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Pancreatic Acinar and Island Neogenesis Correlated with Vascular and Matrix Dynamics

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1. Introduction

The pancreas is an organ that has a remarkable "plasticity" so that the demarcation between normal and pathological is particularly difficult; it is sometimes difficult to determine whether a change in structure is the cause or effect of pathological conditions.

In these circumstances of an increasing incidence of chronic pancreatitis, the question of regeneration of acinar structures and islands, in the context of known etiopathological conditions is imperative.

The prevalence of chronic pancreatitis in the context of different pathologies is difficult to be determined, varying probably between 0.04% and 5%. This signifies a superposition of the etiology of acute and chronic pancreatitis although it is known that the most frequent etiology of chronic pancreatitis is alcoholism, in middle-age patients[6].

Over 40% from the patients with chronic pancreatitis are predisposed to acute pancreatitis. The evaluation of the general medicine consult and of the laboratory data is necessary for the accuracy of the etiology and pathogeny, being known that the metabolic autoimmune pathology, the anatomical anomalies, the abusive consumption of alcohol also induce hepatic lesions, thus it can be spoken from a hepato-pancreatic lesional complex[11]. In the present paper the etiologic agent prime conductor of the pancreatic lesions is the main concern. That is why we consider indispensable the evaluation of the immunohistochemical markers, of involvement for each matriceal component and pancreatic parenchyma. Thus, the fibrotic replacement of the exocrine pancreatic parenchyma and the appearance of the inflammatory infiltrate are the main features of the chronic pancreatitis.

In this context, it is compulsory to add immunohistochemical results, knowing the importance of some of them either in the collagen forming or in acino-island tissue and matrix recovery.

Therefore we consider extremely important to observe in dynamic the histo-architectural changes of the stroma and parenchyma.

This is why the approach of island neogenesis and not of the acinar neogenesis must be done like a more complex lesion in a mutual interdependence and vascular-stromal induction.

Therefore we consider interesting island neogenesis evaluation in dynamics of various lesions, so the immunohistochemical results are much larger, by a wide use of antibodies, whom target is not only parenchyma neogenesis, but the whole context of lesional chronic pancreatitis. We say this because the study is done on humans and not on experimental models.

We believe that in this case, of the island neogenesis, many factorial etio-pathogenesis, history and family history, therapeutic actions, multiple risk factors (alcohol, smoking, food habits) can create more or less favorable conditions, aspects that can not be extrapolated to the experimental models.

Therefore we can not stop only to identify newly formed islands without assessing the context of lesion, which is why we considered it appropriate to use a wider range of antibodies, covering both parenchyma and vascular-matrix elements.

2. Chronic pancreatitis pathogenic mechanisms

2.1 Toxic-metabolic mechanism

Alcohol is directly toxic to acinar cell through a change in cellular metabolism. Alcohol produces cytoplasmic lipid accumulation within the acinar cells, leading to fatty degeneration, cellular necrosis, and eventual widespread fibrosis.

In alcoholics without chronic pancreatitis, cytoplasmic fat droplets were frequently found in the acinar cells. Alcoholic patients with chronic pancreatitis expressed lesions such as atrophy and fibrosis.

Alcohol produced a stepwise progression from fatty accumulation to fibrosis. The morphological changes of the cellular organites may likewise represent a toxic change in cellular metabolism from alcohol.

Alcohol is metabolized in pancreatic acinar cells through oxidative and non-oxidative pathways[13].

A criticism of this theory is the lack of proof that pancreatic steatosis is a true precursor to fibrosis, rather than a parallel, reversible, alcohol-related lesion[1].

We consider that there is an inter-relation between multiple factors and that alcohol could be the precursor of other pathological events that lead to chronic pancreatic disease.

2.2 Necrosis-fibrosis

Inflammation and necrosis from episodes of acute pancreatitis produces scarring in the peri-ductular areas. This scarring leads to obstruction of the ductules, leading to stasis within the duct and secondarily, stone formation. Severe obstruction results in atrophy and fibrosis. It was suggested that there is a stepwise progression of fibrosis emerging from recurrent episodes of acute pancreatitis[1].

We consider that the necrosis-fibrosis mechanism has to be correlated with the destruction of excreto-secretory elements.

2.3 Pancreatic stellate cells

These cells have long been known to contribute to hepatic fibrosis. Inactive pancreatic stellate cells are triangular, lipid-containing cells predominantly located in the perivascular regions. When activated, they lose their lipid droplets and transform into a fibroblast-like morphologic appearance, migrating to the periacinar areas.

There is ample evidence to suggest that stellate cells play a central role in the deposition of collagen in the early stages of chronic pancreatitis. Pancreatic specimens from patients with chronic pancreatitis exhibit staining for α-smooth muscle actin (present in activated stellate cells) in fibrotic areas of the pancreas.

Our studies showed that the fibrosis begins in extra-lobular spaces by a hyper activity of the stellate cells especially in alcoholic patients which suggest that alcohol and the oxidative stress which it induces form a pathogenic triangle of the necrotic and fibrotic lesions[1].

It is known that the cytokine profile within the pancreas in patients with chronic pancreatitis is distinct from normal pancreas. Pancreatic stellate cells are stimulated by a variety of cytokines which are emitted during the inflammatory phase of acute pancreatitis, this suggesting that recurrent acute pancreatitis could lead to chronic pancreatitis.

2.4 Oxidative stress

The pancreas is exposed to "oxidative stress" through the systemic circulation or through the reflux of bile into the pancreatic duct, leading to inflammation and tissue damage. Oxidative stress may be exacerbated by increased mixed-function oxidase activity, either from high levels of substrate (*e.g.*, fats, diabetics) or inducers (*e.g.*, alcohol and drugs).

Oxidized products are capable of damaging cellular compounds, possibly inducing pancreatic autolysis.

Oxidative stress is involved in the pathway to fibrosis, it has never been proven to *initiate* the disease. Pancreatic acinar cells are capable of metabolizing alcohol without the involvement of Langerhans island. Oxidized products along with cyto-toxines released in the inflammation represent the main aggression factor for the pancreatic acinar cells, favoring necrosis and fibrosis[1].

3. Materials and methods

For our study we used pancreas specimens obtained from patients who died having chronic pancreatitis of various etiology: alcoholism, hepatic cirrhosis, diabetes, etc. For the initial diagnosis classic hematoxylin-eozine and Davenport staining were used to identify pancreatic islands and select the most representative samples for the immunohistochemical study.

We used 10% formaline solution as a fixative because it is suitable for classical stainings as well as for immunohistochemistry, preserving the antigen expression pattern of cells. The volume of the solution was 10 times higher that the volume of the sample.

The samples were fixed 3-4 days depending of their size, and were paraffin-wax processed. The paraffin blocks were cut using the microtome to 5μm thick sections. The sections were

harvested on poli-L-lisyne slides in order to have better adherence and to exclude the eventual cross reactions. These sections were stained for different antibodies (Table 1) using the Dako's EnVision detection system, and DAB (3,3'-diaminobenzidine) as chromogen substrate. The nuclei were counterstained using Mayer hematoxylin.

Antibody	Clone	Cod	Antigen retrieval	Dilution
Anti SMA	1A4	M0851 Dako	pH 6 citrate buffer, heat mediated for 11 minutes in the microwave oven	1:100
Anti CD68	IgG1k	M0814 Dako	pH 6 citrate buffer, heat mediated for 11 minutes in the microwave oven	1:100
Anti CD34	QBEnd-10	M 7165 Dako	pH 6 citrate buffer, heat mediated for 11 minutes in the microwave oven	1:50
Anti Cox2	CX229	Cayman Chemical Company	pH 6 citrate buffer, heat mediated for 11 minutes in the microwave oven	1:50

Table 1. Antibodies used for immunohistochemistry

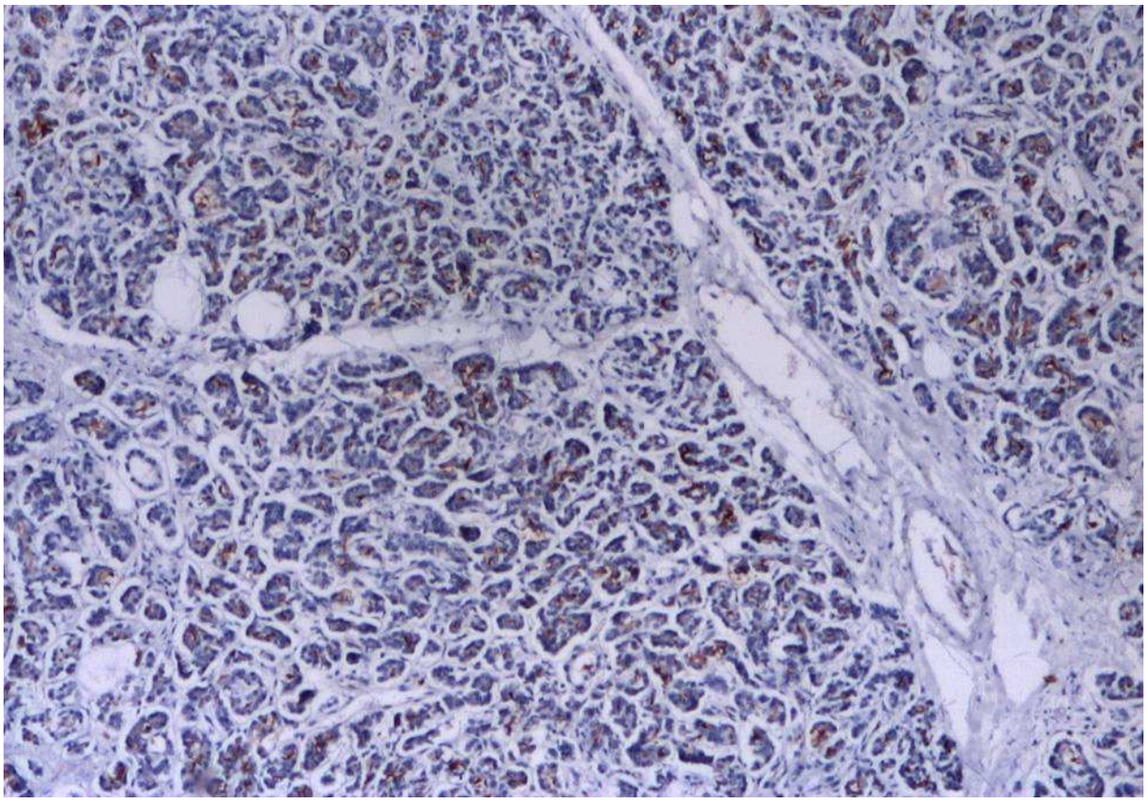


Fig. 1. Cox2 positive immunostaining in acinar cells only

4. Results and discussions

Since inflammatory elements are preserved in vast areas of fibrosis often peri-lesional, we considered interesting to evaluate the COX2[3].

Enzyme inductive COX2 normally absent in cells respond to the action of local and general factors in the evaluation using the immune response by pro-inflammatory role in pancreatitis.

The main features of chronic pancreatitis are involution of exocrine pancreatic parenchyma and endocrine island elements, accompanied by fibril genetics processes and marked inflammatory infiltrate. Therefore, we can not see unilateral these insular and acinar neogenesis, as long as the accompanying inflammatory process may involve prostaglandins.

Inflammatory cells that express COX2, following a specific pancreatic chemo tactics aimed directly the structure, causing necrobiotic damage on one hand, and on the other by phagocytes processes and removing dead cells and cellular debris

It's important to mention that the changes shown in the figure above appear in areas of island neogenesis which in our opinion could be neo-islands. It is possible that the focal positive Cox2 immunostaining to reflect a local immune reactivity to the neo-islets formation. These aspects have been more obvious in patients consuming alcohol comparing to diabetes patients, which suggest the low immune capacity of a diabetic person[8, 19].

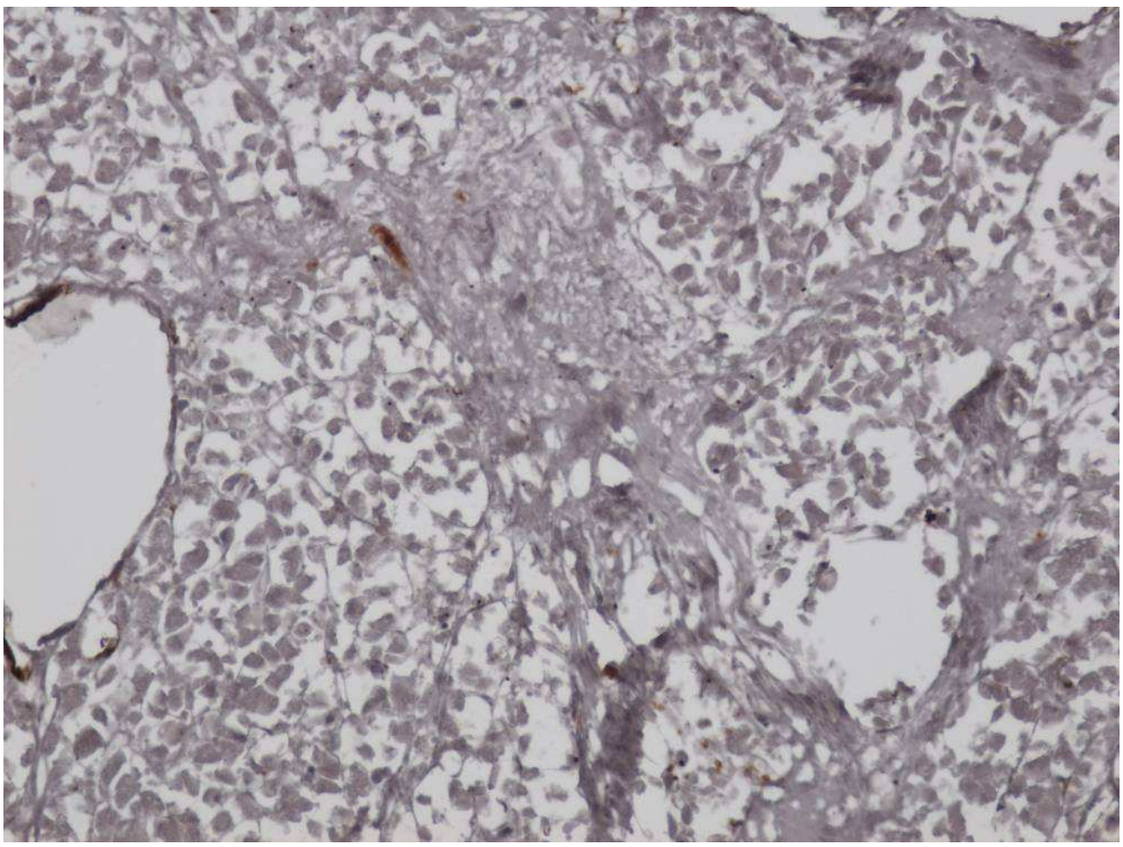


Fig. 2. Focal CD68 immunoreaction in a large area of fibrosis, DAB

So, leukocyte infiltration in chronic pancreatitis is represented by a remarkable percentage of mononuclear cells, which suggests that macrophages have great importance in the inflammatory process. With origin in circulating monocytes, macrophages are activated by certain cytokines and a series of endotoxin, so that their activation can induce phagocytosis. That's why COX 2 inhibitors are accepted therapy of chronic inflammatory lesions[5, 20].

Immunohistochemical response evaluation was approached differently depending on case. For cases diagnosed with early stage chronic pancreatitis imunoreactivity for COX2 was highly positive (62%), while for subjects with diabetes and those diagnosed with advanced chronic pancreatitis was weakly positive (12.7%) or negative response, both ductal and intra-island.

The immunostaining for macrophages (CD68) was reduced compared to Cox2 staining suggesting that the chronic or sub-acute inflammatory reaction is not that much involved in the acino-island regneration.

In advanced chronic pancreatitis, intra and extra-lobular ductal cells were intensely positive for COX-2 compared with islands with variable staining pattern in areas with insulin-positive cells and clinical diagnosis of diabetes[10]. Immunoreactivity was low or absent in people with type II diabetes compared with people consuming alcohol and diabetes type I. These aspects were extremely relevant on the studied samples. Therefore, we consider that a positive COX2 immunoreactivity particularly in intralobular ductal cells enables us to corroborate the involvement of these cellular processes into parenchyma and stroma changes[17,18].

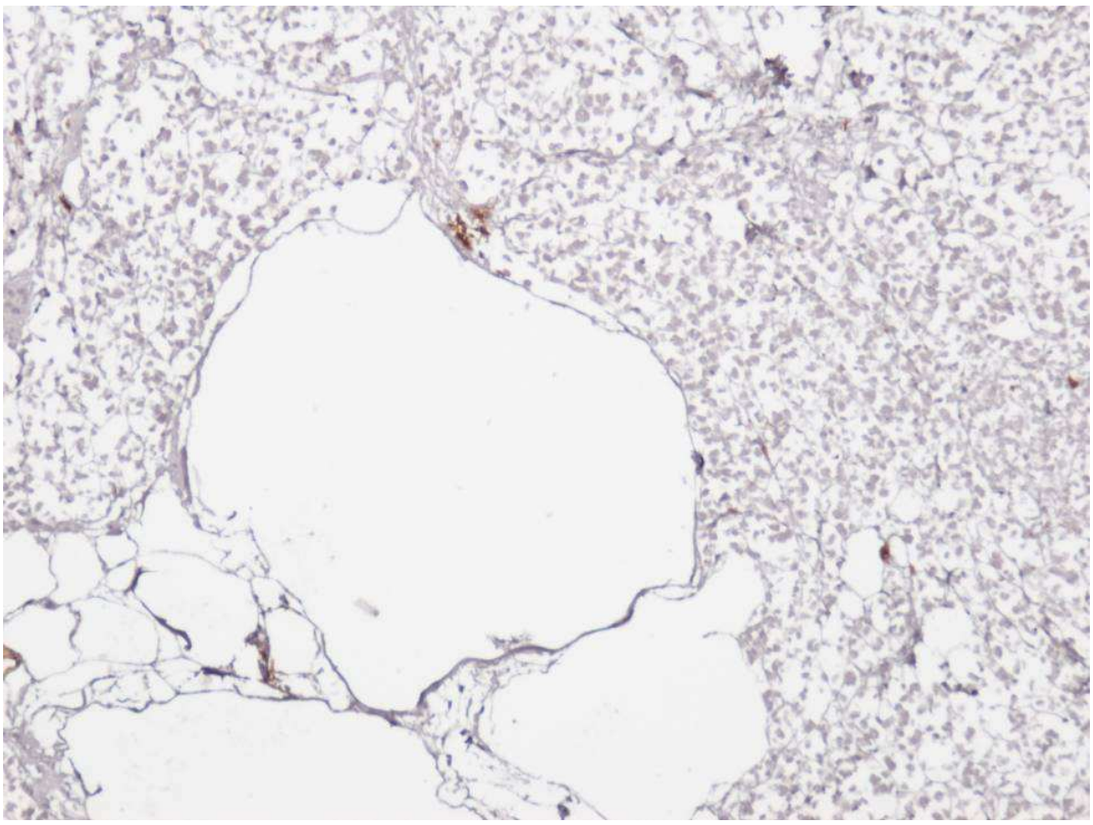


Fig. 3. Focal CD68 immunoreaction near a optic vide areas possible due to focal necrosis, DAB

Due to "pseudo-insular" aspect in areas of parenchyma replacement with remaining acinar structures, the presence of activated macrophages is relevant, stimulating the star-shaped cellularity located at the stromal level, responsible for fibrilogenetics processes in areas with fibrosis[12, 14].

That is why the expression of fibrosis degree with a immunohistochemical response led to the use of matrix metalloproteinases (MMP) involved in regulating fibrilogenesis.

We believe that pancreatic stellate cells (PSC) can act as a central regulator in pancreatic fibrosis in chronic pancreatitis controlling matrix degradation through MMP and TIMP expression, transcriptional regulation process on MMP and TIMP being mediated by cytokines[2].

We consider this issue to be important in chronic early pancreatitis. The immunohistochemical response was highly positive while in diabetics and in subjects diagnosed with pancreatitis due to consume alcohol, immunohistochemical response was weak positive on acinar cells, and even negative in insular cells.

In particular we found in subjects with early-stage chronic pancreatitis, alcohol consumers and non-consumers a binucleation cellularity located in the vicinity of Largerhans islands, and acinar structures with proliferative island aspect, which suggested a possibility of transformation of acinar structures and centro-acinar pseudo-cordonal type items in the drafting of primitive island.

In completing this study, the nestin expression in ductal epithelial cells suggests a possible role in island cells neogenesis. It is believed that the birth of new pancreas endocrine cells occur through mature ductal cell differentiation. That is why there are concepts which suggest that we can not use nestin in human pancreas as a marker of endocrine precursor cells[21].

However, very rarely evidenced in extra-insular cells, with increased nestin expression in neonatal pancreatic islets, we can say, however, it is involved in island neogenesis. This is why it rather indicates a tissue differentiation with diffuse pattern, varying in layout structures with pseudo-insular aspects.

Immunohistochemical nestin positive response was extinguished met both in pancreatic duct cells in appearance and in isolated and small outbreaks in the structures with pseudo-insular aspect, in mature Langerhans island structures, but necrobiotics damages makes difficult to differentiate between different structures.

This reinforces our idea of a possible positivity of tissue remodeling with cell differentiation or functionality exocrine or endocrine-related functionality.

As a result of the vast process of fibrosis processes leading to a reversal of the parenchyma-stroma relationship in favor of the stroma, we were interested in the distribution of collagen IV, a basement membrane major constituent within laminin[13].

Thus, we observed that in subjects with clinically diagnosed early-stage chronic pancreatitis was present a pattern of continuous distribution of collagen IV in basal membrane around ductal cytolysis lesions.

Also, large areas of acinar structures were separated by collagen bands while the remaining islands collagen network sketches pseudo-capsular aspect, so insular cytolysis and modified histo-architecture would be possible by the dual mechanisms.

These issues were particularly characteristic in subjects with advanced chronic pancreatitis. Also, this is very useful especially in differential diagnosis of pancreatic adenocarcinoma where the distribution of collagen IV in basal membrane is discontinuous and irregular or absent around individual cells or groups of tumor cells.

It is known that in normal pancreas, CD 34 positive stromal cells are present predominantly in peri-acinar areas. Isolated CD34 positive cells also were observed in stroma of subjects diagnosed chronic pancreatitis in both advanced and early stage[7,9].

It seems that the presence of significant amounts of CD34 positive stromal cells in primary lesion is characteristic of chronic inflammatory lesions.

In our study, subjects diagnosed with chronic pancreatitis could see an increase in fibrocites CD34 positive. Also, CD34 was positive in vessels in all cases of chronic pancreatitis studied both in diabetics (type I and type II) and drinkers.

This leads us to the idea of involving fibrotic elements which are CD34 positive in a result of stromal remodeling in chronic pancreatitis. Intensively CD34 positive vascular elements were observed in diabetic subjects compared with the rest of the studied

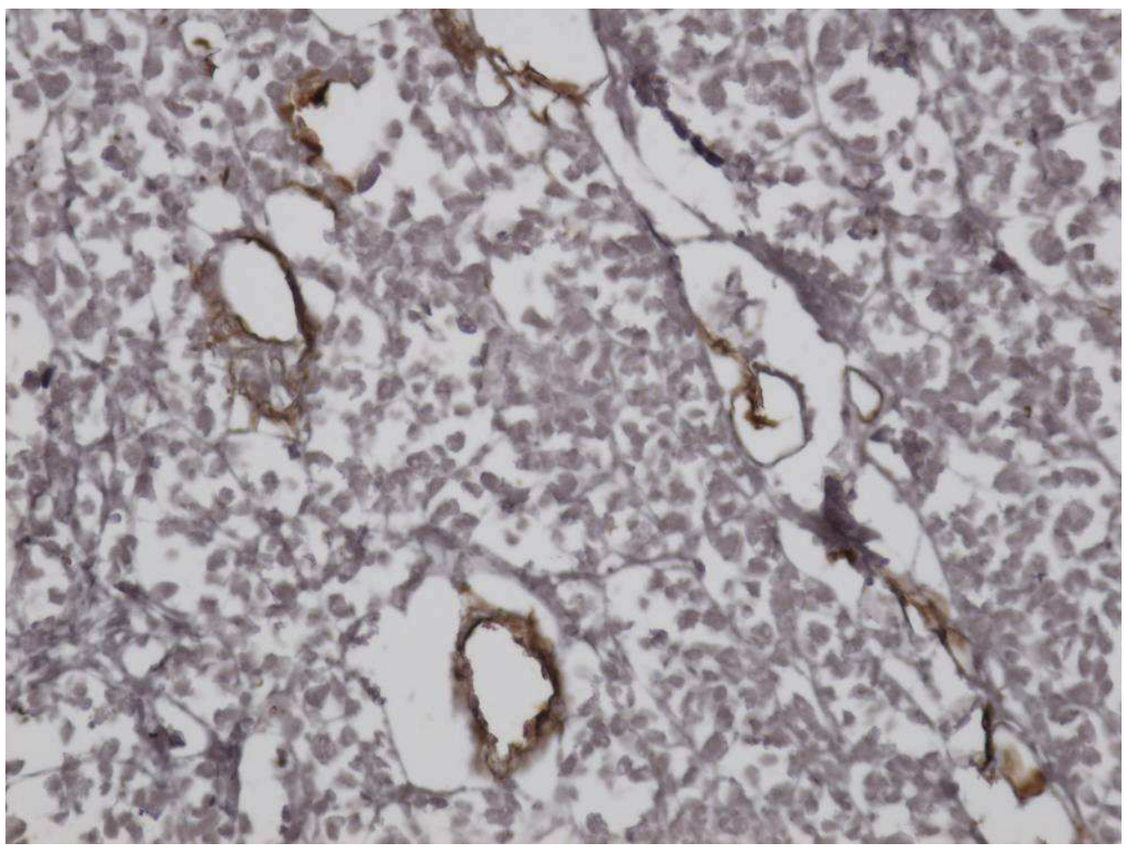


Fig. 4. CD34 immunoreaction in vascular endothelial cells, DAB

Importantly, for an overview of the changes occurring in the matrix and the parenchyma elements, exocrine and endocrine aspects with microscopic positive immunohistochemical markers were mentioned. We consider this relevant because in chronic pancreatitis common lesions can be found but differentiated both at the parenchymal and stromal level. Aspects that we found can be considered to be elements of island neogenesis and are certainly induced by the changes occurring in the overall lesion of chronic pancreatitis. Thus, serous acinar cell nucleus were found in different stages of involution, but the vast majority of nucleus had dispersed chromatin lumps in nucleoplasma or condensed chromatin on nuclear membrane, thereby creating a vacuum optical image space, perinucleolar, something known as "owl eye".

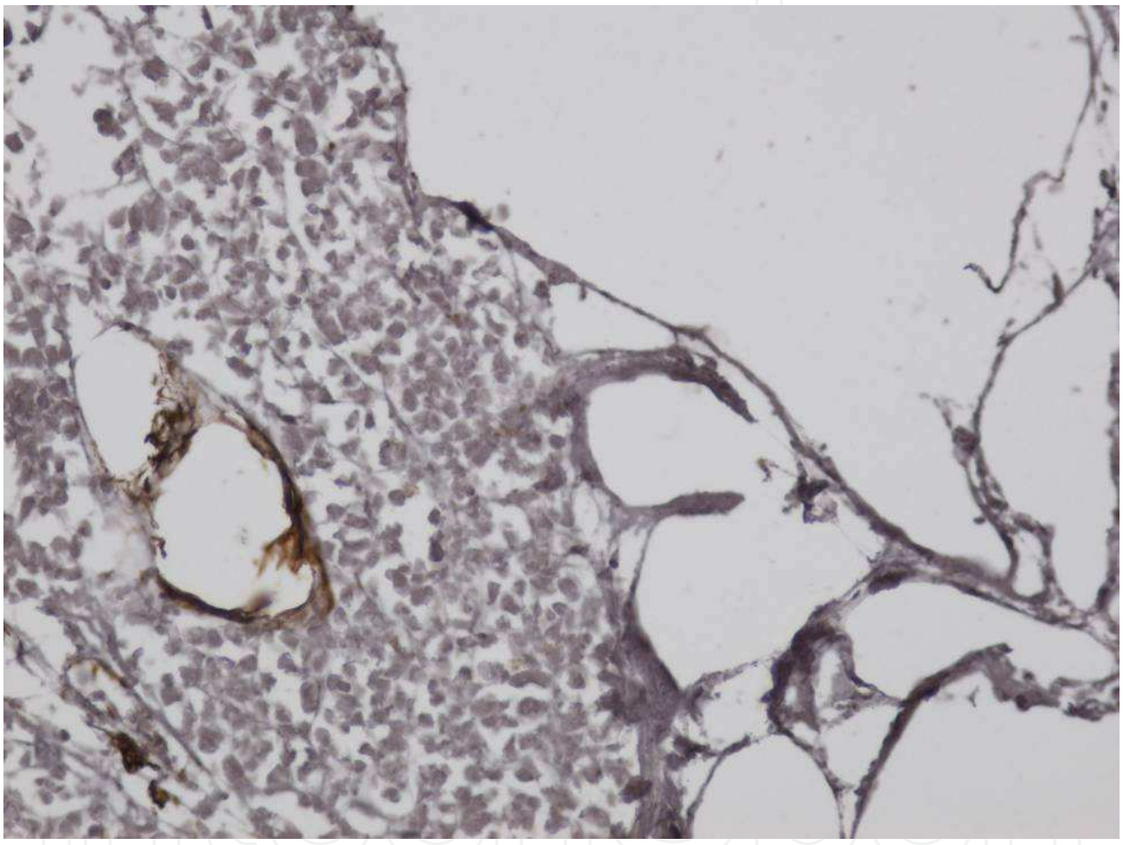


Fig. 5. CD 34 positive in vascular endothelial cells and focal in perivascular cells, DAB

Chronic pancreatitis is characterized by a large number of reactive miofibroblasts to alpha SMA, chronic pancreatitis stromal remodelation being also caused by miofibroblasts, immunoreactive fibroblast-like cells with contractile properties which are considered to be fibroblasts[16, 22]. The TGF-beta has a main role in fibrosis development in liver, but also in pancreas, this suggesting a better research of hepatopathies matter. Many evidences suggest that PSC can be also activated by paracrine profibrogenes cytokines, like trombocytes derivated growth factor and TGF-beta derivated by migratory macrophages. In addition, PSC generate EMC components in return for TGF-beta action, suggesting that the cytokine has an important role in pancreatic fibrogenesis[4, 15, 18].

The apoptosis research, inflammatory injuries, tumoral genesis are controlled by a nuclear transcription factor, NF-kB factor or Kappa B Nuclear Factor. In chronic pancreatitis NF-kB is positive, with intranuclear distribution. Chronic pancreatitis associated hepatic injuries are characterized by hepatocelular apoptosis and necrosis, NF-kB being dependent of liver releasing cytokines and chemakines. Chronic pancreatitis activation can induce hepatic damage through derived Kupfer cells cytokines activation and Fas/Fasl releasing.

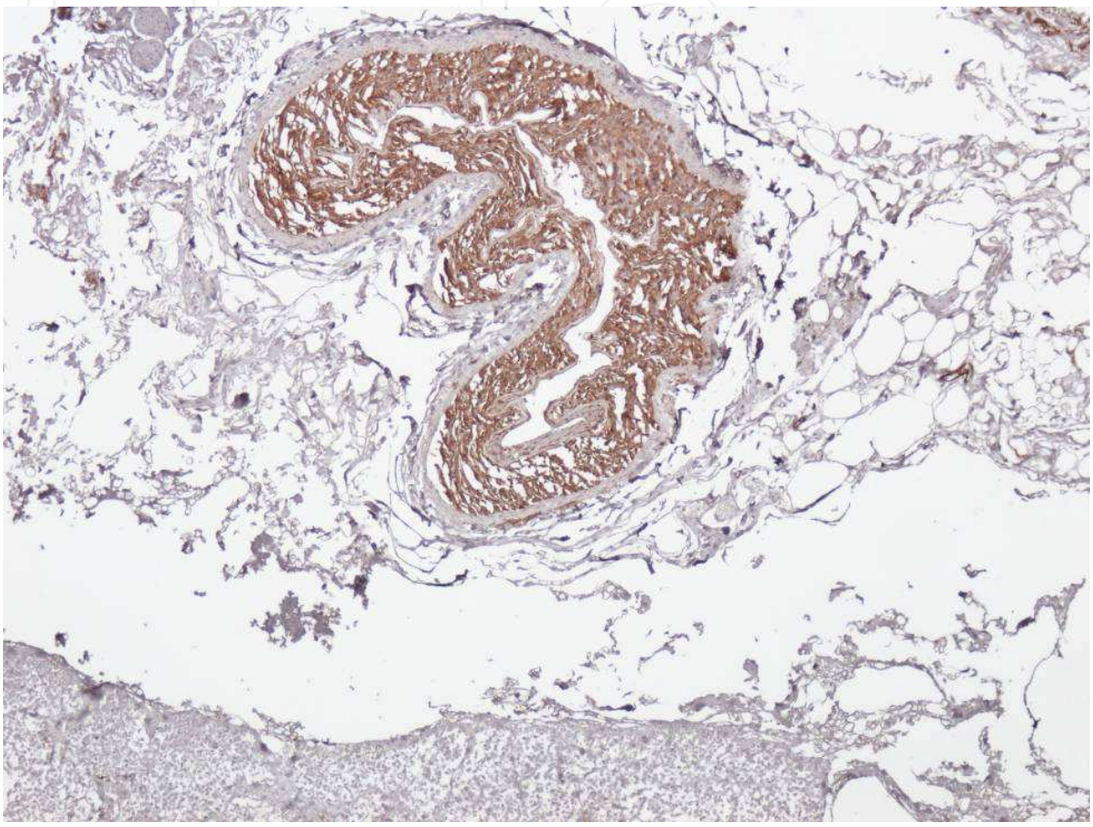


Fig. 6. Anti alpha-SMA staining identifies large vessels with hyaline perivascular deposits, DAB

One aspect we found is that the presence of binucleate cells in the exocrine pancreatic parenchyma. Binucleate cells of polygonal or oval shape present nucleus with condensed chromatin on the nuclear membrane, nucleols and nucleoplasma, obvious tendency to create optically empty spaces. These issues lead us to the possibility of parenchyma neogenesis that we can not exclude taking into account the common embryonic origin of the pancreas with the liver.

Close to capillaries responsible for nutrition of the exocrine parenchyma areas we found the presence of two cell types, some of which were binucleate cells with condensed chromatin on nuclear membrane, with or without obvious nucleoli, and some globular, uninucleate and with nucleoli.

The presence of these cells enables us to believe that they are involved in a possible recovery of pancreatic parenchyma, with the existence of metabolic processes.

Instead, binucleate cellularity was observed in areas of parenchyma completely missing. We noticed the oval binucleate cells with nucleus whose chromatin is cloggy or condensed on the nuclear membrane. Cytoplasm of these cells may present some kind of vacuolization or peri-nuclear argirofile areas in particular.

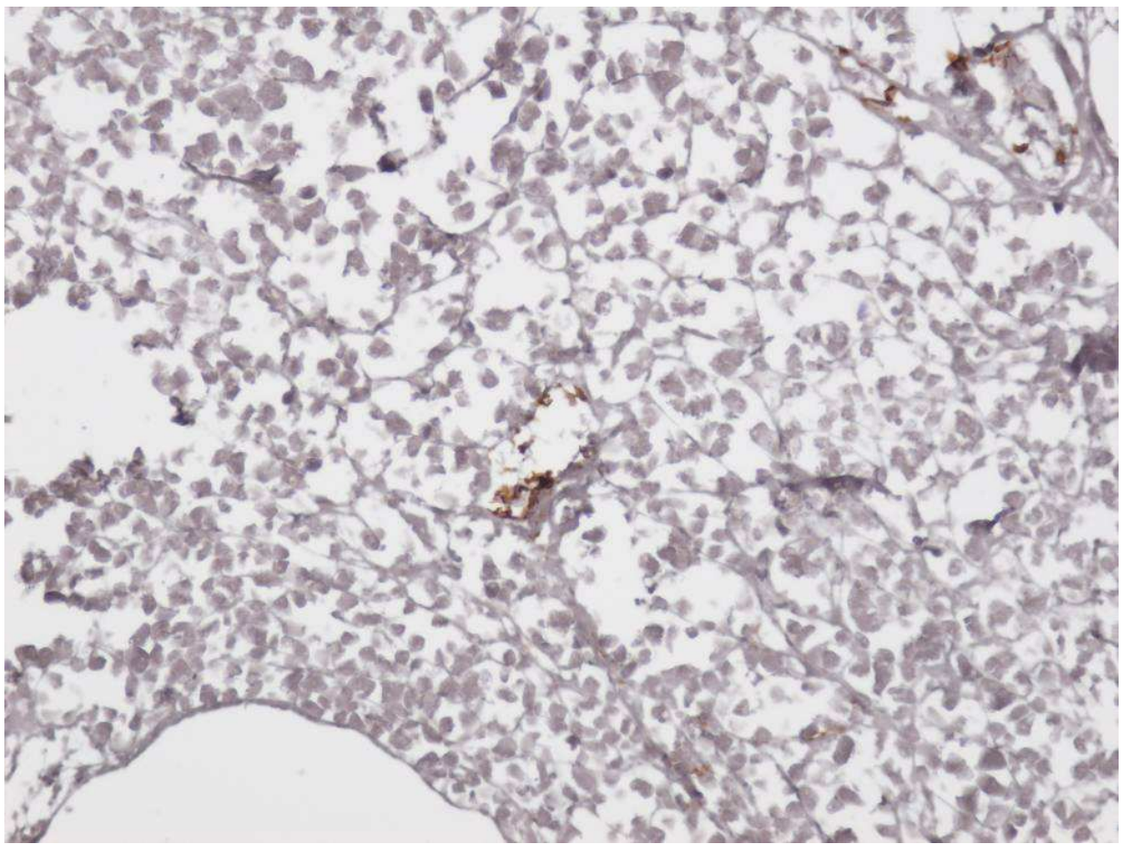


Fig. 7. Anti alpha-SMA staining identifies positive star-shaped cells in parenchyma replacement areas, DAB

Perhaps these cells are involved in pancreatic parenchymal cytological regeneration.

As a result of Davenport staining, we noticed groups of cells containing finely granular and hypo-chromic nuclei, located in the interlobular spaces near the excretory channels. Their appearance is the type of "pseudo-insular" irregular looking with hypo-chromic nuclei and intra-insular argentafine areas.

In the immediate vicinity of these islands we have noted the presence of monoclonal cells with hypo-chromic nucleus fine granular cytoplasm aspect.

These aspects observed in the conjunctive-vascular septas, suggested the hypothesis that, although completely modified, the cyto-architecture of pancreatic parenchyma can regenerate, but without a full morpho-functional reconstruction.

Therefore, we believe that these cell formations are a "primitive form islands."

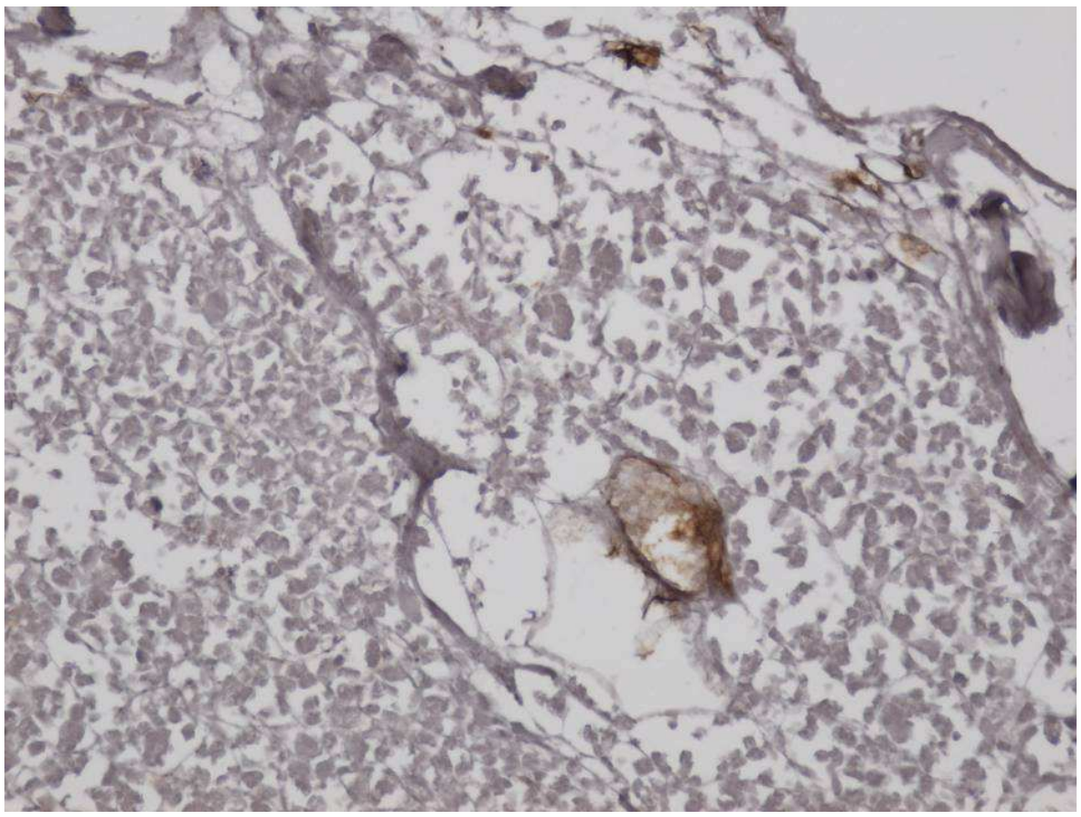


Fig. 8. Alpha-SMA positive staining in middle caliber vessels and intra parenchymatous, DAB

Endocrine parenchymal regeneration issues we noticed in other samples studied, where we found the presence of large cells compared with the rest of the cell population, on the outskirts of Largenhans located islands.

These cells are clearly distinguishable from other island cells, their cell boundaries, appearing not to keep. Cytoplasm of these cells has a fine granular and the nucleus, binucleolat, presents condensed chromatin on the nuclear membrane, giving an embattled appearance.

Besides these large cells, with localization throughout the periphery of the island, we noted the presence of binucleate cells, irregularly shaped. Monoclonal cells with bulky appearance and with binucleate cells were observed mainly in the periphery of Langerhans islands.

That is why the presence of mono-and binucleate cells, large in size compared with the rest of the islet, suggests partial restoration of island celularity.

Pancreatic fibrosis, a characteristic histopathologic appearance of chronic pancreatitis in our study was an active process that, according to some authors, may be reversible in the early stages[13].

Identification and characterization of cells that have fibrilogenesis capacity greatly helped us in the study of pancreatic stroma in chronic pancreatitis. COX-2 played an important proinflammatory role in pancreatitis by regulating prostaglandin synthesis.

As a result of our study we agreed that pancreatic stellar stroma cells mediates fibrosis in chronic pancreatitis with matrix metalloproteinases (MMPS) and tissue inhibitors of metalloproteinases (LONG) -1 and -2 as a modulator of fibrosis

5. Conclusions

We consider that in the pathogenesis of chronic pancreatic disease, multiple factors and theories are involved leading to parenchyma destruction and fibrosis with elements of acino-insular neogenesis.

Immunohistochemical results in the dynamic vascular-stromal and island neogenesis does not clarify the subject. We believe that on the human models we can not have so spectacular results as those experimental models, because the subjects with chronic pancreatitis are exposed to a lot of factors in different evolutionary stages.

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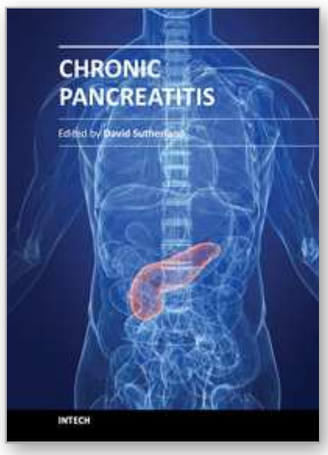
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Chronic pancreatitis is a disease of diverse etiologies in which pain can be devastating, severely impairing quality of life, and treatment is a challenge. This book covers cutting edge basic science research and clinical diagnosis and treatment issues in chronic pancreatitis. Basic science chapters include studies on amelioration of chronic pancreatitis in rats by bone marrow derived mesenchymal cells; on gene therapy using HSV-Enkephalin to reduce fibrosis, inflammation and pain in a rats; and on pancreatic acinar and island neogenesis according to vascular and matrix dynamics of human and animal tissue. In regard to the clinical aspects, the role of endoscopic ultrasound in detecting the changes of chronic pancreatitis are addressed as well as the endoscopic treatment via duct drainage procedures or stone removal. Finally, the surgical options for chronic pancreatitis (there are well over 20 procedures) are extensively discussed, with a final chapter on total pancreatectomy and islet autotransplant to definitively remove the root cause of the pain with preservation of endocrine function. This book will be valued by basic scientists and clinicians striving to understand the mechanisms of pain in chronic pancreatitis and the treatment options in patients so afflicted.

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