



## Commentary

## Shedding light on painless chronic pancreatitis



Chronic pancreatitis (CP) is characterized by a progressive inflammation leading to atrophy, fibrosis, calcification and ductal strictures of the pancreas. A long-lasting CP will result in exocrine and endocrine insufficiency. Well-known etiological risk factors comprise nutritive/toxic, genetic, environmental and autoimmune causes [1].

Classically, abdominal pain is prevalent in 60–94% of patients suffering from CP [2]. In contrast, exocrine or endocrine insufficiency occurs only in 10–33% of patients at diagnosis of the disease [3]. However, the mechanism of pain in CP is poorly understood. It is hypothesized that the repetitive inflammation of the pancreas will result in a release of inflammatory molecules of damaged cells. As a consequence, these molecules will activate mast cells and platelets leading to a transmission of nociceptive signals from the dorsal root ganglia to the cerebral pain centers via the spinal cord [4]. Interestingly, different pain pattern types ranging from intermittent mild pain to constant severe pain were described in CP patients. In this regard it seems comprehensible that CP patients with recurrent episodes of an acute pancreatitis will suffer from episodic acute abdominal pain. Moreover, patients with a ductal pancreatic obstruction, induced by ductal stones and/or strictures that lead to an increased pressure of the pancreatic duct, complain about constant pain accompanied by episodes of acute pain exacerbation. That also applies for structural complications such as inflammatory masses or pseudocysts [5]. However, a few patients suffer from constant pain in the absence of structural abnormalities or inflammation indicating a subgroup of neuropathic pain individuals. In addition, some patients with long-lasting CP will resolve pain as a consequence of pancreatic atrophy as a final condition of the disease. An observational study reported that 57% of patients were free of pain after a 5-year-follow-up [6].

The above mentioned different patterns and courses of pain in CP may, at least in part, explain the often disappointing results of endoscopic or even surgical interventions in the treatment of CP-induced pain [7]. Interestingly, there is another subgroup of patients with CP who never complained of any pain. Characteristics and mechanisms of this so-called painless chronic pancreatitis (PCP) have not been elucidated in a large cohort so far. Maimon et al. firstly described 3 patients with PCP in 1948 [8]. In all of the published case series steatorrhea and weight loss were the main reported symptoms. In addition, PCP was more frequently observed in elderly individuals with a late-onset of the disease [9,10]. However, pathophysiology and consequences of PCP, in particular in elderly people, are poorly understood.

Therefore, the study by Amodio et al. [11] published in this issue of the journal aimed to shed more light to the clinical implication of PCP in daily practice. They analyzed more than 700 patients with CP between 2010 and 2016. The minority (9.5%) revealed a PCP. As suggested by previous works, mean age of patients was about 60 years and exocrine pancreatic insufficiency was the most frequent reported symptom. Interestingly, although nearly all patients showed calcifications and/or pancreatic alterations, about half of the patients did not report any symptoms. The diagnosis was an incidental finding in these patients. Only one patient developed a course of acute pancreatitis with pain in a mean follow-up of nearly three years.

So, what could we learn from this study? Obviously, PCP is a subgroup of idiopathic CP and thus is not related to alcohol or nicotine consumption. Moreover, patients with autoimmune pancreatitis were excluded from this study. Genetic mutations were infrequently tested; a hereditary form of CP cannot be excluded. However, the cause for the development of PCP remains unresolved in the majority of patients. There are various etiopathogenic hypotheses of PCP. Many PCP patients have coronary heart disease and atheriopathy that could impact on pancreatic pathology [12]. In this regard, most patients are elderly and nearly half of them did not suffer from any symptoms. Thus, PCP could be more related to a painless pancreatic failure than an inflammation. The main complaints in symptomatic patients in this study were related to exocrine and endocrine insufficiency and support this assumption. So, one could argue that the diagnosis of PCP in elderly patients is often a consequence of aging and does not necessarily reflect a pathologic condition or require medical thoughtfulness. Although this study by Amodio et al. [11] addressed PCP in a large cohort, several issues were not analyzed or could be biased. First, this is a retrospective study and there is by the nature of this study an uncertainty of reliability and completeness of data. In addition, the follow-up time is insufficient to evaluate PCP as possible risk for the development of pancreatic cancer. This issue cannot be neglected as CP is the main risk factor for pancreatic cancer [13,14]. Furthermore, the diagnostic criteria to characterize a chronic pancreatitis are far from being widely accepted and reliable. The sensitivity of CT, MRI or endoscopic ultrasound in the diagnosis of CP ranges between 66% and 89% [4]. Thus, in particular in asymptomatic patients, the distinction between a CP and a “physiological” senile evolution towards pancreatic atrophy can be challenging. In addition, it is important to distinguish a CP from cystic neoplasms of the pancreas, e.g. intraductal papillary mucinous

neoplasia (IPMNs), especially the main-duct and the mixed-type IPMNs.

In conclusion, the study by Amodio et al. [11] highlighted the clinical presentation of patients with PCP in the largest published cohort thus far. The majority of these elderly patients were asymptomatic or suffering from endocrine or exocrine pancreatic insufficiency. However, evidence is still lacking regarding the pathophysiologic mechanisms, clinical consequence and risk of development of pancreatic cancer. Actually, the significance of PCP remains unclear and warrants further research.

Marcus Hollenbach\*

*Division of Gastroenterology, Medical Department II – Oncology, Gastroenterology, Hepatology, Pulmonology, Infectious Diseases, University of Leipzig Medical Center, Leipzig, Germany*

Luca Barresi

*Endoscopy Service, Department of Diagnostic and Therapeutic Services, Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IRCCS - ISMETT), Palermo, Italy*

\*Corresponding author.

E-mail address: [marcus.hollenbach@medizin.uni-leipzig.de](mailto:marcus.hollenbach@medizin.uni-leipzig.de) (M. Hollenbach)

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