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Review Article

Pancreatic cancer as a complication of chronic pancreatitis – diagnostic approach

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Abstract: Patients with underlying chronic pancreatitis (CP) are at increased risk of pancreatic cancer (PC) development. The pathogenesis of the neoplastic transformation remains unclear. However, chronic inflammation, pancreatic stellate cells over-proliferation and genetic alterations play a major role in carcinogenesis progression. Early diagnosis and differentiation between benign and malignant disease is of a great importance. Better understanding the connection of the two entities could provide new therapeutic options.

Keywords: chronic pancreatitis, pancreatic cancer, computed tomography, MRI

Introduction:

Chronic pancreatitis (CP) is a progressive inflammatory disease that causes replacement of normal parenchyma with fibrotic tissue. The process leads to irreversible anatomical changes and damage with destruction of the structure of the gland. The reported European prevalence of CP is 120 / 100.000 people. Many studies demonstrate a significant association between CP and the development of the very aggressive and with poor prognosis pancreatic cancer (PC). Environmental and genetic factors might together contribute to cell transformation and degradation. According to recent analysis, PC incidence and death rates in both men and women are increasing. Patients with CP have a markedly increased with 2.3 to 18.5-fold risk of malignancy, which is higher in younger cancer cases (1-4).

Two forms of CP (tropical and hereditary pancreatitis) more often are complicated with PC. Tropical pancreatitis is often diagnosed in younger patients, leads to early pancreatic exocrine dysfunction. Hereditary pancreatitis is an autosomal dominant disease due to multiple PRSS1 mutation. This form of pancreatitis is characterized by onset in childhood and increases 53-fold the risk for PC. Furthermore, SPINK-1 mutations are observed in CP patients with PC progression. Diabetes mellitus secondary to CP is known as type 3c or pancreatogenic. Endocrine pancreatic insufficiency is a later CP manifestation, which is well-established PC risk factor (1-3).

A high proportion of CP patients are tobacco and alcohol users. Smoking is one of the best known risk factors for PC. Recent studies confirm the association between alcohol abuse as a contributing factor for PC development. Although the malignant transformation of CP to PC remains unclear, a molecular pathway with increased cell turnover and DNA damage due to inflammatory cytokines and reactive oxygen species could explain the tumorogenesis. One of these earliest occurrences is the activation of MMP-7 by the activated via chronic inflammatory processes trypsin. While K-ras mutations are demonstrated in ductal lesions with minimal atypia, suggesting an early involvement in carcinogenesis, p16 alterations are later events, which are observed more often in higher grade formations. Mutations in p53 further contribute to metaplasia and neoplastic degeneration (4, 5, 6).

Stellate cells activation predominantly by alcohol has an undoubtedly role in carcinogenesis. Interacting pancreatic stellate cells with cancer cells leads to desmoplastic reaction, which play a role in chemotherapy resistance, as well as to MMP-2 activation, which results in higher invasiveness and tumourigenicity. It is proposed that pancreatic stellate cells might further activate themselves in autocrine or paracrine way by producing growth factors and/ or cytokines (2, 7).

Differentiation between CP and PC in cases of head mass formation or early stage adenocarcinoma remains challenging. Tumor marker CA 19-9 is widely used in patients with head mass suspected for PC and is the only one serum biomarker for clinical use in respect to PC. Its sensitivity and specificity are circa 65% and 60%, which could reach 85.7 % and 96.5 % respectively, if CA 19-9 cut-off higher than 127 IU/ml is accepted. However, false positive results are observed in patients with jaundice, cirrhosis, CP and other gastrointestinal malignancies. In 2002 Maire et al. evaluated the role of KRAS2 mutations in codon 12 to distinguish between CP and PC. Due to the low sensitivity (47%) a combination of KRAS2 and CA 19-9 is recommended. In 2018 Mayerle et al. conducted a large study to estimate a tumour biomarker signature of 10 metabolites to differentiate CP from PC, including CA 19-9, Proline, Sphingomyelin (d18:2,C17:0), Phosphatidylcholine (C18:0,C22:6), Isocitrate, Sphinganine-1-phosphate (d18:0), Histidine, Pyruvate, Ceramide (d18:1,C24:0), Sphingomyelin (d17:1,C18:0). The main aim of this panel is to achieve higher accuracy and to find out patients in an early and respectable stage of PC. In this study the biomarker proposed panel had a specificity of 85% and a sensitivity of 94.9% and in addition could evaluate 98% of the resectable PC cases. The overall false positive results were 6% as jaundice did not lead to false positive results. PAM4 (Clivatuzumab) is a monoclonal antibody, which is observed in a vast majority of cases with PC (up to 90%), making it a possible biomarker for PC detection. miRNAs are other promising biomarkers for PC diagnosis (1, 2, 8, 9, 10).

Imaging techniques should provide information regarding PC, local tumor invasion, present metastases and further to follow-up the treatment. Transabdominal ultrasound (US) is a non-invasive, widely available and an acceptable screening

method. However, US has lower sensitivity as body and tail localization complicate the diagnosis of PC, and CP and neuroendocrine tumors are often difficult to distinguish. Multi-detector row computed tomography (MDCT) is the technique of choice for initial evaluation of suspected to have PC patients and in addition it provide best information regarding local invasion and vascular involvement. A typical PC image is a hypoattenuating mass, often cystic or necrotic (figure 2).

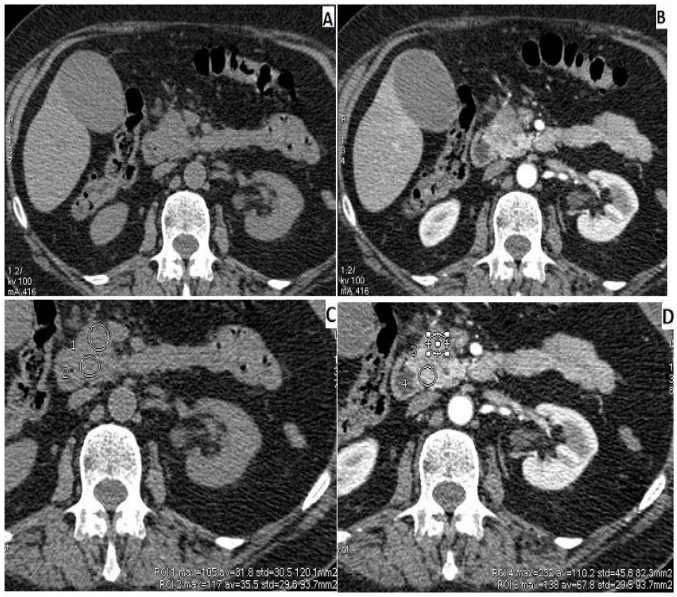

Figure 1 MDCT using dedicated pancreatic protocol. Tumor can`t be distinguished on non-contrast enhanced images (A and C), due to the similar density to pancreatic parenchyma. Carcinoma is best depicted on images in the pancreatic (late arterial) phase when the greatest difference between the densities of the tumor and normal pancreatic tissue is observed (B and D).

Magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) are currently widely used modalities as MRI provides better soft-tissue contrast than CT and MRCP is of a great importance for ducts visualization (figure 2). PC on MRI is often seen as hypointense on fat-suppressed, T1-weighted imaging and on pancreatic parenchymal phase, and dynamically enhanced, fat-suppressed, T1-weighted sequences. Secretin-enhanced MRCP becomes a flavored method as it allows not only morphological assessment of the pancreatic structure, but also a quantitative assessment of pancreatic exocrine function through semiquantitative assessment of duodenal filling with pancreatic juice at 10 minutes after secretin insertion (figure 3). The method is costly and is currently limited to large centers, where it is often used in combination with other tests. Endoscopic ultrasound (EUS) is of a great importance for small relatively curable lesions (< 3 cm) identification and is a modality of choice for histopathological study. Contrast-enhanced EUS and EUS elastography are new modalities with improved sensitivity and specificity, which gain growing interest. Despite its limitations (false positive results), PET/CT provides information regarding all possible metastases. Other recently introduced techniques are dual-energy CT; dynamic, contrast-enhanced-MR, DWI, and gadoxetic acid-enhanced liver MR for liver metastasis investigation, hybrid PET/MR (11-14).

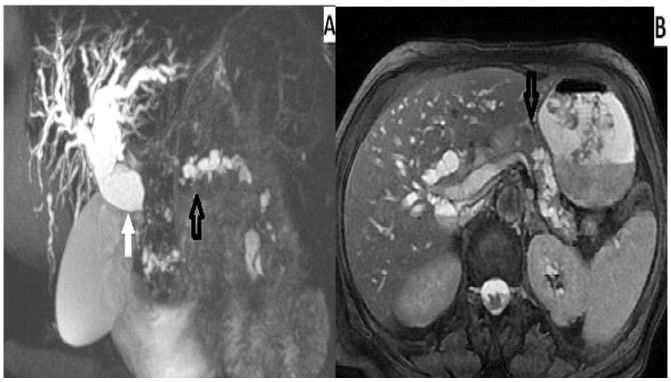

Figure 2. MRI in pancreatic cancer. A. MRCP: the tumor causes dilatation of the pancreatic duct (black arrow) and extrahepatic bile duct (white arrow), also known as double duct sign. B. T2 FIESTA with fat saturation: hypointence mass in pancreatic body.

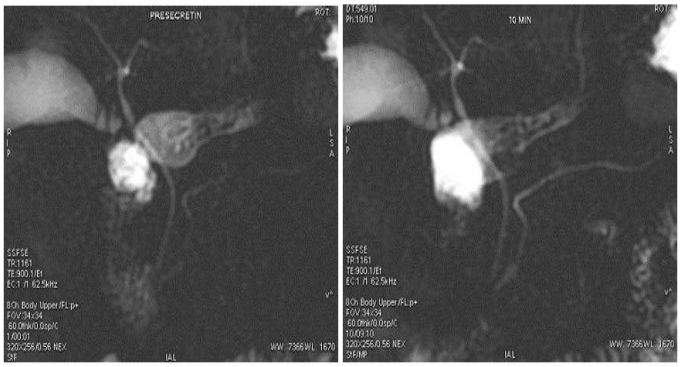

Figure3. Secretin-enhanced MRCP before and after secretin administration at 10th minute, demonstrating reduced pancreatic exocrine function.

Patients with PC, mostly those with head localization, develop pancreatic exocrine insufficiency in circa 60% due to loss of parenchyma or duct obstruction. Patients experience weight loss in respect and to malabsorption, which correlates with poor prognosis and increased death rates. However, pancreatic function should be screened in every PC patients as long as steatorrhea as a typical clinical manifestation of pancreatic exocrine insufficiency (PEI) is presented at a later stage, when more than 90% of the parenchyma is damaged. PEI is diagnosed with direct and indirect tests. Direct tests, including secretin stimulation test, cholecystokinin stimulation testing, secretin-cholecystokinin testing and endoscopic testing, determine the quantitative secretion in pancreatic gland stimulation by intravenous hormones administration (21). Direct tests are considered to be standard in the diagnosing PEI regardless of its severity. Due to their invasiveness, labor intensity and high cost, they are rarely used in clinical practice and are overturned by indirect methods, among which fecal elastase 1 is used to screen PEI as an easy and widely available test. Values below 200 μg / g feces indicate reduced pancreatic function. The mixed triglyceride breath test (^{13}C-MTG-breath test) evaluates PEI with a sensitivity of over 90%, could diagnose mild and moderate PEI and can be used to monitor the effect of pancreatic enzyme replacement therapy (PERT). Secretin-enhanced MRCP (figure 3) has been already briefly reviewed (20). Patients with mild and moderate PEI are also at risk for developing nutritional deficiencies (proteins and fat-soluble vitamins A, D, E, K) and associated complications (osteoporosis, cardiovascular events, etc.). Fundamental aspects of the treatment of PEI include PERT, smoking cessation and alcohol consumption, diet (frequent

small meals with normal fat intake), fat-soluble vitamins and systemic follow-up, including BMI and nutrition parameters (prealbumin, RBP, fat-soluble vitamins, trace elements). The purpose of this concept is to normalize the digestive process, alleviate symptoms and complications, and prevent associated with PEI morbidity and mortality (14-19).

Conclusion

Pancreatic cancer is the fourth leading cause of cancer-related death and remains one of the deadliest cancers worldwide. Due to increased incidence of PC in respect to chronic inflammation, CP raises attention to the necessity of introduction of PC screening programs based on methods combination in high-risk cohorts. Intention should be paid for risk factors illuminating and avoidance if possible.

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