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Editorial

Comments on Acute Pancreatitis' Progression Hypotheses to Chronic Pancreatitis

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Dear Editor,

From our experience and several research studies, acute pancreatitis (AP) progression to chronic pancreatitis (CP) is a complex issue in the medical field. The progression was hypothesized many years ago but still, many controversies are not clarified in the present literature.

CP is a well-known invaliding disease that causes a sensitive decrease in life expectancy. This pathology is associated with several genetic alterations that can provoke morphological abnormalities.[1]

On the other hand, AP is a syndrome (and it must be considered more a systemic than confined pathology) caused by the release of pancreatic enzymes into the bloodstream and subsequent activation of systemic inflammatory systems (as complements).[2]

The two pathologies were correctly identified by Marseilles classification in 1963-1984.[3] Recently, numerous articles suggested the progression from AP to CP. Two main theories followed this progression. Amman et al[4] with the necrosis-fibrosis hypothesis and Whitcomb[5] with the sentinel AP event. Several pathological mechanisms (such as repeated inflammations of the gland, and loss of functional tissue due to necrosis) were proposed to explain the eventual progression from AP to CP. Nonetheless, this progression hypothesis from AP to CP seems based more on superficial considerations than solid evidence.

Hegyi et al[6] reported early chronic pancreatitis onset after a few acute pancreatitis episodes. The authors displayed a significant AP and CP association after three episodes. In their group, called RAP-3, the biliary etiology decreased up to 9.3% compared with the previous group (24.9%), and that demonstrates how other risk factors—alcohol and smoking, generally recognized as main risk factors for CP, became more influential. The alcoholic etiology distribution moved from 19.4% in AP to 51.6% in CP, confirming that data.

Another weak point is considering the CP only in the presence of morphological changes. The pathology starts to damage the gland because of genetic alterations, so morphological changes appear years after the trigger event.

Multiple studies quoted in the Hegyi et al[6] research indicated that CP was already established by the time of the alcoholic pancreatitis first attack and not the result of previous AP.

Hori et al[7] described the association of CP with prior acute pancreatitis in 50% of cases. Interestingly, the authors did not find significant differences in comparing patients with or without AP preceding CP. The differences were a higher prevalence of diabetes, less pain, higher rates of diarrhea, and weight loss. Older age suggests that CP started many years before without clinical symptoms. To confirm the non-progression, patients with a diagnosis of idiopathic recurrent AP subsequently receive the diagnosis of CP.

Ahmed Ali et al[8] studied the association between CP and recurrent AP. The authors evidenced how CP was diagnosed within the first three months of the primary AP in 12% of patients; that finding suggests that AP was the first onset of existing CP. Furthermore, risk factors for progression to CP were identified in alcoholic etiology and smoking; whenever these two factors coexist, the cumulative risk increased by up to 30%. Once again, all these conditions are associated with CP, not AP.

Sankaran et al[9] performed a meta-analysis on the frequency of progression from AP to CP. Ten percent of patients with AP and 36% of patients with recurrent AP developed CP. The main risk factors identified were smoking, alcoholic abuse, and male sex. All these findings align with the previous studies and did not evi-

dence any actual progression to CP because recurrent AP can be easily confused with CP's relapses. The risk factors are, once again, the ones of CP. Male gender—as discussed in the study—is associated with genetics, especially with *CLDN2* mutations.

One exciting datum presented is the development of CP from biliary etiology. However, the low pooled prevalence (9%) with 88% of statistical heterogeneity between the studies cannot lead to any conclusion.

Beyer et al[10] elucidated that CP differs from other inflammatory pancreas diseases. In AP and recurrent AP, the organ fully recovered. Even if pancreatic insufficiency developed after necrotizing AP, other CP features are missing. A very variable percentage of patients (3-35%) with a first episode of AP progressed to CP, and this finding was related mainly to genetic factors in the paper.

Thinking more about pathophysiological mechanisms than morphological features of CP is crucial to understanding the differences with AP. It has been confirmed also in experimental models of chronic pancreatitis.[11]

Protease-dependent, endoplasmic reticulum stress-related, ductal dysfunction-related mechanisms are typical of CP and related to glandular pathology. The metabolomics approach to pancreatic pathologies is a direct derivation of considering pathological mechanisms and will help to distinguish better between these pathological identities.[12]

Machicado et al[13] analyzed similarities and differences in the epidemiology of AP and CP. Two to six percent of patients were reported to develop CP after the first episode of biliary pancreatitis. The authors concluded that AP is not related to the presence of gallstones but to other unappreciated causes in this setting. On the other hand, the risk of disease progression was linked to the continuation of drinking and smoking habits.

In conclusion, the progression theories from AP to CP have weak and dated evidence. The genetic alterations play a crucial role in developing CP pathophysiological mechanisms, and AP episodes should be considered as the clinical onset of CP in this patient setting.

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