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Pancreatitis in Rheumatoid Arthritis and the Role of Systemic AA Amyloidosis in the Pathogenesis of Pancreatitis – A Postmortem Clinicopathologic Study of 161 Patients

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Abstract

*The prevalence of pancreatitis is higher in rheumatoid arthritis (**RA**) than in the general population.*

*The **aim** of this study was to determine the prevalence of* **acute liponecrotic** *(**aLnP**),* **acute relapsing liponecrotic** *(**aRelLnP**), and* **chronic liponecrotic pancreatitis** *(**chrLnP**) in **RA**, and analyze the possible role of systemic and pancreatic AA amyloidosis (**sAAa** and **pAAa**) in the pathogenesis of pancreatitis.*

***Patients and Methods:** At the National Institute of Rheumatology **9475** patients died between 1969 and 1992; among them **161** with **RA** and all of them were autopsied.*

***RA** was confirmed clinically according to the criteria of the American College of Rheumatology (**ACR**).*

*Tissue samples of pancreas were available for histologic evaluation in **118** of 161 patients.*

*Prevalence and histological patterns of pancreatitis were determined at autopsy and characterized histologically. **sAAa** and **pAAa** was specified histologically, based on evaluation of **5** organs (heart, lung, liver, kidney and pancreas) in each of the patients.*

*Demographics of different patient cohorts were compared with the Student (Welch) t-probe. The rerelationship between **aLnP**, **aRelLnP** or **chrLnP** and **sAAa** or **pAAa** were analyzed by Pearson's chi-squared (χ^2) test.*

***Results:** Multiple liponecrotic foci (**LnP**) were found in **15 (12.71 %)** of 118 patients; **aLnP** existed in **8 (53.33 %)**, **aRelLnP** in **4 (26.67 %)**, and liponecrotic foci in combination with chronic fibrotic pancreatitis (**chrLnP**) in **3 (20.0 %)** of these 15 patients.*

*Systemic **AAa** complicated **RA** in **29 (24.58 %)** of 118 patients. Amyloid **A** deposition was detected in blood vessel walls, and on different tissue structures of pancreas in **26 (89.66 %)** of 29 cases; in **3 (10.34 %)** of 29 patients Amyloid **A** depositis were not found in the pancreas. In **8 (30.77 %)** of 26 patients with **pAAa** was extreme severe.*

***Discussion and Conclusions:** In elderly **female RA** patient the risk of **LnP** was higher comparing those with **males** or with **LnP** not associated **RA** patient, and the elderly female patients with **LnP** died significantly earlier.*

***sAAa**, as basic complication of **RA**, **may develope in both sexes**, and **at any time in the course of the disease**, and **pAAa** is **closely connected with it**.*

*In essence **sAAa** not influence the prevalence of pancreatitis, but at higer disease activity, massive amyloid **A** deposition in the walls of the pancreatic arterioles, small and medium size arteries can cause local ischemia and lead to a special form of **LnP**, namely to **aRelLnP** (the connection between extreme severe **pAAa** and **aRelLnP** was significant). Marked **pAAa** should be regarded an important vasculogenic factor in pathogenesis of **aRelLnP**, which may be regarded as a special manifestation of autoimmune pancreatitis or a new vasculogenic entity in **RA**.*

*Long term progressive accumulation of amyloid A deposits in the vessel walls and different structures of the pancreas may be associated with **chrLnP**, but the connection (link) between **pAAa** and **chrLnP** was not siginificant. This means, that **pAAa** is only partially responsible for **chrLnP, and other reasons should be considered as well.***

Keywords: *Rheumatoid arthritis, pancreatitis, systemic and pancreatic AA amyloidosis*

Abbreviations

RA = **R**heumatoid **A**rthritis

ACR = American College of Rheumatology

aLnP – acute liponecrotic pancreatitis

aRelLnP – acute relapsing liponecrotic pancreatitis

chrP – chronic pancreatitis

chrRelP – chronic relapsing pancreatitis

chrLnP – chronic liponecrotis pancreatitis

eIP – edematous inflammatory pancreatitis or "serous" infection associated pancreatitis

sAAa – **s**ystemic **AA a**myloidosis

pAAa – **p**ancreatic **AA a**myloidosis

SD – Standard **D**eviation

NS – Not **S**ignificant

H-E – Hematoxylin-**E**osin staining

PAS – Perjodic **A**cid **S**chiff reaction

Introduction

The prevalence of pancreatitis is higher in rheumatoid arthritis (**RA**) than in the general population [1].

The **aim** of this study was to determine the prevalence of ***acute liponecrotic*** (**aLnP**), ***acute relepsing liponecrotic*** (**aRelLnP**), and ***chronic liponecrotic pancreatitis*** (**chrLnP**) in **RA**, and analyze the possible role of systemic and pancreatic AA amyloidosis (**sAAa** and **pAAa**) in the pathogenesis of pancreatitis.

Patients and Methods

At the National Institute of Rheumatology **9475** patients died between 1969 and 1992; among them **161** with **RA** and all of them were autopsied [2].

RA was confirmed clinically according to the criteria of the American College of Rheumatology (**ACR**) [3].

Tissue samples of pancreas were sutable for histologic evaluation in **118** of 161 patients.

Prevalence and histological patterns of pancreatitis were determined at autopsy and characterized histologically [4, 5].

Systemic **AAa** was specified histologically, based on evaluation of **5** organs (heart, lung, liver, kidney and pancreas) in each of the patients. Amyloid A deposiotion was diagnosed according to Romhányi [6] by a modified (more sensitive) Congo red staining [7]. Amyloid A deposits were identified in serial sections by immunohistochemical and histochemical methods [8. 9].

The extent of amyloid A deposition was evaluated by semi-quantitative, visual estimation on a 0 to 3 plus scale, based on the number of involved tissue structures in a light microscopic field [2].

("**0**": no amyloid deposits, "**1**": Sporadic, minimal amyloid deposits on different tissue structures,

"**2**": less than five, resp. "**3**": five or more involved tissue structures in a microscopic field at objective magnification of x20)

Demographics of different patient cohorts were compared with the Student (Welch) t-probe [10]. The rerelationship between **aLnP**, **aRelLnP** or **chrLnP** and **sAAa** or **pAAa**, furthermore between **sAAa** and **pAAa** were analyzed by chi-squared test [10].

Glossary of Definitions

Histologic Patterns of Pancreatitis [4, 5]

Liponecrotic pancreatitis (**LnP**) –multiple acinar liponecrotic foci, with or without inflammatory reaction, with or without hemorrhages

Acute liponecrotic pancreatitis (**aLnP**) – acinar liponecrotic foci usually in the same stage and similar size of necrosis, with or without inflammatory reaction, with or without hemorrhages

Acute relapsing liponecrotic pancreatitis (**aRelLnP**) – acinar liponecrotic foci in different stage and size of necrosis, with or without inflammatory reaction, hemorrhages, calcification (saponification) or liquefaction (pseudocyst formation)

Chronic pancreatitis (**chrP**) – multifocal or diffuse fibrotic interstitial pancreatitis with more or less explicit (pronounced) glandular atrophy, with or without ductal changes: plugges (concentrated secretum of exocrine glands), ductal dilatation (ductectasia), ductal proliferation, and metaplasia

Chronic relapsing pancreatitis (**chrRelP**) – focal accentuated diffuse fibrotic interstitial pancreatitis usually with pronounced glandular atrophy and ductal changes

Chronic liponecrotic pancreatitis (**chrLnP**) – liponecrotic foci in combination with histological characteristics of **chrP** or **chrRelP**

Edematous inflammatory pancreatitis or "serous" infection associated pancreatitis (**eIP**) – usually a mild diffuse edematous inflammatory interstitial pancreatitis without acinar cell necrosis or hemorrhages

The prevalence of **chrP**, **chrRelP** and **eIP were not evaluated** in this study

"**Prevalence" of systemic AA amyloidosis** – concerns the presence of amyloid A deposits in the wall of blood vessels of different calibers or on different tissue structures of various organs

Size of Blood Vessels [11] in Tissue Samples with Branches of Splenic Artery, Upper and Lower Gastroduodenal Arteries

Arteriole (**a**) – no internal or external elastic membrane, <500 micrometers in diameter

Small artery (**A**) – only internal elastic membrane present, vessels 500-1000 micrometers in diameter

Medium size artery (**AA**) – internal and external elastic membrane are present – vessel >1000 micrometers in diameter

Venule (**v**), ***small vein*** (**V**), ***medium size vein*** (**VV**) –accompanying (**a**), (**A**) or (**AA**)

Results

Multiple liponecrotic foci (**LnP**) were found in **15 (12.71 %)** of 118 patients; **aLnP** existed in **8** (**53.33** %), **aRelLnP** in **4** (**26.67** %), and liponecrotic foci in combination with chronic fibrotic pancreatitis (**chrLnP**) in **3 (20.0 %)** of these 15 patients.

Systemic **AAa** complicated **RA** in **29 (24.58 %)** of 118 patients. Amyloid **A** deposition was detected in blood vessel walls (arterioles, small and medium size arteries, veins), and on different tissue structures (interstitial and reticular collagen fibres, nerves, periductal basal membranes) of pancreas in **26** (**89.66** %) of 29 cases; in **3 (10.34 %)** of 29 patients Amyloid **A** depositis were not found in the pancreas.

Marked (extreme severe) amyloid **A** deposition (**≤1.3**/pancreas) was found in the walls of arterioles, small and medium size arteries, and on different tissue structures of the pancreas in **8** (**30.77** %) of 26 patients with **pAAa**.

Demographics, onset and duration of **RA** associated or complicated by **LnP** and **sAAa** or **pAAa** are summarized in Table 1.

Table 1. *Sex, mean age with SD, range, onset and disease duration of RA patients with (n=15) or without LnP (n=103), and with (n=29) or without sAAa (n=89), furthermore with pAAa (n=26) including extreme severe (n=8) or moderate cases (n=18)*

Sex	Number of autopsies	Mean age in years at death ± SD	Range (in years)	Mean age at onset of disease ± SD	Disease duration (in years) mean ± SD
RA patients (total)	**161**	**65.32±12.95**	**16 – 88**	**50.83±16.96**	**14.43±10.51**
Female	116	64.95±11.79	16 – 87	50.19±15.70	14.79±10.65
Male	45	66.29±15.50	19 – 88	52.57±19.88	13.46±10.08
RA patients (pancreas)	**118**	**64.97±12.84**	**16– 88**	**51.44±16.80**	**13.84±10.40**
Female	80	64.41±11.95	16 – 87	50.75±15.03	13.84±10.43
Male	38	66.13±14.48	19 – 88	53.03±20.20	13.29±10.31
With LnP	**15**	**65.13±14.12**	**32 – 87**	**56.63±13.03**	**9.79±8.19**
Female	10	65.10±11.43	51 – 87	55.44±12.72	7.44±7.64
Male	5	65.20±18.35	32 – 82	59.00±13.32	14.50±7.16
Without LnP	**103**	**64.95±12.65**	**16 – 88**	**50.75±17.13**	**14.38±10.54**
Female	70	64.31±12.01	16 – 84	50.15±15.19	14.93±10.43
Male	33	66.27±13.80	19 – 88	52.15±20.88	13.11±10.68
With sAAa	**29**	**62.14±15.30**	**19 – 88**	**47.59±16.66**	**15.59±9.35**
Female	24	64.42±9.34	44 – 82	48.70±12.66	15.74±9.96
Male	5	51.20±28.18	19 – 88	41.25±30.07	14.75±4.44
Without sAAa	**89**	**65.90±11.79**	**16 – 87**	**52.83±16.64**	**13.21±10.68**
Female	56	64.41±12.90	16 – 87	51.73±15.95	13.29±10.55
Male	33	68.39±9.07	52 – 87	54.78±17.63	13.07±10.89
AAa of pancreas (pAAa)	**26**	**61.96±15.47**	**19 – 88**	**47.88±16.86**	**15.25±9.07**
Female	21	64.52±8.55	44 – 82	49.20±12.24	15.35±9.74
Male	5	51.20±28.18	19 – 88	41.25±30.07	14.75±4.44
Extreme severe pAAa	**8**	**56.75±19.12**	**19 – 82**	**36.57±17.80**	**19.14±7.94**
Female	5	63.60±5.54	58 – 73	42.50±6.58	21.00±9.67
Male	3	45.33±26.74	19 – 82	28.67±23.92	16.67±3.40
Mild or moderate pAAa	**18**	**64.33±12.88**	**32 – 88**	**52.65±14.05**	**13.59±9.06**
Female	16	64.88±9.27	44 – 82	51.00±12.79	13.88±9.27
Male	2	60.00±28.00	32 – 88	79.00±00.00	9.00±00.00

Glossary to Table 1

RA: Rheumatoid **A**rthritis; **LnP**: **L**iponecrotic **P**ancreatitis (including **aLnP**, **aRelLnP** and **chrLnP**)

sAAa: systemic **AA a**myloidosis; **pAAa: p**ancreatic **AA a**myloidosis; **SD**: Standard deviation

Comparing the **age, sex, onset of RA**, and **duration of disease** at the time of death there was **no significant** difference between **female** (p< 0.85, p< 0.33, **p< 0.039**) and **male** (p< 0.91, p< 0.47, p< 0.78) **RA** patients **with** (n=15) and **without** (n=103) **LnP** (p< 0.96, p< 0.19, p< 0.11) except duration of **RA** of female patients.

The mean age of **female** patients, complicated by or associated with **LnP** was higher at onset of **RA** comparing those without **LnP** (55.44 years versus 50.15; p< 0.333 – NS), and the elderly female patients with **LnP** died significantly earlier (7.44 years versus 14.93; **p< 0.0396**) (Tables 1-2).

Comparing the **age, sex, onset of RA**, and **duration of**

disease at the time of death there was **no significant** difference between **female** (p< 0.998, p< 0.40, p< 0.36) and **male** (p< 0.29, p< 0.50, p< 0.63) **RA** patients **with** (n=29) and **without sAAa** (n=89) (p< 0.24, p< 0.17, p< 0.29).

The **age, sex of RA** patients and **onset of disease** did not influence the amyloid A deposition in the pancreas; there was **no significant** difference between **female** (p< 0.81, p< 0.23, p< 0.43) and **male** (p< 0.82, p< 0.63, p< 0.61) **RA** patients **with sAAa** (n=29) and **pAAa** (n=26) (p< 0.51, p< 0.20, p< 0.36); furthermore between **female** (p< 0.73, p< 0.13, p< 0.30) and **male** (p< 0.71) **RA** patients **with extreme severe AAa** of **pancreas** (n=8) and **mild** or **moderate AAa** of **pancreas** (n=18) (p< 0.36, p< 0.08, p< 0.18) (Table 2).

sAAa and **pAAa complicated RA in both sexes**, and **at any time in the course of the disease**. The relationship between **sAAa** and **pAAa** was very strong positive and significant (association's coefficient=1, χ^2=97.191, **p <0.00000**).

Table 2. *The statistical correlations ("p" values of significance) between female and male RA patients with and without LnP and sAAa or pAAa*

RA patients n=118	Age	Onset of disease	Disease duration
RA pts. n=118 versus RA with **LnP** n=15	p< 0.97	p< 0.24	p< 0.15
Female n=80 versus n=10	p< 0.87	p< 0.38	p< 0.064
Male n=38 versus n=5	p< 0.93	p< 0.52	p< 0.80
RA pts. n=118 versus RA with **sAAa** n=29	p< 0.36	p< 0.29	p< 0.40
Female n=80 versus n=24	p< 0.99	p< 0.51	p< 0.49
Male n=38 versus n=5	p< 0.35	p< 0.55	p< 0.66
with LnP n=15 versus **without LnP** n=103	p< 0.96	p< 0.19	p< 0.11
Female n=10 versus n=70	p< 0.85	p< 0.33	**p< 0.0396**
Male n=5 versus n=33	p< 0.91	p< 0.47	p< 0.78
with sAAa n=29 versus **without sAAa** n=89	p< 0.24	p< 0.17	p< 0.29
Female n=24 versus n=56	p< 0.99	p< 0.40	p< 0.36
Male n=5 versus n=33	p< 0.29	p< 0.50	p< 0.63
with sAAa n=29 versus **pAAa** n=26	p< 0.51	p< 0.20	p< 0.36
Female n=24 versus n=21	p< 0.81	p< 0.23	p< 0.43
Male n=5 versus n=5	p< 0.82	p< 0.63	p< 0.61
Extreme severe pAAa (≤1.3) n=8 versus **mild** or **moderate (>1.3) pAAa** n=18	p< 0.36	p< 0.08	p< 0.18
Female n=5 versus n=16	p< 0.73	p< 0.13	p< 0.30
Male n=3 versus n=2	p< 0.71	-	-

Glossary to Table 2

RA: Rheumatoid **A**rthritis; **LnP**: **L**iponecrotic **P**ancreatitis (including **aLnP**, **aRelLnP** and **chrLnP**)

sAAa: systemic **AAa**myloidosis; **pAAa: p**ancreatic **AAa**myloidosis

Four (**2 aRelLnP** and **2 chrLnP** – **26.66** %) of 15 **LnP** were associated with **sAAa** (**aLnP** was not associated with **sAAa**). There was no significant correlation between **LnP** and **sAAa** (χ^2=0.0405, p <0.840). The link between **aRelLnP** and **sAAa** (χ^2=0.3730, p <0.541) or **chrLnP** and **sAAa** was also not significant (χ^2=1.0734, p <0.30) (Table 3).

The same cases of **LnP** (**aRelLnP** n=2 and **chrLnP** n=2) were associated with **pAAa** (**aLnP** was not associated with **pAAa**). There was no significant correlation between **LnP** and **pAAa** (χ^2=0.2146, p <0.643). The link between **aRelLnP** and **pAAa** (χ^2=0.5765, p <0.447) or **chrLnP** and **pAAa** was also not significant (χ^2=1.4014, p <0.236) (Table 3).

Two (**50.0** %) of 4 patients with **aRelLnP** was accompanied by extreme severe amyloid **A** deposits (**≤1.3**/pancreas) in the walls of arterioles, small and medium size arteries, and on different tissue structures of the pancreas (**aLnP** or **chrLnP** was not associated with marked **pAAa**). There was a significant correlation between **aRelLnP** and **marked pAAa** (χ^2=6.1825, **p <0.013**) (Table 3).

Table 3. *The statistical correlations ("p" values of significance) between LnP, aRelLnP or chrLnP and sAAa or pAAa, furthermore between LnP, aRelLnP or chrLnP and marked pAAa (≤1.3/pancreas) (aLnP was not associated with sAAa or pAAa or marked pAAa)*

Pancreatitis	LnP	aRelLnP	chrLnP
sAAa	χ^2=0.0405, p <0.840	χ^2=0.3730, p <0.541	χ^2=1.0734, p <0.30
pAAa	χ^2=0.2146, p <0.643	χ^2=0.5765, p <0.447	χ^2=1.4014, p <0.236
Marked pAAa	χ^2=0.2819, p <0.595	**χ^2=6.1825, p <0.013**	χ^2=0.4761, p <0.490

Amyloid **A** deposits in the wall of blood vessels, with acinar liponecrotic foci are demonstrated in Figures 1-4.

Original magnifications correspond to the 24x36 mm transparency slide – the correct height: weigth ratio is 2:3.

The printed size may be different, therefore it is necessary to indicate the original magnifications corresponding to a fixed size.

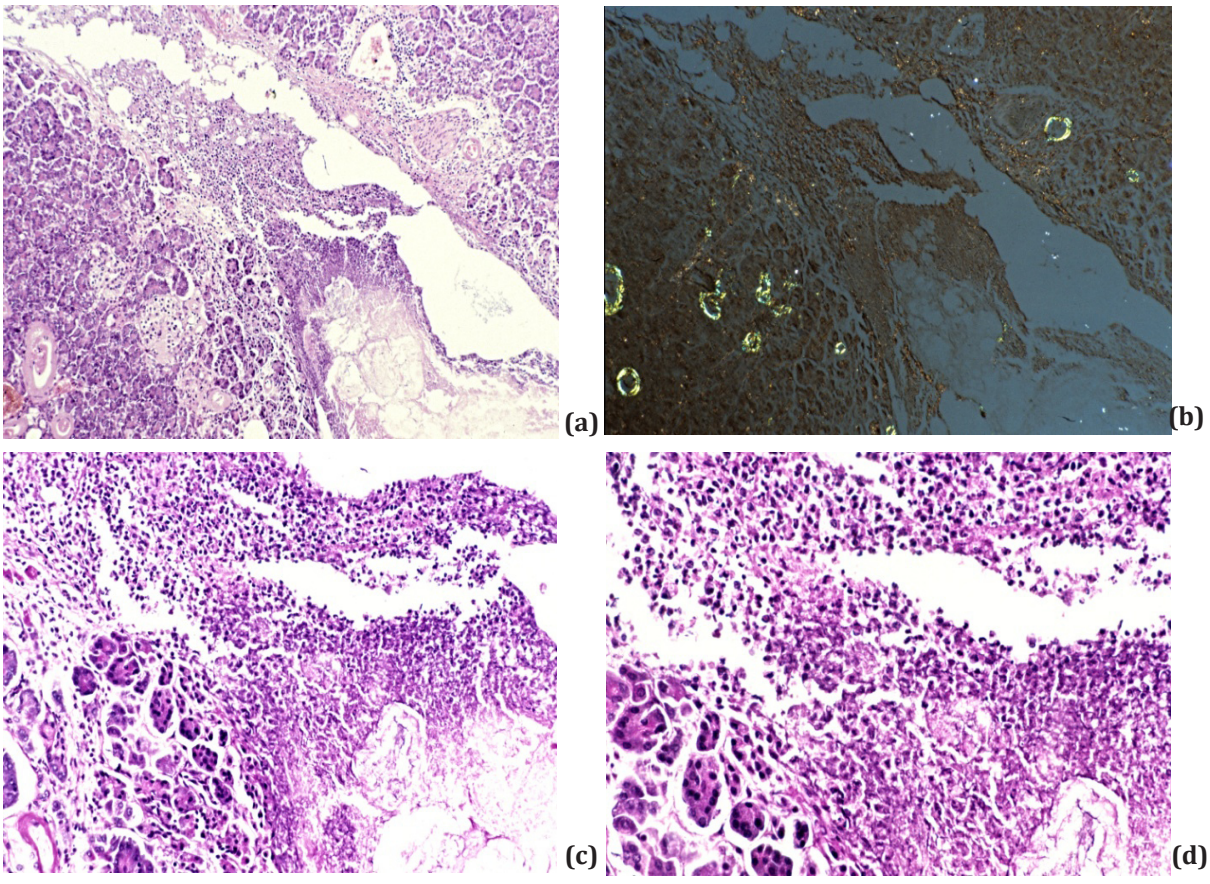

Figure 1a-d. *RA, AAa, Pancreas*

Amyloid A deposits in the wall of arterioles in association with liponecrotic pancreatitis

(a) H-E, x20 **(b)** Same as (a) Congo red, x20 **(c)** Same as (a), H-E, x50 **(d)** Same as (a), H-E, x125

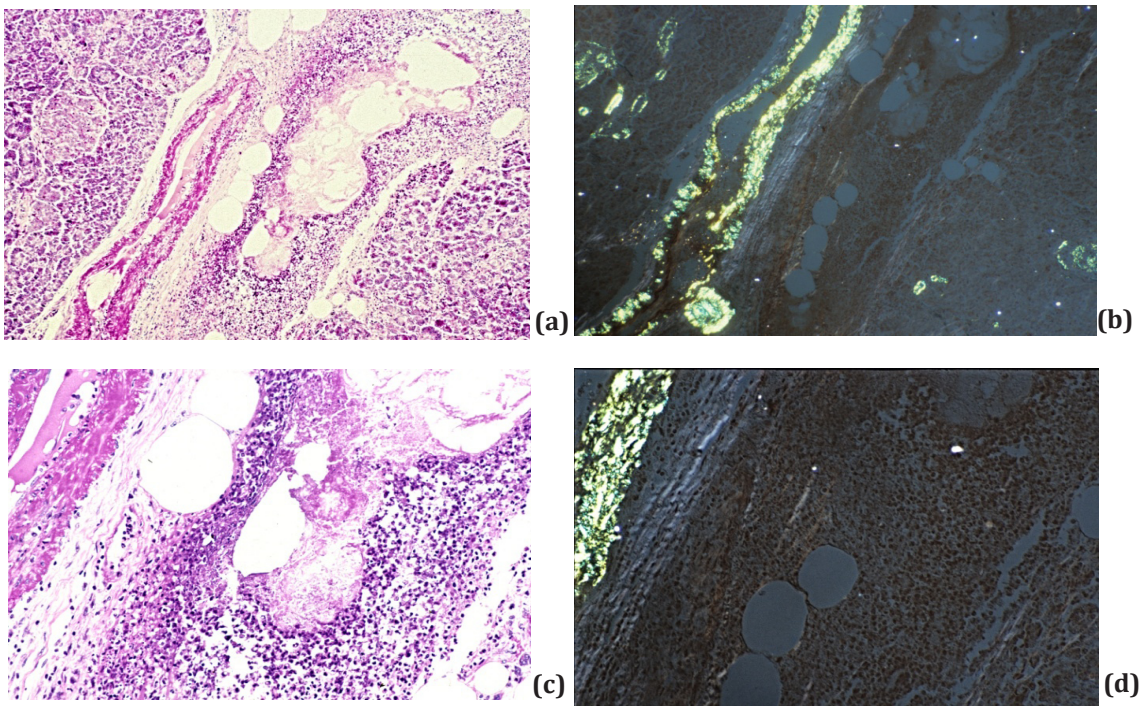

Figure 2a-d. *RA, AAa, Pancreas*

Marked amyloid A deposits in the wall of arterioles and small artery in association with focal liponecrotic pancreatitis (**a**) PAS, x125 (**b**) Same as (a) Congo red, x50 (**c**) Same as (a) PAS, x125 (**d**) Same as (b) Congo red, x125

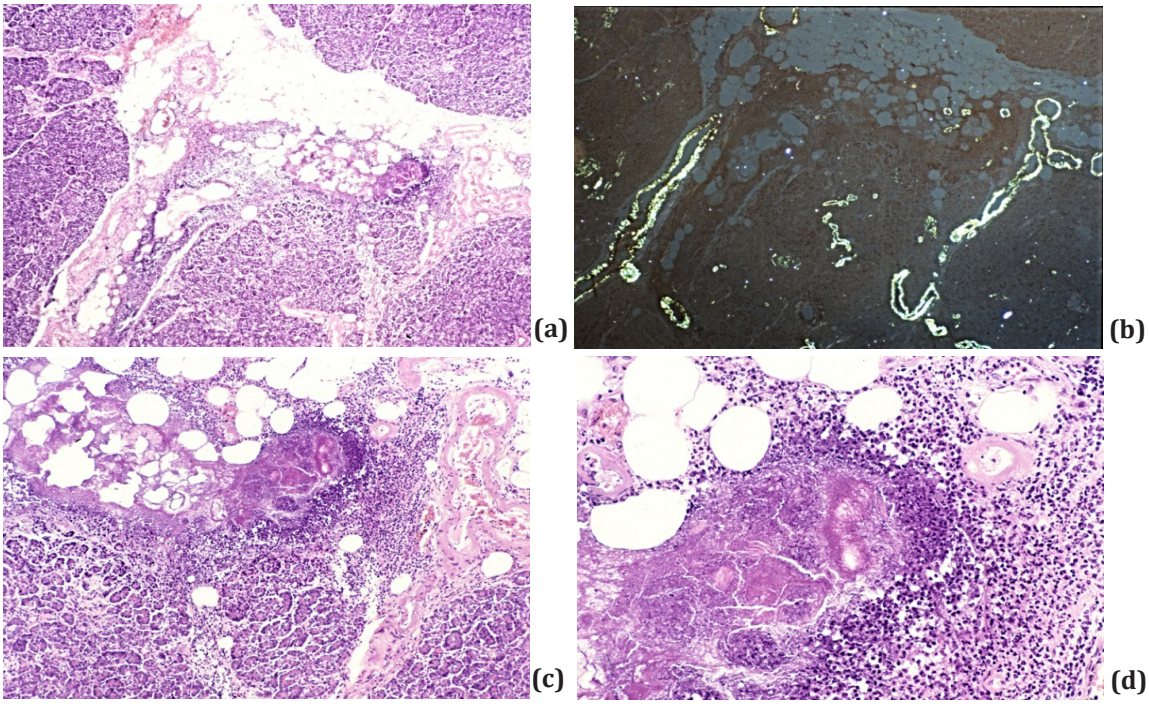

Figure 3a-d. *RA, AAa, Pancreas*

Marked amyloid A deposits in the wall of arterioles, small arteries and medium size arteries in association with focal liponecrotic pancreatitis

(**a**) H-E, x20 (**b**) Same as (a) Congo red, x20 (**c**) Same as (a) H-E, x50 (**d**) Same as (a) H-E, x125

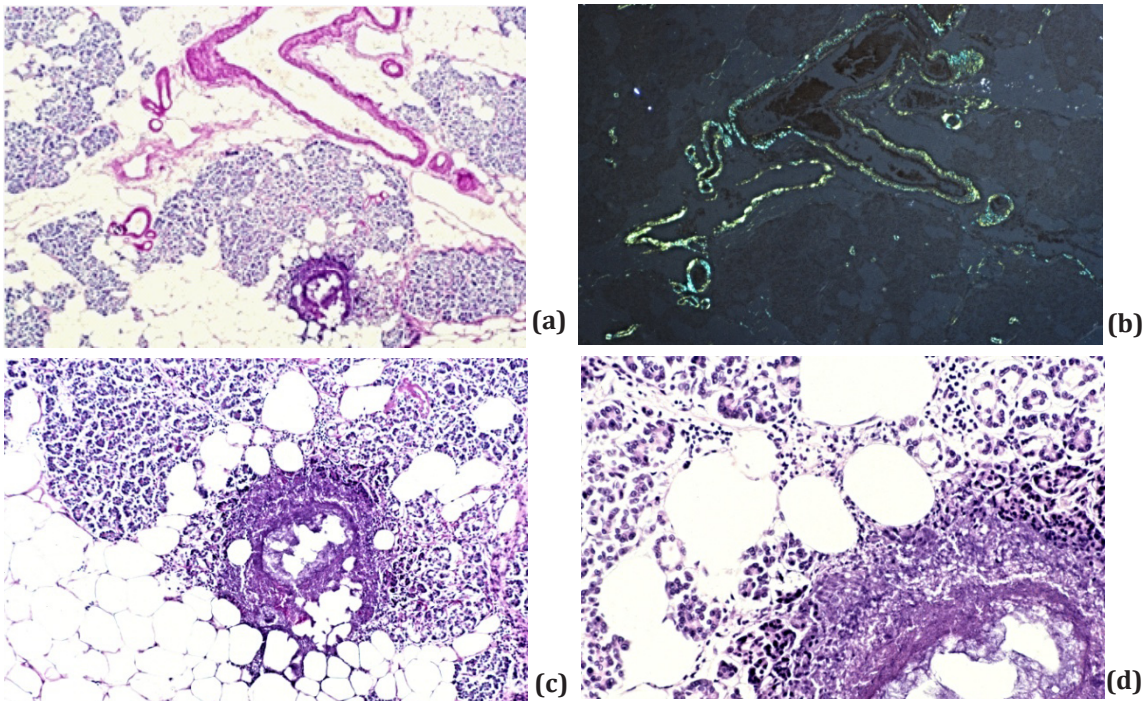

Figure 4a-d. *RA, AAa, Pancreas*

Marked amyloid A deposits in the wall of arterioles, small and medium size arteries in association with multifocal liponecrotic pancreatitis

(**a**) PAS, x20 (**b**) Same as (a) Congo red, x20 (**c**) PAS, x50 (**d**) PAS, x125

Discussion

It is generally accepted, that multi-organ dysfunction associated with sAAa hampers the chances of survival of **RA** patients [13]. Acute pancreatitis caused by **sAAa** is a rare, and late complication of **RA** and the fatal outcome can be expected [14, 15, 16].

According to our data **sAAa** or **pAAa may develope in both sexes**, and **at any time in the course of the disease**. Systemic **AAa** or amyloid A deposits in the pancreas not increased the risk of **LnP** (χ^2=0.0405, p <0.84 – NS; χ^2=0.2146, p <0.64 – NS resp.). In our patient cohorts the prevalence of liponecrotic (**aRelLnP** or **chrLnP**) pancreatitis in association with **sAAa** or **pAAa** was present in the same **4** (**3.39 %**) of 118 patients, and complicated **RA** in the later stage of the disease, in agrrement of others [14, 15, 16]. The mean age of our patients complicated with **sAAa** or **pAAa** was more than 47 years at onset of **RA**, and the mean age of the patiens was more than 61 years at death.

The precursor of amyloid A is produced by the liver, and the amount of amyloid A deposits in the pancreas depend on the amount of production, namely on the activity of the disease.

Progressive deposition of amyloid A may lead to **chrLnP** in time, but its role in the pathogenesis of **chrLnP** was not exclusive in our patient cohorts; the correlation between tham was not significant (χ^2=1.4014, p <0.236 – NS). Other reasons of **chrLnP** (gallstones, acute alcohol abusus, etc. [4, 5, 12] could have played also a role.

The close and significant connection between **severe pancreatic AAa** and **aRelLnP** (χ^2=6.1825, p <0.013) suggests a causal relationship between them; even the massive amyloid A deposition in the blood vessels of pancreas may lead to a special multi (mico) focal acute pancreatitis.

Massive amyloid **A** deposition in the walls of the pancreatic arterioles, small and medium size arteries (branches of splenic artery, upper and lower gastroduodenal arteries) can lead to local ischemia and to regressive changes in the pancreatic gland. This process is more or less widespread and multifocal,

depending on the number of involved vessels. The size of necrobiotic areas is determined by the size of involved blood vessels. Multi-(micro)-focal necrosis of the pancreas caused by diminished blood supply is followed by regressive (necrotic) acinar changes, with or without reactive inflammation, hemorrhages, calcification (saponification) or liquefaction (pseudocyst formation), and later fibrosis, depending on the stages of the pathological process.

sAAa and **pAAa** is a progressive cumulative process [17]. The progressive and cumulative deposition of amyloid A in the pancreas involving more and more blood vessels of different sizes, thus the regressive changes accumulate with time, and exist in different stages at death. Different size and stage of focal necrosis, and the co-existent marked **pAAa**, furthermore the lack of vasculitis, ductal or other reasons may identify this type of pancreatitis.

The progressive and cumulative process of **pAAa** with multi-(micro)-focal necrosis in the pancreas (**aRelLnP** or **chrLnP** pancreatitis) may cause recurrent or intractable pain in the upper abdomen [2, 15].

This form of pancreatitis may be regarded a special manifestation of **sAAa** or a new vasculogenic entity caused by massive pancreatic amyloid A deposition in **RA**. The strong and significant statistical association between severe **pAAa** and **aRelLnP** support the relationship between these two pathological process in **RA**.

Plausible similar changes of pancreas may be expected in other autoimmune diseases complicated with **sAAa**, involving marked (massively) the pancreatic blood vessels.

Conclusion

In elderly **female RA** patient the risk of **LnP** was higher comparing those with **males** or with **LnP** not associated **RA** patient, and the elderly female patients with **LnP** died significantly earlier.

sAAa, as basic complication of **RA**, **may develope in both sexes**, and **at any time in the course of the disease**, and **pAAa** is **closely connected with it**.

In essence **sAAa** not influence the prevalence of pancreatitis, but at higer disease activity, massive amyloid **A** deposition in the walls of the pancreatic arterioles, small and medium size arteries can cause local ischemia and lead to a special form of **LnP**, namely to **aRelLnP** (the connection between extreme severe **pAAa** and **aRelLnP** was significant). Marked **pAAa** should be regarded an important vasculogenic factor in pathogenesis of **aRelLnP**, which may be regarded as a special manifestation of autoimmune pancreatitis or a new vasculogenic entity in **RA**.

Long term progressive accumulation of amyloid A deposits in the vessel walls and different structures of the pancreas may be associated with **chrLnP**, but the connection (link) between **pAAa** and **chrLnP** was not siginificant. This means, that **pAAa** is only partially responsible for **chrLnP, and other reasons should be considered as well.**

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