus causing obstructive-type CP. This may also occur in the case of formation of pseudocysts, more often in the head of the pancreas [7], due to AP and Wirsung duct rupture [8, 9]. If the stenosis of the main duct is in the head, then, of course, most of the pancreatic ducts will be affected by the obstruction. Sometimes the obstruction is in the body of the gland, with the result that distinct abnormalities of the main duct are observed in the body and tail, whereas the head portion presents normal morphological characteristics. Sarles *et al.* believe that the only way that AP can progress to CP is essentially via fibrotic-cicatricial stenosis of

the ducts which may occur as a result of the acute episode [10]. In effect, evidence has been found to show that AP does not always heal without abnormalities of the main duct, though the latter usually tend to be fairly mild in nature [11, 12]. In the past it often happened that the obstructive origin of chronic pancreatitis with involvement of Wirsung's duct was neither recognized nor treated; in such cases, with the passing of time and the subsequent occurrence of lesions, the endoscopic retrograde cholangiopancreatography findings revealed morphological changes progressing from a state of homogeneous dilatation of the duct above the stenosis to major irregularities with calcifications [13], and ultimately leading, after many years of disease, to a condition which can hardly be distinguished from CP of non-obstructive origin. There is no doubt that alcohol may have an impact on this process; in experiments in mongrel dogs, alcohol intake in the presence of Wirsung duct obstruction aggravated what would otherwise have been a mild CP [14].

A third possibility is that repeated episodes of AP may lead to CP [15]. Support is lent to this hypothesis above all by morphological studies conducted by Klöppel who believes that the changes occurring in CP stem initially from an AP according to a necrosis-fibrosis sequence. As he sees it, AP characterised by peripancreatic necrosis does not develop into CP, whereas intrapancreatic necrosis may cause perilobular fibrosis and interlobular duct distortion with resulting stenosis of the ducts and a classic picture of CP [16, 17]; the stenosis is then thought to be responsible for the difficult outflow of pancreatic secretions with protein precipitation and subsequent calcification. This hypothesis is at variance with that of the 1963 Marseilles classification in which AP and CP are two distinct entities caused by different aetiological factors and in which it is postulated that the lesion responsible for CP originates within the pancreatic duct [1, 2 ,10].

Other possible pathogenetic mechanisms, however, may be involved. In rats, for instance, the role of ischaemia induced by microvascular hyperfusion in AP would appear to be associated with the subsequent development of anatomico-pathological abnormalities characteristic of CP [18].

A major contribution to explaining the relationship between AP and CP has recently been made by the discovery that genetic abnormalities underlie some forms of pancreatitis. In particular, in hereditary pancreatitis, an autosomal dominant disease, mutations have been identified in the trypsinogen gene: this makes prematurely activated trypsin resistant to inactivation through autolysis [19]. Hereditary pancreatitis is characterised by repeated attacks of AP which set in mainly in infancy [20], but also at a later age, and then go on to develop into CP characterized by the usual picture of calcifications, ductal distortion, fibrosis, exocrine pancreatic insufficiency and diabetes [21-24]. Hereditary pancreatitis appears to represent a practically ideal model of how several episodes of AP can lead to CP. Perhaps in non-hereditary AP, too, one of the first steps in the development of CP is activation of trypsinogen at the intrapancreatic level [25]. According to Whitcomb, the comparison between hereditary and non-hereditary AP can be further extended by postulating the following process: an initial episode of what he calls "sentinel" AP attracts monocytes to the pancreas which become resident macrophages. These, in turn, cause infiltration, differentiation and/or proliferation of pancreatic stellate cells; these latter cells produce collagen if stimulated by transforming growth factor beta (TGF-beta) produced by the macrophages in response to inflammation. At this point, deposition of collagen leads to fibrosis and ultimately to CP [25].

As far as the aetiology of AP is concerned, cases of biliary origin would not appear to progress to CP, unless obstruction (Oddi's sphincter or Wirsung duct stenosis) is present [26], whereas, despite the considerations outlined here above, AP in alcohol abusers sometimes does not develop into CP [5, 27]. If the AP is associated with alcohol abuse, the patient may, for psychological reasons due to the severity of the acute episode, stop

drinking and sometimes even stop smoking, as observed also in our experience [5]. Abstaining from alcohol in a very early phase of CP may possibly modify the course of the disease; arrest of the progression of pancreatographically detected main duct abnormalities has, in fact, recently been documented after abstaining from alcohol in patients with a suspected initial CP [28]. In addition, it should be stressed that in most studies no account has been taken of cigarette smoking, which would appear to play a more important role than was previously believed in the pathogenesis [29] and evolution [30] of CP; In our own series, in fact, it is fairly rare for a non-smoker to develop CP [31].

Therefore, despite the difficulty of access to the pancreas for experimental observations in man and the shortage of animal models, we can conclude that an association exists between these two pancreatic diseases, though there may be different physiopathological explanations of this link, involving, in all probability, several pathogenetic mechanisms.

Relationship Between Chronic Pancreatitis and Pancreatic Cancer

Pancreatic cancer as a cause of chronic pancreatitis

It should be stressed right from the outset that pancreatic cancer is capable of causing obstruction of the ducts giving rise to secondary CP which is well documented in anatomico-pathological terms [32-34]. The presenting symptoms of pancreatic cancer at the onset may mimic those of CP [35] and it is for this reason that, in all studies investigating the risk of pancreatic cancer in the course of CP, those cases in which pancreatic cancer was diagnosed shortly after a diagnosis of CP have always been excluded [36-39]. In actual fact, the association between pancreatic cancer and CP is relatively rare, estimates indicating that only approximately 5% of all pancreatic cancer arise in patients who have been suffering from CP for lengthy periods [36, 38, 40].

In our experience, pancreatic cancer may have been misdiagnosed in approximately 1% of our CP diagnoses [41]. This means that approximately one-third of all pancreatic cancer diagnoses after a diagnosis of CP are likely to be late diagnoses of tumour.

Furthermore, not only pancreatic cancer, but also pancreatic intraductal tumours may manifest with symptoms and, even more importantly, imaging appearances which are fairly similar to, and can easily be mistaken for those of CP. In particular, if the intraductal tumour affects the ducts of the head of the pancreas, a picture of chronic obstructive pancreatitis above the tumour is possible, due to, amongst other things, the high viscosity of the pancreatic secretions; if such tumours are not detected and treated, they are likely to degenerate into invasive cancer [42-44].

Chronic pancreatitis as a cause of pancreatic cancer

In many diseases characterised by chronic inflammation (e.g. chronic gastritis, ulcerative rectocolitis, Crohn's disease, Barrett's oesophagus, etc.), there is an increased risk of cancer of the organ affected. The cause is most probably related to the increased cell turnover and/or damage to the genome induced by the inflammation [45]. This would also appear to be true of CP, which various studies have now shown to be associated with an increased risk of pancreatic cancer.

The first report of an increased incidence of pancreatic cancer in the course of CP was by Rocca *et al.* in 1987 [46]. After a debate lasting several years, the present estimate of the risk in the Western population is based on the multicenter study by Lowenfels *et al.* [38]: approximately 4% of patients with CP develop pancreatic cancer within 20 years of the onset of the disease, i.e. at a rate which is 15- to 16-fold greater than that of the general population. As far as the Italian population is concerned, the estimated increased risk is approximately 13.3-fold greater than that of the general population [39]. In all the cohort studies conducted to date [39, 46-53], this finding has invariably been confirmed with fairly similar values ranging from a minimum of 0.8% as reported by Levy *et al.* [49] to the 8.3% figure reported by Augustine *et al.* [50].

Studies of the case-control type, despite being far less reliable in this field owing to the greater number of sources of potential bias they are subject to, have substantially confirmed this association [36, 40]; the studies by Ekbom *et al.* [37] and the subsequent extension by Karlson *et al*. [54], present quite different values [55]. In the more recent of the two studies, in fact, early detection of pancreatic cancer is frequent (Standardized Incidence Ratio 22.2; Confidence Interval 16.2-29.6), whereas there appears to be little or no increase 10 years after diagnosis of CP (Standardised Incidence Ratio 2.2; Confidence Interval 0.9-4.4).

The aetiology of CP is a factor conditioning the risk of pancreatic cancer. In tropical-type CP, whose pathogenesis is still undefined but is probably related to undernutrition, the risk of pancreatic cancer is much higher, affecting 8.3% of patients [50] with a roughly 100-fold increased incidence compared to the general population [53]. In this latter study, the incidence is still very high even when excluding patients with no histological diagnosis of pancreatic cancer. In hereditary CP the risk is exceptionally high: approximately 40% of patients develop pancreatic cancer by 70 years of age [56]. This finding is probably accounted for by the early age of onset of hereditary CP, which gives rise to a lengthy duration of the disease and to a proportional increase in the risk of neoplastic degeneration.

Up until only a few years ago, cystic fibrosis, an autosomal recessive disease which has recently been shown to be associated with CP [57, 58], offered only a short life expectancy. In recent years, as a result of improvements in knowledge of the disease and in therapeutic methods, the life expectancy has risen considerably and may now be as much as 50 years in subjects with limited manifestations of the disease. An increased risk of pancreatic cancer has also been found in cystic fibrosis [59, 60]. Since no increase has been observed in extrapancreatic tumours, the risk must be regarded as organ-specific.

Western-type CP is associated with alcohol intake in 75% of the cases. In those cases where smoking data are reported, a strong association with cigarette smoking has also been noted as a risk factor for the development of the disease [29, 61-63]. In our region of Italy, approximately 90% of CP cases are heavy smokers and 80% of cases are both heavy smokers and drinkers, whereas combined smoking and drinking is present in no more than 16% of the general male population [31]. Among the various risk factors for pancreatic cancer, the only major factor, apart from black race [64] and exposure to certain chemicals [65, 66], is cigarette smoking; alcohol, in fact, is not a risk factor for pancreatic cancer in the vast majority of studies conducted [65, 67, 68]. Since both smoking and inflammation can cause the onset of pancreatic cancer various studies have failed to assess their relative incidence [36-38, 56]. Assessing simultaneously the smoking habits of the general population and of patients with pancreatic cancer and CP from the same geographical area in comparable years, we evaluated the risk of pancreatic cancer associated with smoking alone: approximately one-third of all tumours arising in the course of CP are attributable to cigarette smoking, whereas the remaining two-thirds are due to other factors such as chronic inflammation or to other factors operating in combination with smoking [69]. The cancer risk, on the other hand, would appear to be low and comparable to that of the general population in non-smokers and ex-smokers; none of the 82 CP patients who stopped smoking after onset of CP has yet developed a cancer after 12 years of follow-up [39]. It may be important to advise CP patients, particularly those who are still fairly young, to stop smoking, since this may have a major preventive impact, though our findings are as yet insufficient to allow any precise quantitative assessment of the benefit it affords.

Genetics; Incidence; Neoplasms; Risk Factors; Smoking

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