Chapter 2

Pancreatic Acinar and Island Vascular Apparatus Associated with Acute and Chronic Inflammatory Processes

Garofita-Olivia Mateescu, Bogdan Oprea, Liliana Stanca, Mihaela Hincu, Malina Coman, Stelian Mogoanta, Dragos Voicu, Relu Stanescu and Ion Rogoveanu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/58921

1. Introduction

Pancreatitis is the inflammation of the pancreas parenchyma with alterations of the stroma and acinar structures. It may be classified as either acute or chronic. Acute pancreatitis is the reversible injury to the pancreatic parenchyma associated with inflammation. Its reversibility depends on the degree and surface of the lesions and eventually on the co-existent morbidities.

Etio-pathogenesis of acute pancreatitis begins by the activation of pancreatic enzymes. Acute pancreatitis has as main physiopathological event the destruction of the parenchymal architecture. The parenchymal changes induce matrix alteration accompanied by vascular and nervous destruction. All these events have as main cause enzymatic mechanisms [1].

The mechanism behind this activation may be pancreatic duct obstruction, primary acinar cell injury, hyperstimulation of pancreas, reflux of bile, defective intracellular transport of proenzymes within acinar cells. Among the numerous causes, two factors which account for about 70-80% of cases of acute pancreatitis are biliary tract disease and alcoholism [1].

The acute inflammatory process associate with acute pancreatitis induces lesions due to the activation of immunity involved cell that produce TNF, nuclear factor kB and STAT1, that may lead to the overexpression of the pancreatic lesions and to the possibility of secondary infections. All the described events may lead in the end to SIRS, MOD or even death [2,3].

Recent studies have proposed chronic pancreatitis to develop through stimulation of stellate cells into myofibroblasts, which are responsible for the production of collagen and parenchymal fibrosis [4-7]. However, a molecular study has referred to important role of genetic polymorphism in the pathobiology of pancreatic diseases. [8]

Several studies proved that the prevalence of chronic pancreatitis tends toward 0.6% in several countries of Europe and United States [8,9], with an annual incidence of 10 cases for 100000 persons [10]. The most frequent factors that may lead to the appearance of chronic pancreatitis are: the obstruction of main excretory ducts, autoimmunity or individual risk factors (working and life conditions, alcohol consumption, smoking, different drugs, etc.) [11]. Chronic pancreatitis is characterized by the replacement of the secretory and endocrine parenchyma by the matrix elements with the predominance of fibrillar collagen structures, associated with the atrophy of the secretory and endocrine units. The fibrotic scar is triggered by the activation of the pancreatic stellate cells which appear in parenchyma destruction areas. These lesions induce severe disorganization of the architecture of the pancreatic lobules, associated with atrophic processes and dilations of the remaining intra and extra lobular excretory ducts. These aspects constitute the bases of multiple associated diseases as malnutrition or more frequently diabetes [12-14].

The lesions of acute and chronic pancreatitis and are especially related to chronic alcoholism. The alcohol may act directly as a parenchyma toxic through blood vessel wall absoption activating the stellate cells. They may be indirectly activated by alcohol metabolites and by cytokines and growth factors. The growth factors may also initiate angio and vasculo-genesis.

Necrosis and hemorrhage in acute pancreatitis are initiated by intracapillary leucocyte accumulation that adheres to capillary endothelium leading to capillary occlusion and lysis. This aspect may be observed in larger vessels with tunica media present. Leucocytes can substantially plug capillaries under pathological conditions leading to disturbances in microvascular blood flow which induces a so-called ''no-reflow'' condition with subsequent tissue damage [15-17].

Vascular lesions in chronic pancreatitis are different that in the case of acute pancreatitis, being characterized by vascular occlusion due to fibrosis.

In acute pancreatitis, the vessel destruction is due to the elastic fibers digestion by elastases [18]. In chronic pancreatitis the reticular network is ruptured by endothelial cells function and fibrosis in the tunica media.

2. Material and methods

We used 20 tissue samples from deceased patients diagnosed during necropsy with either chronic or acute pancreatitis. The inclusion criterion was the macroscopic examination of harvested samples. Thus the sclerotic pancreas was microscopically confirmed as chronic pancreatitis in 6 cases. The visible increasing of the gland's volume with pale aspect and diffuse edema or fatty necrosis with hemorrhage areas was diagnosed as acute pancreatitis in 14 cases.

http://dx.doi.org/10.5772/58921

The samples were fixed in 10% buffered formalin solution for 3-4 days depending of their size, and were paraffin-wax processed. The 10% buffered formaline solution is a soft fixative that preserves the antigen expression of various cells, thus being suitable for immunohistochemistry. It also maintains the morphology of the tissue without alteration of the histo-architecture of the pancreas. A higher fixative volume compared with the volume of the sample insures the optimization of the fixation process. 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.

For the histological evaluation we used the standard hematoxylin-eosin staining, Goldner-Szeckelly trichrome staining and Gőmőri silver staining.

The immunohistochemical procedure was carried out after previous heat mediated antigen retrieval in the microwave oven, using the Mouse anti Human CD34 and Col IV (Dako) primary antibody in 1:50 dillution each. For detection we used Dako's EnVision system, and DAB *(3,3'-diaminobenzidine)* as chromogen substrate. The nuclei were counterstained using Mayer hematoxylin.

The obtained slides were examined using the Nikon Eclipse 90i microscope.

3. Results and discussion

Acinar and isle lesions in acute and chronic pancreatitis with blood vessel alterations differ regarding the etiologic agent of the disease. As it is already known the etiology of pancreatitis may be metabolic, genetic, mechanic, infectious or vascular. No matter which etiology the characteristic lesions in acute pancreatitis with parenchyma and stroma involvement imply inflammatory processes, edema, focal hemorrhage and severe necrotic lesions [4] (figure 1).

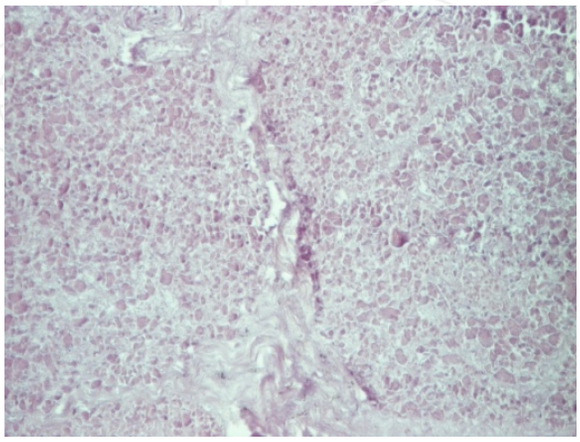

Figure 1. Histo-architecture changes of stroma and parenchyma-acute pancreatitis. HE x100

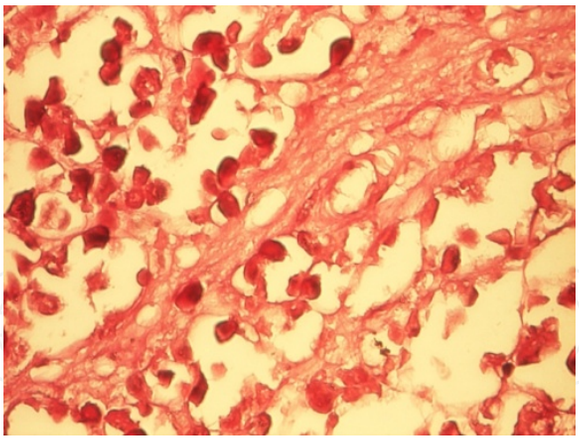

Figure 2. Isolated exocrine parenchymal cells surrounded by necrotic lesions and incipient fibril-genesis. HE x200

In the vicinity of the necrosis areas we observed the presence of isolated cells remained in the formed acinar and ductal structures zones. These cells may be involved in the initiation of partial remodeling processes or in the initiation of fibril-genesis along with already known myofibroblasts [19-21] (figure 2). In these areas the vascular apparatus lacks. We consider that necrotic lesions involve the capillaries with the appearance of parenchymal focal micro-hemorrhages.

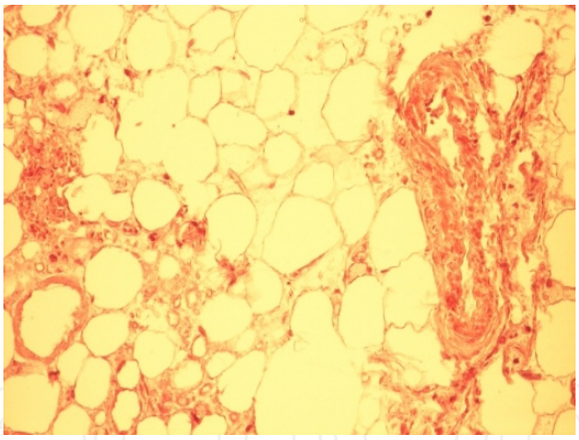

Figure 3. Reminiscent vascullar apparatus in an area of fat necrosis. HE x100

In areas of necrosis or fatty necrosis the remained vessels are of venular or arteriolar type. This aspect leads to the idea that pancreatic enzymes first target the reticular febrile network (this being the reason for capillary disappearance) and then the collagen and elastic network in the tunica media of arterioles or small veins (figure 3).

In acinar and isle dystrophic lesions areas we frequently observed with or without micro-thrombosis. We consider that these "gemini" vessels in acinar-isle transition zones may provide the vascular support for acino-isle reconversion (figure 4).

These aspects were not observed in areas of pure exocrine parenchyma.

http://dx.doi.org/10.5772/58921

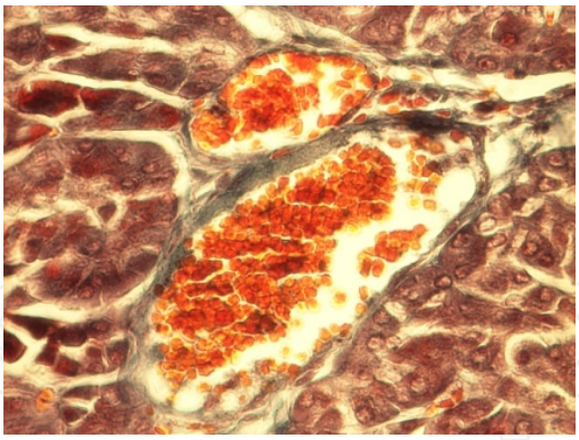

Figure 4. Micro-thrombosis of "gemini" vessels in an area of acinar and isle architecture partially unaltered. Goldner Szeckelly trichrome x200

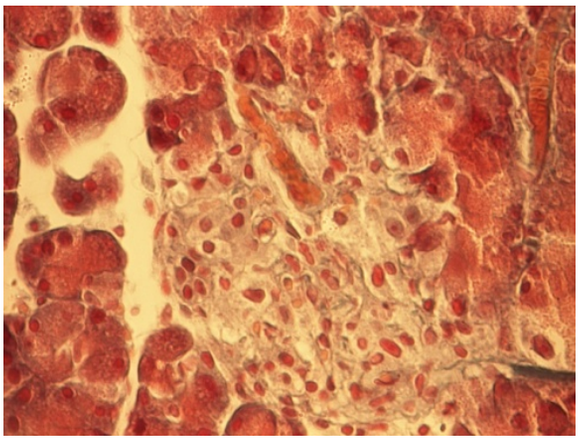

Figure 5. Peripheral vascularization of a Langerhans isle. Goldner Szeckelly trichrome x200

The characteristic of dystrophic Langerhans isles is the presence of capillaries in the periphery under the pseudo-capsule and their disappearance in medial and central areas. This aspect supports the above mentioned theory of the "gemini" vessels.

Recent studies [22] have reported that Langergans isles maintain their structure despite the necrotic surrounding, due to two main factors: the resistant collagen pseudo-capsule and the peripheral vascularization (figure 5).

Isle lesions associated to the acino-ductal ones are represented by focal accumulation of sclerotic islets of variable size; occasional neoformation of islets by ductoinsular proliferation (neosidioblastosis); and peri-capillary fibrosis in atrophic islets.

At the periphery of the pseuo-isle structures consequent to necrotic lesions, the pericytes are activated and develop myo-fibroblastic like characteristics, initiating the perivascular fibrosis.

The alterations of the vascular wall (endothelium and basement membrane of the capillary), focal ischemia, induce important dystrophic lesions of the endocrine and exocrine parenchy-

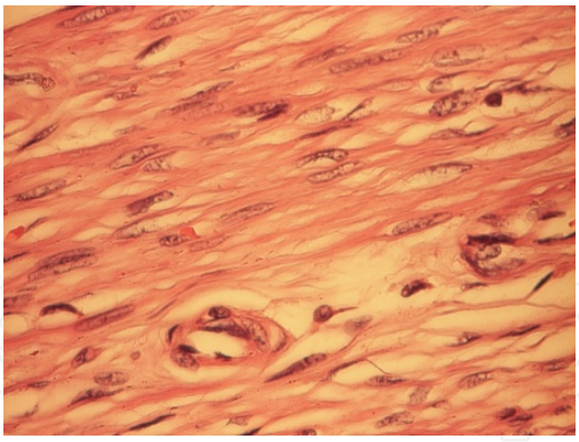

Figure 6. Capillary in a fibrosis area. HE x200

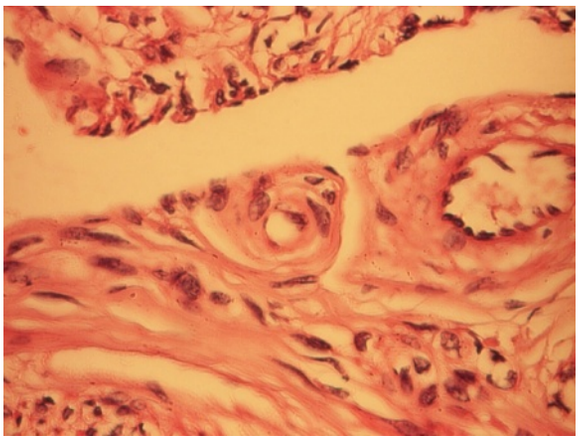

Figure 7. Vascular apparatus in a fibrosis area. HE x200

ma. This may have the pathologic support the alterations of endothelial and lysosome dynamics (figure 6 and 7).

In fibrosis areas characteristic to chronic pancreatitis, we observed capillaries with turgescent endothelia, nuclear hypertrophy of the pericytes. These may be the beginning of angio and vasculo-genesis with later differentiation into veins and arteries.

The fibroblastic, myo-fibroblastic-like cells in the fibrosis areas support the above mentions, being involved in collagen secretion and matrix remodeling as well as angioblastic cyto-formation substrate (figure 8).

Medium caliber vessels presented discontinuous endothelium with edema and myo-lytic lesions in the tunica media, the adventitia being completely modified by edema (figure 9). The myocytes or endothelial cell apoptosis may lead to the appearance of focal micro-hemorrhages.

In the inter-acinar spaces there are some CD34 positive groups of cells without lumen, possibly as angio genesis precursors (figure 10).

http://dx.doi.org/10.5772/58921

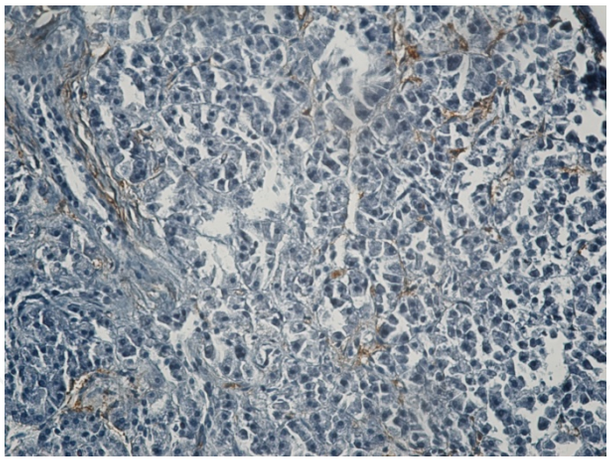

Figure 8. Immunostaining for Col IV, Collagen sinthesys at the periphery of the Langeshans isle. DAB x200

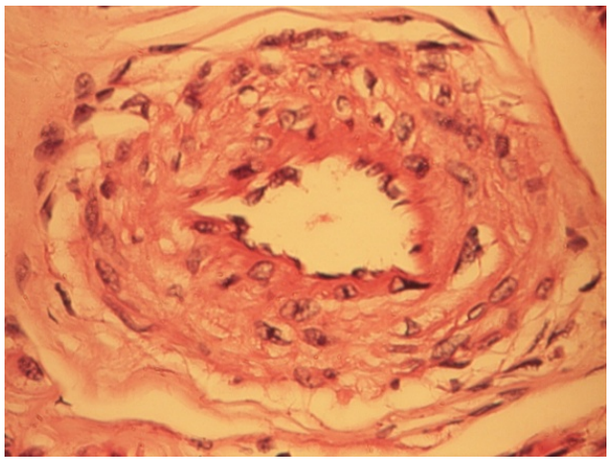

Figure 9. Myocytes lysis and edema in tunica media of the arteriole. HE x200

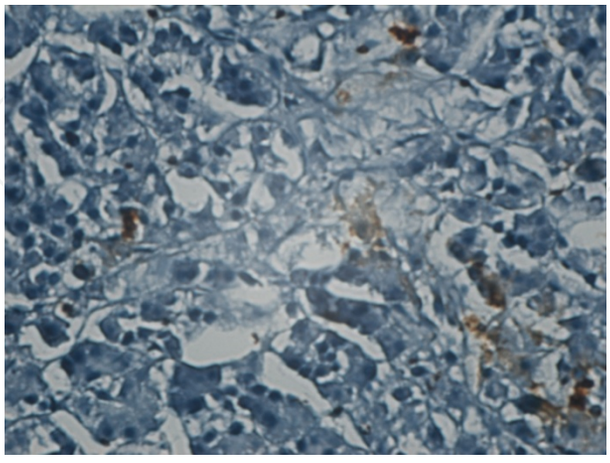

Figure 10. Issolated inter-acinar cells positive to CD34 immunostaining. DAB x400

The appearance of some fibrosis areas initiated in the peri-lobular septum, and the replacement of the parenchyma may lead to vessel "suffocation" (the fusion of the extracellular matrix with the vessels' adventitia and media with vascular collapse).

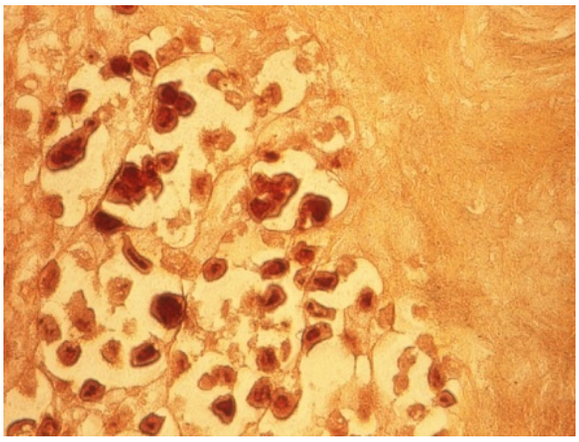

Figure 11. Argirophil cells anchored to the basement membrane in the neighboring of a fibrosis area. Silver staining x200

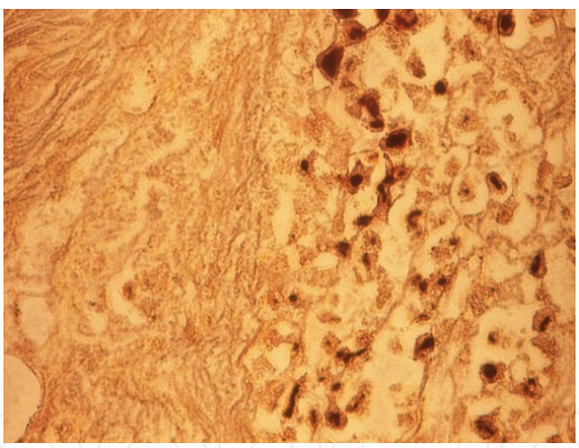

Figure 12. Argirophil stellate cells anchored to the basement membrane in the neighboring of a fibrosis area. Silver staining x200

In case of acute pancreatitis we observed isolated cells in the vicinity of intense necrotic lesions, this aspect being maintained in the vicinity of fibrosis zones in chronic pancreatitis (figure 11 and 12). These argirophils may provide the reticular fibril-genesis for vascular apparatus of the parenchyma [23].

The inhibition of MMP-3 and MMP-9 reduce the collagen degradation having as consequence the enhancement of fibriologenesis. This process is mediated by the pancreatic stellate cells in the matrix that produces regulatory cytokines involved in matrix remodeling [24].

http://dx.doi.org/10.5772/58921

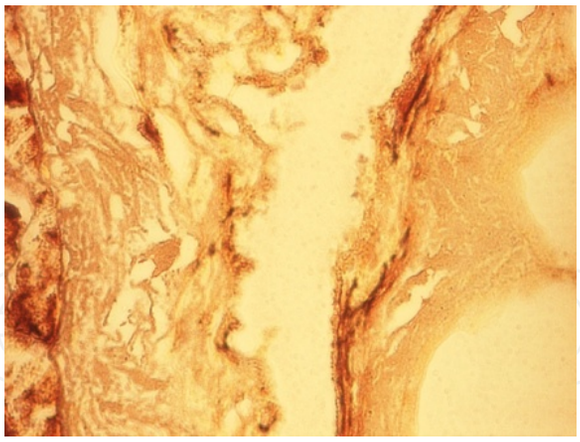

Figure 13. Ruptured reticular network in vessel's wall. Silver staining x200

In chronic pancreatitis fragmentations of the reticular fibers appear (figure 13). The fusion of the fibrosis area with the adventitia and media of the vessels lead to the maintenance of the vascular shape, this being the reason for the lack of hematic extravasations. The continuous of reticular network may lead to intravascular micro-thrombosis.

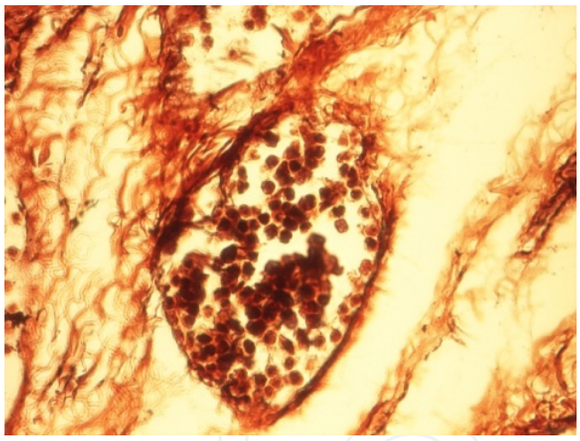

Figure 14. Partially kept reticular network with micro-thrombosis. Silver staining x200

The partial or total invasion of the fibrotic process in the tunica media of the arteriole may lead to the formation of high resistivity pseudo-fibrotic vascular apparatus (figure 14 and 15). This may be the pathogenic mechanism of low peripheral irrigation and eventually ischemia that may lead to a new acute pancreatic episode.

The described aspect is confirmed by collagen IV immunohistochemistry, that proves the accumulation of uni-directional fibers surrounding a former arteriole (figure 16).

In acute pancreatitis the characteristic dystrophic and necrotic lesions involved especially the intra-lobular vasculo-parenchymatous possibly due to aggressive protolithic attack. In chronic pancreatitis due to oxidative lesions there is an "activation" of the peri-lobular areas (stroma-

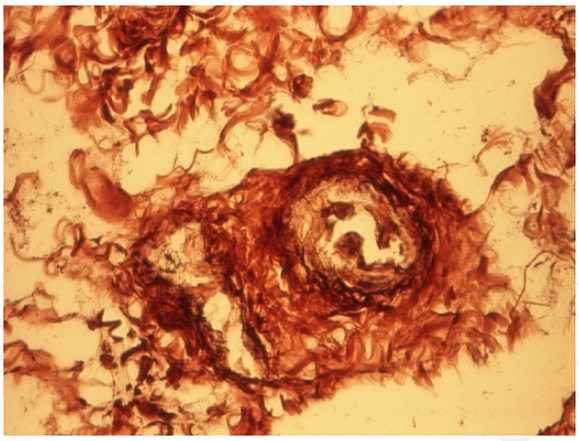

Figure 15. Blood vessels in a fibrosis area. Silver staining x200

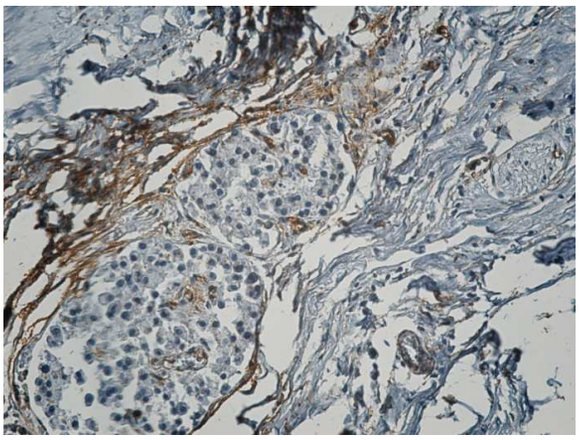

Figure 16. Unidirrectional collagen fibers surrounding blood vessels. Immunostaining for Col IV, DAB x200

septum) that lead to the "suffocation" of the blood vessels in some areas and to the appearance of pseudo-fibrotic arterioles as a compensation mechanism.

The endothelial and pericytar apoptosis may be the reason for the initial destruction of capillaries in acute pancreatitis, while in chronic pancreatitis there is a endothelial and pericyte hypertrophy is found as part of angio and vasculo genesis, Due to the non-typical aspect of the isle's capillaries, they disappear in isle involvement of acute pancreatitis, the vascularization being provided by the "gemini" vessels in the periphery of the Langerhans isle.

Vascular endothelial discontinuities and stasis associated to hemolysis, are typical lesion that occur in the small blood vessels areas that subsequently evolves into thrombosis. It it possible for this micro-thrombosis to be the key vascular event in acute necrotic pancreatitis [25-29]. These lesions may be observed in the early stages when stromal edema appears and there is no necrosis as yet. The thrombosis does not produce occlusion, only partial stenosis that leads to distal ischemia. This leasions often associate myo-lysis in the tunica media of and endothelial apoptosis. The necrosis appears as a consequence of vascular occlusion. Studies report as main vascular changes in chronic pancreatitis, the tortuosity and liminal irregularities of the

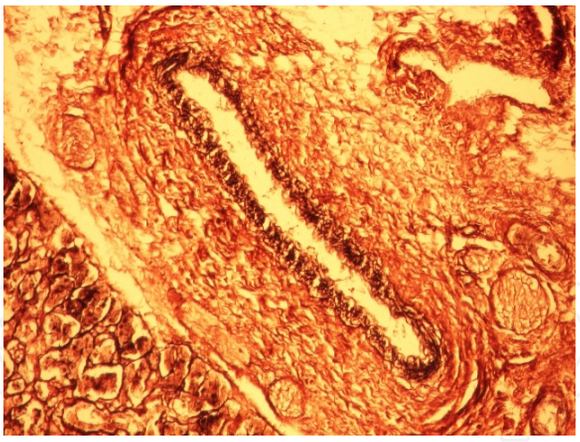

Figure 17. Blood vessels and nerves in a necrosis area. Silver staining x200

pancreatic arteries [30]. Those changes observed by angiography and micro-angiography [31-33] are confirmed by the microscopic aspect described in our study.

The argyrophilic structures of the pancreatic parenchyma is partially maintained even in necrosis areas, compared with the argyrophilic architecture of the small or large vesse Early or late acino-isle changes associated with stromal alterations do not usually involve the nerves, which are resistant to destruction [34-36] (figure 17). Pancreatic pain is characteristically described as a constant, severe, dull, epigastric pain that often radiates to the back and typically worsens after high-fat meals. However, many different pain patterns have been described, ranging from no pain to recurrent episodes of pain and pain free intervals, to constant pain with clusters of severe exacerbations [35-37].

Nerve structure of the nerve remains intact in fields of total necrosis, this being reflected in the noisy clinical symptoms associated to pancreatitis.

Pancreatic acinar cells seem to be especially vulnerable to endoplasmatic reticulum (ER) dysfunction owing to their dependence on high ER volume and functionality [38]. Pancreatic acinar cells, which are specialized in synthesis, storage and secretion of digestive enzymes, have the highest rate of protein synthesis among human tissues [39-41] and possess characteristically rich volume of ER. Thus, owing to the dependence on high ER volume and functionality, pancreatic acinar cells might be especially susceptible to perturbations in ER homeostasis. Indeed, ER stress has been previously described in pancreatic acinar cells during L-arginine induced experimental acute pancreatitis [42]. ER stress is newly considered to be a trypsinogen independent causing factor of pancrestitis.

4. Conclusions

Vascular dynamics differs in acute versus chronic pancreatitis.

In acute pancreatitis, areas of necrosis lack the vascular apparatus of capillary type with the appearance of focal intra-parenchymatous hemorrhages. In border zone, peri-necrotic, arterio-venullar apparatus remains.

In areas with acinar and isle architecture partially maintained, we identified "gemini" vessels with double involvement. They represent the starting point of the exocrine, respectively endocrine vascularization of the pen-umbra, with dystrophic Langerhans isles. The presence of capillaries in the periphery of the isle under the pseudo-capsule is a phenomenon frequently observed.

Partial lesions of capillary wall induce the activation of pericytes which acquire myo-fibroblast-like proprieties, initiating the perivascular fibrosis in the vicinity of necrotic areas.

In the fibrosis-necrosis border, we identified isolated argirophilic stellate cells presumably initiating the fibrosis. Due to their anchoring in the basement membrane of the former acinus we may assume the involvement of stellate cells in post-necrotic phagocytosis generating optically-void spaces.

In acute pancreatitis edema and myocytolysis was observed in the tunica media of large caliber vessels, while in chronic pancreatitis the fibrotic process of the media dominates leading to vessel "suffocation".

In chronic pancreatitis the hemorrhages are rare or absent due to the fusion of partially fragmented reticular network with the collagen fibers of the fibrosis areas.

We observed that in chronic pancreatitis, the nerva vasorum remains intact, leading to the idea of their resistance to the characteristic lesions of the acute event.

The most important difference, in our opinion, between chronic and acute pancreatitis is that the physiopathologic cascade is induced by the vascular apparatus. Thus in acute pancreatitis the lesions have a centrifuge evolution, while in chronic pancreatitis the centripetal evolution is characteristic.

Author details

Garofita-Olivia Mateescu[1], Bogdan Oprea[1], Liliana Stanca[2], Mihaela Hincu[3], Malina Coman[4], Stelian Mogoanta[5], Dragos Voicu[4], Relu Stanescu[6] and Ion Rogoveanu[7]

1 University of Medicine and Pharmacy Craiova, Histology Department, Romania

2 University of Medicine and Pharmacy Craiova, Forensic Department, Romania

3 University "Ovidius" Constanta, Histology Department, Romania

4 "Dunarea de Jos" University Galati, Morphology Department, Romania

5 University of Medicine and Pharmacy Craiova, General surgery Department, Romania

6 University of Medicine and Pharmacy Craiova, Anatomy Department, Romania

7 University of Medicine and Pharmacy Craiova, Gastroenterology Department, Romania

References

[1] Glasbrenner B., Adler G. Pathophysiology of acute pancreatitis. Hepatogastroenterology 1993;40(6) 517-521.

[2] A. Izakson, T. Ezri, Dana Weiner, Diana Litmanovich, E.V. Khankin New developments in understanding of pathophysiology, diagnosis and treatment of severe acute pancreatitis. Jurnalul Roman de Anestezie Terapie Intensiva 2012;19(1) 39-50.

[3] Oiva J, Mustonen H Patients with acute pancreatitis complicated by organ failure show highly aberrant monocyte signaling profiles assessed by phospho-specific flow cytometry. Crit Care Med 2010;38 1702-1708.

[4] B. Suresh Kumar Shetty, Ramdas Naik, Adithi S. Shetty, Sharadha Rai, Ritesh G. Menezes and Tanuj Kanchan. Acute Pancreatitis-The Current Concept in Ethiopathogenesis, Morphology and Complications, Pancreatitis-Treatment and Complications, Prof. Luis Rodrigo (Ed.), ISBN: 978-953-51-0109-3: InTech; 2012.

[5] Apte MV, Wilson JS. Stellate cell activation in alcoholic pancreatitis. Pancreas 2003;27 316-320.

[6] Bachem MG, Zhou Z, Zhou S, Siech M. Role of stellate cells in pancreatic fibrogenesis associated with acute and chronic pancreatitis. J Gastroenterol Hepatol 2006;21Suppl 3 92-96.

[7] Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology 2008;134 1655-1669.

[8] Christina Brock, Lecia Moller Nielsen, Dina Lelic, and Asbjørn Mohr Drewes, Pathophysiology of chronic pancreatitis. World J Gastroenterol. 2013;19(42) 7231-7240.

[9] Lévy P, Barthet M, Mollard BR, Amouretti M, Marion-Audibert AM, Dyard F. Estimation of the prevalence and incidence of chronic pancreatitis and its complications. Gastroenterol Clin Biol. 2006;30 838-844.

[10] Andersen BN, Pedersen NT, Scheel J, Worning H. Incidence of alcoholic chronic pancreatitis in Copenhagen. Scand J Gastroenterol. 1982;17 247-252.

[11] Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol. 2007;42 101-119.

[12] Klöppel G, Detlefsen S, Feyerabend B. Fibrosis of the pancreas: the initial tissue damage and the resulting pattern. Virchows Arch. 2004;445 1-8.

[13] Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120 682-707.

[14] Andrén-Sandberg A, Hoem D, Gislason H. Pain management in chronic pancreatitis. Eur J Gastroenterol Hepatol. 2002;14 957-970.

[15] Pace A, Weerth AD, Berna M, Hillbricht K, Tsokos M, Bläker M, et al. Pancreas and liver injury are associated in individuals with increased alcohol consumption. Clin Gastroenterol Hepatol 2009;7 1241-1246.

[16] Whitcomb DC. Genetic polymorphisms in alcoholic pancreatitis. Dig Dis 2005;23 247-254.

[17] E Ryschich, V Kerkadze, O Deduchovas, O Salnikova, A Parseliunas, A Marten,W Hartwig, M Sperandio, J Schmidt, Intracapillary leucocyte accumulation as a novel antihaemorrhagic mechanism in acute pancreatitis in mice. Gut 2009;58 1508-1516.

[18] Schmid-Schonbein GW. The damaging potential of leukocyte activation in the microcirculation. Angiology 1993;44 45–56.

[19] Fitzal F, Delano FA, Young C, et al. Early capillary no-reflow during low-flow reperfusion after hind limb ischemia in the rat. Ann Plast Surg 2002;49 170-180.

[20] Helin H, Mero M, Helin M, Markkula H., Elastic tissue injury in human acute pancreatitis, Pathol Res Pract. 1981;172(1-2) 170-175.

[21] Garofita-Olivia Mateescu, Contribution to the histological study of the pancreas in ethanol consummators, PhD thesis. University of Medicine and Pharmacy of Craiova;

[22] Hu W, Fu L., Simultaneous characterization of pancreatic stellate cells and other pancreatic components within three-dimensional tissue environment during chronic pancreatitis, J Biomed Opt. 2013;18(5) 56002.

[23] Apte M V, Pirola RC, Wilson JS. Mechanisms of alcoholic pancreatitis. J Gastroenterol Hepatol 2010;25 1816-26.

[24] Shek FW, Benyon RC, Walker FM, McCrudden PR, Pender SL, Williams EJ, Johnson PA, Johnson CD, Bateman AC, Fine DR. Expression of transforming growth factor-beta 1 by pancreatic stellate cells and its implications for matrix secretion and turnover in chronic pancreatitis. Am J Pathol. 2002;160 1787–1798.

[25] I. Kovalska, O. Dronov, S. Zemskov, E. Deneka, M. Zemskova, Patterns of Pathomorphological Changes in Acute Necrotizing Pancreatitis, International Journal of Inflammation, 2012 1-4.

[26] Mann DA, Mann J. Epigenetic regulation of hepatic stellate cell activation. J Gastroenterol Hepatol 2008;23Suppl 1 108-111.

[27] D. Uhlmann, H. Lauer, F. Serr, and H. Witzigmann, Pathophysiological role of platelets and platelet system in acute pancreatitis. Microvascular Research. 2008;76(2) 114-123

[28] C. M. Cuthbertson and C. Christophi, Disturbances of the microcirculation in acute pancreatitis, British Journal of Surgery. 2006;93(5) 518–530.

[29] T.Hackert,D. Pfeil,W.Hartwig Platelet function in acute experimental pancreatitis. Journal of Gastrointestinal Surgery. 2007;11(4), 439–444.

[30] Pekka Pítkäranta, Leena Kivisaari, Stig Nordling, Pekka Nuutinen, Torn Schröder, Vascular changes of pancreatic ducts and vessels in acute necrotizing, and in chronic pancreatitis in humans. International Journal of Pancreatology. 1991;8(1) 13-22

[31] Reuter SR, Redman HC, Joseph RR. Angiographic findings in pancreatitis. Amer. J. Roentgenol. 1969;107 56–64.

[32] Boijsen E, Tylen U. Vascular changes in chronic pancreatitis. Acta Radiol. Diagn. 1972; 12 34–48.

[33] Tylen U, Arnesjö B. Angiographic diagnosis of inflammatory disease of the pancreas. Acta Radiol. Diagn. 1973;14 215–240.

[34] T. Kerner, B. Vollmar, M. D. Menger, H. Waldner, and K. Messmer. Determinants of pancreatic microcirculation in acute pancreatitis in rats. Journal of Surgical Research. 1996;62(2) 165–171.

[35] E. Malecka-Panas, A. Gasiorowska, A. Kropiwnicka, A. Zlobinska, and J. Drzewoski, Endocrine pancreatic function in patients after acute pancreatitis, Hepato-gastroenterology. 2002;49(48) 1707–1712.

[36] Kumar V., Abbas A.K., Fausto N., Aster J.C., Robins and Cotran Pathologic Basis of Disease, 8th Edition, Philadelphia, Elsevier, 2010, 850.

[37] Poulsen JL1, Olesen SS, Malver LP, Frøkjær JB, Drewes AM. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. World J Gastroenterol. 2013;19(42) 7282-7291.

[38] Fasanella KE, Davis B, Lyons J, Chen Z, Lee KK, Slivka A, Whitcomb DC. Pain in chronic pancreatitis and pancreatic cancer. Gastroenterol Clin North Am. 2007;36 335-364.

[39] Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. Gastroenterology. 1999;116 1132–1140.

[40] Sah RP, Garg SK, Dixit AK, Dudeja V, Dawra RK, Saluja AK2. Endoplasmic Reticulum stress is chronically activated in chronic pancreatitis. J Biol Chem. 2014.

[41] Case, R. M. Synthesis, intracellular transport and discharge of exportable proteins in the pancreatic acinar cell and other cells. Biol Rev Camb Philos Soc. 1978;53 211-354.

[42] Kubisch, C. H., Sans, M. D., Arumugam, T., Ernst, S. A., Williams, J. A., and Logsdon, C. D. Early activation of endoplasmic reticulum stress is associated with arginine-induced acute pancreatitis. Am J Physiol Gastrointest Liver Physiol 2006;291 238-245.

IntechOpen