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Complications of Rheumatoid Arthritis and Associated Diseases of the Liver – A Postmortem Clinicopathologic Study of 152 Patients

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Summary

Background: *Systemic rheumatoid vasculitis of autoimmune origin, systemic (secondary, inflammatory) AA amyloidosis and acute bacterial septic infection with lethal outcome are major complications of rheumatoid arthritis (RA), which may involve the liver.*

In addition to these complications of RA, a wide spectrum of liver diseases, such as reactive, viral, toxic or eosinophilic hepatitis, fatty liver changes, etc. with or without cirrhotic transformation may associate with RA.

The aim of this study was to determine the prevalence of RA related complications and associated diseases of the liver, and to analyze the possible relationship between them.

Patients and Methods: *152 random autopsy patients with RA were studied. RA was confirmed clinically according to the criteria of the ACR.*

The prevalence of complications and associated diseases of the liver were confirmed by a detailed review of extensive histological material.

Results: *There was a very strong statistical relationship between RA related complications and their manifestation in the liver.*

The links were also positive and significant between systemic rheumatoid vasculitis and eosinophilic hepatitis, furthermore between chronic passive hepatitis or alcoholic hepatitis and alcoholic steatosis.

The statistical correlation between RA related complications and associated diseases of the liver were not significant, even in most of the cases inverse with negative colliquations coefficient.

Conclusions: *A distinct liver disease specific for RA was not found in our autopsy population.*

RA related systemic complications and associated diseases of the liver are independent entities.

We found that the patients' life expectancy was declining with acute bacterial septic infection or hepatitis, and with amyloid A deposition in the liver, and these patients died earlier.

The risk of chronic active hepatitis (with or without cirrhotic transformation) increased in the late stage of RA.

Apart from these exceptions RA related complications or associated diseases of the liver developed in both sexes, and at any time in the course of RA; onset or duration of RA did not influence the prevalence of RA related complications or associated diseases of the liver

Keywords: *Rheumatoid arthritis, autoimmune (rheumatoid) vasculitis, AA amyloidosis, lethal septic infection, associated diseases of the liver.*

Abbreviations (thematically):

RA – Rheumatoid **A**rthritis

ACR – **A**merican **C**ollege of **R**heumatology

sRhV – systemic **Rh**eumatoid **V**asculitis of autoimmune origin

hRhV – hepatic **Rh**eumatoid **V**asculitis

ns – non specific **hRhV**

fn – fibrinoid necrotic **hRhV**

gr – granulomatous **hRhV**

AA – **A**myloid **A** protein (precursor polypeptide: **s**erum **a**myloid **A** – **SAA**)

AAa – **A**myloid **A** protein **a**myloidosis

sAAa – **s**ystemic **AA a**myloidosis (**s**ystemic **A**myloid **A** protein **a**myloidosis)

hAAa – **h**epatic **AA a**myloidosis (**AA** protein deposition in the liver)

AbSI –**A**cute **b**acterial **S**eptic **I**nfection of lethal outcome

AbSH –**A**cute **b**acterial **S**eptic (serous) **H**epatitis

EoH – acute **Eo**sinophilic **H**epatitis

RH – **R**eactive **H**epatitis (nonspecific)

ChrAH – **Chr**onic **A**ctive **H**epatitis

ChrPH – **Chr**onic **P**assive (non agressive) **H**epatitis

PhC – **P**ost**h**epatitic **C**irrhosis

aLN – **a**cute "yellow" **L**iver **N**ecrosis of toxic (medicamentous) origin

saLN – **s**uba**c**ute "red" **L**iver **N**ecrosis of toxic (medicamentous) origin

PnC – **P**ost**n**ecrotic **C**irrhosis (late stage of **saLN**)

AlcSt – **Alc**oholic **St**eatosis (alcoholic fatty change of the liver)

AlcH –**Alc**oholic **H**epatitis

AlcC –**Alc**oholic **C**irrhosis

PBC – **Pr**imary **B**iliary **C**irrhosis

CT – total number of **C**irrhotic **t**ransformations

AIH – **A**uto**i**mmune **h**epatitis

Atr –zonal lobular **Atr**ophy of converging liver cell plates

BrAtr –**Br**idging **Atr**ophy of the lobules

KnSc – **Kn**odell **Sc**ore

CLL – Chronic **L**ymphocytic **L**eukemia)

CoD – Cause of death

U – Uremia

Cl+ = clinically diagnosed

Cl- = clinically not diagnosed

SD – Standard **D**eviation

ND – No **D**ata

NS – Not **S**ignificant

HE – Hematoxylin **E**osin staining

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

c – Coefficient of colligation (coefficient of association); range of values from "-1" to "+1": „-1" indicates a perfect inverse (negative) relationship, „0" indicates no relationship, and „+1" means a perfect positive correlation (***** – Asterisk indicates negative value of association's coefficient (inverse relationship)

Introduction

Systemc rheumatoid vasculitis of autoimmune origin (**sRhV**), systemic (secondary, inflammatory) AA amyloidosis (**sAAa**) and acute bacterial septic infection with lethal outcome (**AbSI**) are major complications of rheumatoid arthritis (**RA**) [1]. Systemic complications of **RA** may modify the clinical course and symptoms of allied disorders of the liver leading to missed diagnosis or late recognition of associated diseases. and vica versa [2].

The **aim** of this study was to assess the ***prevalence*** of **sRhV**, **sAAa**, and **AbSI** in **RA** with demonstration of their manifestation in the liver, furthermore to determine the ***existence*** of ***associated diseases*** of the liver, and to analyse the possible relationship between them.

The following associated disease and disorders of the liver were considered: ***nonspecific reactive hepatitis*** (**RH**), ***acute eosinophilic hepatitis*** (**EoH**), ***chronic passive (non aggressive) hepatitis*** (**ChrPH**), ***chronic active hepatitis*** (**ChrAH**), ***posthepatitic***

cirrhosis (**PhC**), ***acute "yellow"*** or ***subacute" red" liver necrosis*** (**aLN** or **saLN**), ***postnecrotic cirrhosis*** (**PnC**), ***alcoholic fatty change*** (***Alcoholic Steatosis*** – **AlcSt**), ***alcoholic fatty hepatitis*** (**AlcH**), ***alcoholic cirrhosis*** of Läennec (**AlcC**), and ***primary biliaryc cirrhosis*** (**PBC**), furthermore ***zonal lobular*** (**Atr**) and/or ***bridging atrophy*** (**BrAtr**) of the lobules.

Patients and Methods

The complication of **RA** and associated disease of the liver were analyzed on **152** autopsy patients. The patients were treated and died in the National Institute of Rheumatology, Budapest, Hungary between 1969 and 1992.

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

The prevalence of **sRhV**, **sAAa** and **AbSI**, and manifestation of these in the liver (**hRhV**, **hAAa** and **AbSH**) were confirmed histologically. From each patient a total of 50-100 tissue blocks of 12 organs (heart, lung, liver, spleen, kidneys, pancreas, gastrointestinal tract, adrenal glands, skeletal muscle, peripheral nerve, skin and brain) were studied microscopically [1].

Amyloid A deposition in different tissue structures of various organs was diagnosed histologically according to Romhányi [4] by a modified (more sensitive) Congo red staining [5].

Prevalence and histological patterns of associated liver diseases and disorders were determined at autopsy and characterized histologically [1].

Demographics of different patient cohorts were compared with Student's (Welch) t-probe [6]. The relationships between complication of **RA** (**sRhV**, **sAAa**, **AbSI**, and **hRhV**, **hAAa**, **AbSH**), furthermore associated liver diseases (including **RH**, **EoH**, **ChrPH**, **ChrAH**, **PhC**, **aLN** or **saLN**, **PnC**, **AlcSt**, **AlcH**, **AlcC**, **PBC**), and disorders of the liver (**Atr** or **BrAtr**) were analyzed by Pearson's chi-squared (χ^2) test [6].

Glossary of definitions

Entities and definitions of glossary are based on Symmers WStC: Systemic Pathology [7], Zollinger HU: Pathologische Anatomie [8], Sternberg: Histology for Pathologists [9] and Sternberg: Diagnostic Surgical Pathology [10].

To assess the histological activity of chronic active hepatitis (**ChrAH**) we used the Knodell score system [11]. The extent (degree) of fatty changes was estimated according to Dietrichson et al. [12].

Systemic rheumatoid vasculitis of autoimmune origin (**sRhV**) was defined as one of the basic manifestations of **RA** involving blood vessels (other causes of systemic vasculitis, like hypertension, diabetes mellitus, tumors, septic infections etc. were excluded) [1].

Prevalence of RhV in the liver (**hRhV**) concerns the inflammatory infiltration and structural changes in blood vessels of different calibers [arteriole (**a**), small artery (**A**) or medium size artery (**AA**), venule (**v**), small vein (**V**) or medium size vein (**VV**)] in the liver.

Prevalence of systemic AA amyloidosis (**sAAa**) was specified histologically in each patient, based on the presence of amyloid A in blood vessels of different calibers or in different tissue structures of twelve organs [1].

Prevalence of hepatic AA amyloidosis (**hAAa**) concerns the presence of amyloid A (**AA**) protein deposits in the liver [7].

Acute **b**acterial **S**eptic **I**nfection (**AbSI**) **–** only a lethal septic infection with clinically identified pathogenic agents was considered.

Acute **b**acterial **S**eptic **H**epatitis (**AbSH**) – Edematous, "serous" or infection associated hepatitis was characterised by extended (edematous) portal tracts, and Disse spaces with portobiliary and lobular leukocytic infiltration (without histological evidence of chronicity, i.e. without fibrous portal expansion, proliferation of biliary ducts etc.).

Nonspecific **R**eactive **H**epatitis (**RH**) means ***mild lympho- plasmacellular infiltration*** (1-25/portal tract) ***in less than one third of portal tracts***, ***without fibrous portal expansion***; the limiting plates of the lobules and the structure of the liver are intact.

Chronic **P**assive (non agressive) **H**epatitis (**ChrPH**) denotes ***mild*** (1-25) or ***moderate*** (26-50) lympho-plasma***cellular infiltration in more than one third of portal tracts***. The portobiliar ***cellular infiltration*** is accompanied by ***fibrous portal expansion***, the limiting plates of the lobules are intact and there is no cirrhotic transformation (liver cell degeneration, regeneration and remodeling with pseudolobules).

Marked mononuclear infiltration (more than 50/portal tracts) was not detected in our patient population, and was detected only in **non**-RA patients with chronic lymphocytic leukemia, **CLL**.

Chronic **A**ctive **H**epatitis (**ChrAH**) implies ***in one third of portal tracts mild*** (KnSc: 1), ***in two thirds moderate*** (KnSc: 3) or ***in three thirds marked*** (KnSc: 4) ***inflammatory infiltration*** (neutrophils, lymphocytes, plasmacells, macrophages, and fibroblasts) ***with sporadic piece meal necrosis*** of the limiting plates (KnSc: 1), ***in less than 50 %*** (KnSc: 3) or ***in more than 50 %*** (KnSc: 4) of the lobules. The portobiliary inflammatory infiltration is accompanied by ***fibrous portal expansion*** (KnSc: 1) or ***bridging fibrosis*** (KnSc: 3), ***intralobular cell-degeneratio***n (acidophilic bodies of Councilman, balloon cells), and ***focal liver cell necrosis***, without structural remodeling (cirrhotic transformation).

Post**h**epatitic **C**irrhosis (**PhC**) connotes ***chronic cirrhotic transformation of the liver*** with histological sing of **ChrAH** (KnSc: 4).

Alcoholic fatty change or alcoholic **s**teatosis (**AlcSt**) is characterized by accumulation of fat in hepatocytes (intracytoplasmic small droplets and/or large drops of signet ring' appearance or cobweb-like changes), involving less than one third (Grade 1), two thirds (Grade 2) or more than two thirds of the liver cells (Grade 3) [10].

We used Dietrichson's stages, modified according to zonal approach: **AlcSt** (alcoholic fatty change or steatosis) was characterized by accumulation of fat in the hepatocytes ('signet ring' appearance), involving only the central region (Grade 1), two thirds of the lobules (Grade 2) or diffusely the whole lobules (Grade 3).

Alcoholic **H**epatitis (**AlcH**) assumes fatty liver with acute or chonic inflammation of portal tracts, occasionally with lipogranulomas, neutrophils around degenerated parenchymal cells ('satellitosis'), alcoholic hyalin (Mallory bodies) in hepatocytes, mostly in the central region of the lobules without fibrosis (stage 1), with condensed reticulin framework (central hyaline sclerosis: stage 2) or with formation of septa (stage 3); there is no cirrhotic transformation.

Alcoholic **C**irrhosis (**AlcC**) presumes **AlcH** accompanied by cirrhotic transformation.

Acute "yellow" or **s**uba**a**cute "red" **L**iver **N**ecrosis („atrophy") (**aLN** or **saLN**) and **p**ost**n**ecrotic **C**irrhosis (**PnC**) – Only a toxic (drug inuced) origin was considered; viral etiology was clinically and/or histologically excluded.

Primary **B**iliary **C**irrhosis (**PBC**) was defined as autoimmune disease of biliary tract (granulomatous cholangitis) in association with rheumatoid arthritis.

Atrophy (**Atr**) and **Br**idging **atr**ophy **(BrAtr**) was registered as an accompanying phenomenon (due to different causes like chronic stasis, cardiac insufficiency, amyloid A deposition etc.), and not as a distinct entity.

Atrophy (**Atr**) was characterized by thinned converging liver cell plates involving central and/or peripherolobular zones of the lobules.

Bridging **atr**ophy **(BrAtr**) – **Atr** with portal-central linkage.

Results

Complications of rheumatoid arthritis (prevalence of sRhV n=32, sAAa n=32 or AbSI n=23)

Rheumatoid vasculitis

Systemic rheumatoid vasculitis (**sRhV**) complicated **RA** in **32** (**21.05** %) of 152 patients. Branches of blood vessels of different calibers of the liver were involved in **12** (**37.5** % of 32, 7.89 % of 152) cases; **hRhV** was histologically excluded in **20** (**62.5** % of 32) patients with **sRhV**.

There was a very strong positive relationship between **sRhV** (n=32) and **hRhV** (n=12) (c=1.0, χ^2=43.8361, p <**0.0000**).

Three types of **hRhV** were distinguished: nonspecific (**ns**), fibrinoid necrotic (**fn**), and granulomatous (**gr**) types of **hRhV**. Different types of **hRhV** existed together: **ns hRhV** was present in 9, **fn** in 6, and **gr** in 1 of 12 patients.

AA amyloidosis

Systemic AA amyloidosis (**sAAa**) complicated **RA** in **32** (**21.05** %) of 152 patients. Amyloid A deposits were found in the liver in **26** (**81.25** % of 32, 17.11 % of 152) cases; **hAAa** was histologically excluded in **6** (**18.75** % of 32) patients with **sAAa**.

There was a very strong positive relationship between **sAAa** (n=32) and **hAAa** (n=26) (c=1.0, χ^2=111.959, p <**0.0000**).

Acute bacterial septic infection

Generalized acute bacterial septic infection with lethal outcome (**AbSI**) complicated **RA** in **23** (**15.13** %) of 152 patients. Acute bacterial septic (serous) hepatitis (**AbSH**) accompanied to **AbSI** in **9** (**39.13** % of 23 and 5.92 % of 152) c4ases; **AbSH** was histologically excluded in **14** (**60.87** % of 23) patients with **AbSI**.

There was a very strong positive relationship between **AbSI** (n=22) and **AbSH** (n=9) (c=1.0, χ^2=46.0685, p <**0.0000**).

Complications of RA (n=87 of 152)

Aforementioned **87** (**sRhV**: n=32, **sAAa**: n=32 and **AbSI**: n=23) complications were present in **78** (51.32 % of 152) patients; in **69** patients only one and in **9** patient 2 complications existed at the same time.

Seventy-four (48.68 %) of 152 patients showed no evidence of **sRhV**, **sAAa**, or **AbSI**.

Forty-seven (**hRhV**: n=12, **hAAa**: n=26 and **AbSH**: n=9) of 87 **RA** related systemic complication involved the liver in **45** (57.69 % of 78) patients; in **43** patients only one and in **2** patients two complications existed simultaneously in the liver.

Systemic complications were not detected in the liver in **33** (42.31 % of 78) patients.

Figures 1-6 demonstrate the **RA** related complications of the liver by traditional HE (or combined HE-PAS) and Congo red staining, viewed by light microscopy and under polarized light, respectively.

Original magnifications correspond to the 24x36 mm transparency slide; the correct height: width ratio is 2:3. The printed size may be different; therefore, it is necessary to indicate the original magnifications.

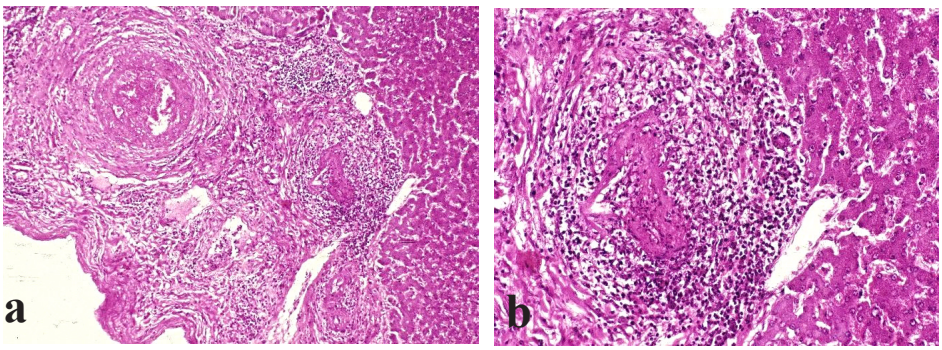


Figure 1a-b. *Rheumatoid arthritis, liver with systemic rheumatoid vasculitis*

(**a**) arteriole with nonspecific rheumatoid thrombovasculitis, HE-PAS, x50

(**b**) arteriole with sectorial fibrinoid necrosis, same as Figure (a) x125

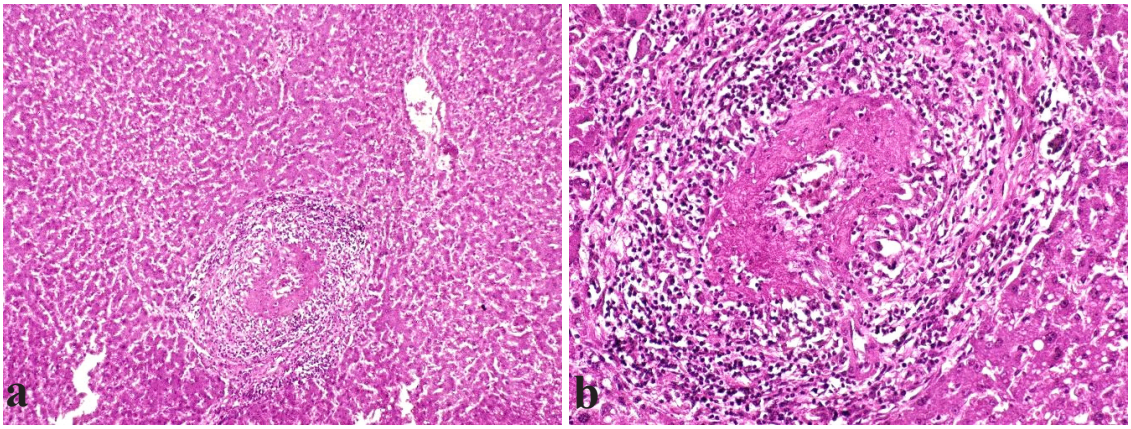


Figure 2a-b. *Rheumatoid arthritis, liver with systemic rheumatoid vasculitis*

(**a**) fibrinoid necrotic rheumatoid vasculitis. HE-PAS, x50 (**b**) same as Figure (a) x125

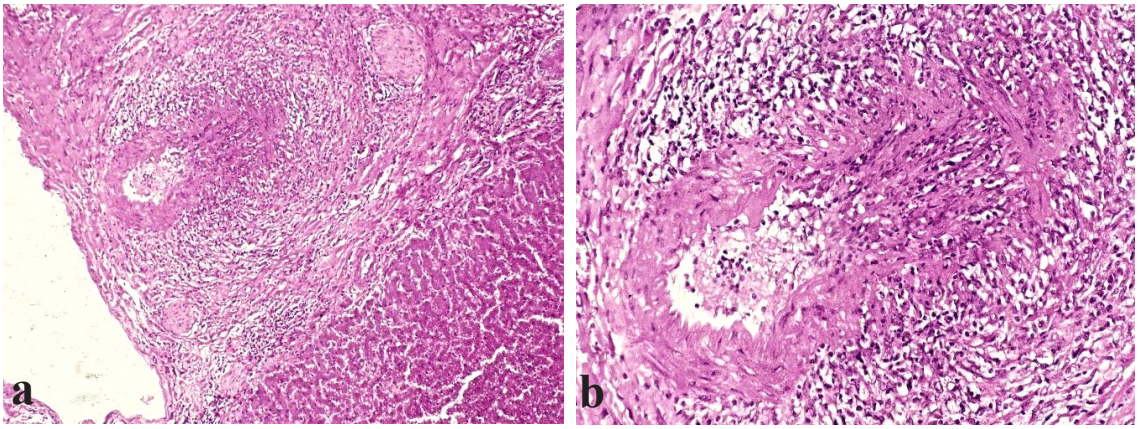


Figure 3a-b. *Rheumatoid arthritis, liver with systemic rheumatoid vasculitis*

(**a**) small artery, granulomatous rheumatoid vasculitis. Sectorial granulomatous involvement of vessel wall characterized by lymphocytic and plasma cellular infiltration and histiocytes, HE-PAS, x50

(**b**) same as Figure (a) x125

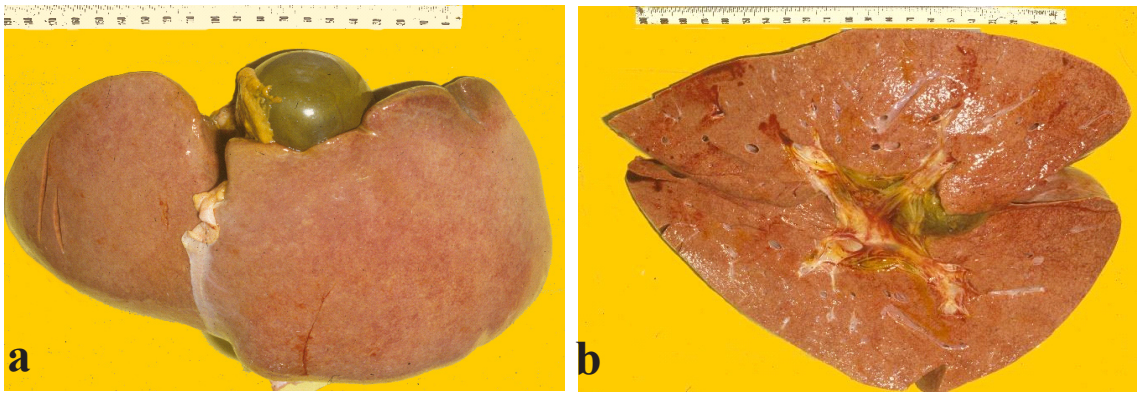


Figure 4a-b. *Rheumatoid arthritis, liver with systemic AA amyloidosis*

(**a**) Macrophotograph, surface,

(**b**) Macrophotograph, same as Figure (a), cut surface

Figures 5 and 6 demonstrate the extent of amyloid A deposits in the liver with HE and Congo red staining, viewed by light microscopy and under polarized light, respectively.

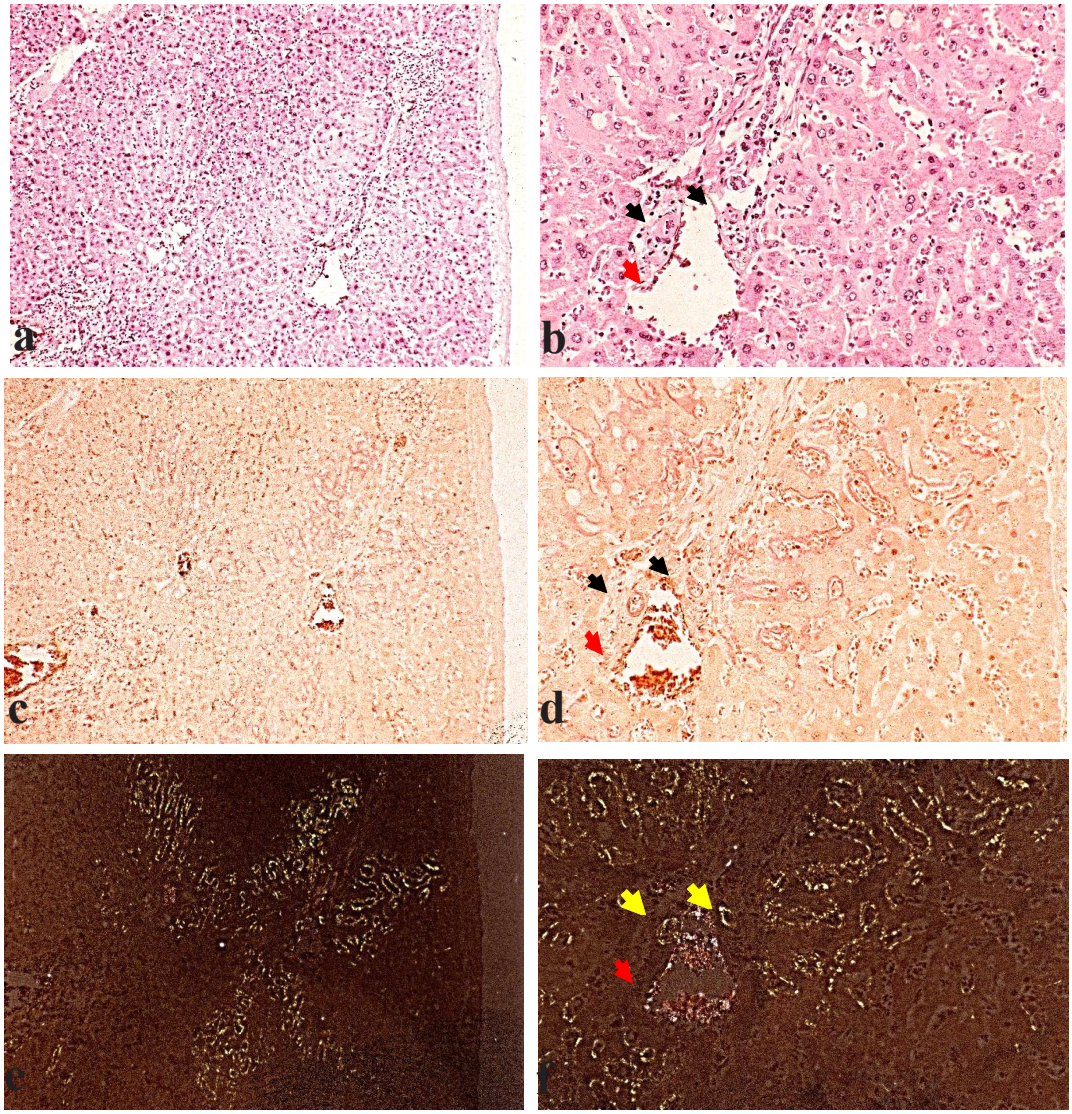


Figure 5a-f. *Rheumatoid arthritis, liver, subcapsular region with amyloid deposits in portal triad and peri-lobular, within spaces of Disse, advanced stage of amyloid A deposits*

(**a**) Massive amyloid A deposits within the perisinusoidal areas of Disse along the reticulin fibers and in the wall of a blood vessels (black and yellow arrowheads respectively indicate an arteriole of a portal triad, and the red one a distended venule, liver cell plates are atrophic, HE, x50, (**b**) same as (a) x125

(**c**) Congo red staining, without alcoholic differentiation, covered with gum Arabic, same as (a) x50, (**d**) same as (c) x125

(**e**) same as (a) Congo red staining, without alcoholic differentiation, covered with gum Arabic, viewed under polarized light, x50, (**f**) same as (e) x125

The intensity of birefringence is relatively moderate compared to the massive deposition of amyloid A wih traditional staining and light microscopy.

The "white" birefringence is caused by paraffin remnants due to imperfect deparaffinization.

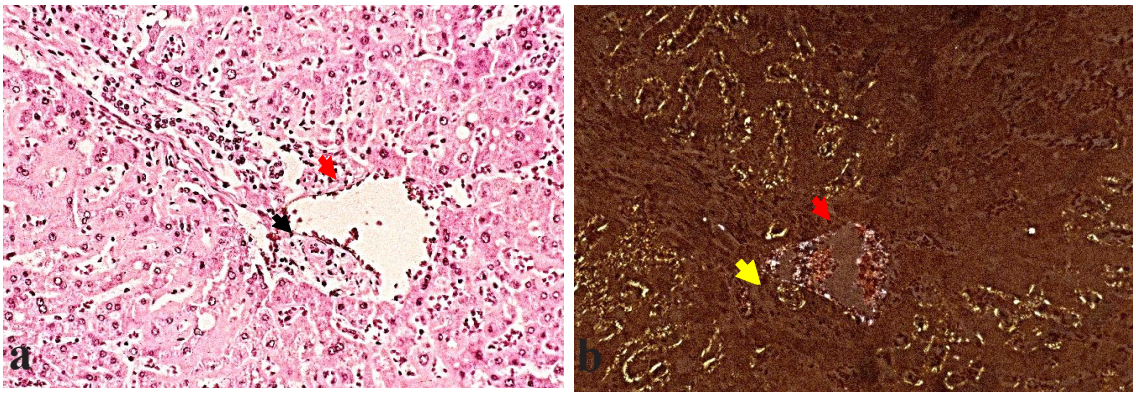


Figure 6a-b. *Rheumatoid arthritis, liver, subcapsular region with portal triad and peri-lobular amyloid deposits within spaces of Disse, advanced stage of amyloid A deposits*

(**a**) Massive amyloid A deposits within the perisinusoidal areas of Disse along the reticulin fibers and in the wall of a blood vessels (black and yellow arrowheads respectively indicate an arteriole of a portal triad, and the red one a distended venule, liver cell plates are atrophic, HE, x125

(**b**) same as (a) Congo red staining, without alcoholic differentiation, covered with gum Arabic, viewed under polarized light, x125

Associated diseases of ther liver

One hundred fifty-five (n=155) associated diseases or allied disorders of the liver [nonspecific reactive hepatitis (**n=62**), eosinophil hepatitis (**n=4**), chronic active hepatitis (**n=6**), chronic passive hepatitis (**n=19**), alkoholic changes (**n=60**), toxic liver necrosis (**n=2**), **PBC** (**n=2**)] **were present in 115 patients**; in **37** patients only one and in **39** patient two complications existed at the same time.

Eosinophilic hepatitis

In **4** patients the acute leucocytic cellular infiltration of the liver was expressly eosinophilic, characterized by an overhelming majority of eosinophilic leukocytes; in three patients independently of the above-mentioned **RA** related 9 **AbSH**, and in one patient overlapping with it; these 4 cases were considered as **eosiniphilic hepatitis** (**EoH**) (Figure x).

Nonspecific reactive hepatitis

Nonspecific reactive hepatitis (**RH**) was detected in **62** (**40.79** %) of 152 **RA** patients, and was excluded in **90** (**59.21** %) cases.

Chronic active or passive hepatitis with or without cirrhosis

Chronic **A**ctive **H**epatitis (**ChrAH**) was found in **6** (**3.95** %) and **chr**onic **P**assive (non-agressive) **H**epatitis (**ChrPH**) in **19** (**12.50** %) of 152 patients.

ChrAH and **ChrPH** were detected as separate entities; the relationship between **ChrAH** and **ChrPH** was inverse with a negative colliquation coefficient (c=-1.0*, χ^2=0.0991, p <0.7528 – NS).

ChrAH was combined with **p**ost**h**epatitic **c**irrhosis in **4** (**75.0** % of 6) patients (**PhC – 2.63** % of 152). There was a strong, significant and positive correlation between **ChrAH** (n=6) and **PhC** (n=4) (c=1.0, χ^2=75.639, p <**0.0000**).

ChrPH was not combined with **PhC**.

Alcoholic changes of the liver with or without cirrhosis

Alcoholic fatty changes (**Alc**oholic **St**eatosis **– AlcSt**) of different degree (Grade 1: n=43, grade 2: n=15, and grade 3: n=2) were detected in **60** (**39.47** %) of 152 **RA** patients. **AlcSt** was accompanied by alcoholic hepatitits (**AlcH**) in **10** (**16.67** % of 60, 6.58 % of 152) patients. **One** of these 10 **AlcH** was complicated by alcoholic cirrhosis (**AlcC**) (**1.67** % of 60, **10.0** % of 10, **0.66** % of 152 patients).

The correlation was significant between **AlcSt** (n=60) and **AlcH** (n=10) (c=1.0, χ^2=13.8134, p <**0.0002**). The relationships between **AlcSt** (n=60) and **AlcC** (n=1) (c=1.0, χ^2=0.0467, p <0.828 – NS) or **AlcH** (n=10) and **AlcC** (n=1) were positive, but not significant (c=1.0, χ^2=3.0879, p <0.078 – NS).

Toxic liver necrosis with or without cirrhosis

Acute liver necrosis (**aLN**) existed in one patient (**0.66** % of 152), and subacute liver necrosis (**saLN**) was detected in one other (**0.66** % of 152), which was complicated by postnecrotic cirrhosis (**PnC**).

There was a strong, significant and positive correlation between **saLN** (n=1) and **PnC** (n=1) (c=1.0, χ^2=37.4987, **p <0.0000**).

Primary biliary cirrhosis

Primary biliary cirrhosis (**PBC**) was accompanied by systemic rheumatoid vasculitis (**sRhV**) in 2 patients (1.32 % of 152) and one of these two (0.66 % of 152), it was combined with **hRhV** as well.

The relationship between **sRhV** or **hRhV** and **PBC** was positive, but not significant.

Cirrhosis

Cirrhotic transformation (**CT**) of the liver was present in **8** (5.26 %) of 152 patients; due to acute hepatitis (**PhC**: n=4 of 6), chronic alcoholism (**AlcC**: n=1 of 10 alcoholic hepatitis), subacute liver necrosis (**PnC**: n=1 of 2) or primary biliary cirrhosis (**PBC**: n=2).

Associated diseases or allied disorders of the liver

Aforementioned **155** associated diseases or allied disorders [**RH** n=62, **EoH** n=4, **ChrAH** n=6 (including four PhC), **ChrPH** n=19, **alcoholic changes** n=60 (including 10 AlcH with one AlkC), **aLn** or **saLn** n=2 (including one PnC), **PBC** n=2] were present in **115** (75.66 % of 152) patients; in **37** patients only one and in **39** patient two associated disease existed at the same time. Associated diseases or allied diroders were not detected in the liver in **37** (24.34 %) of 152 patients.

Eighty-seven (**87**) systemic complications (**sRV, sAAa, AbSI**) were detected in **78** patients, and **155** associated diseases in **115** patients. The systemic complications of **RA** were accompanied by associated diseases of the liver in **47** patients.

The total number of involved patients in the relationship between **RA** related systemic complications and associated diseases of the liver was significant, but inverse with the negative colligation's coefficient (c***=-**0.7640, χ^2=20.6357, p <**0.000006**).

Fourty-seven (**47**) of **87 RA** related systemic complications (54.02 % of 87) were present in the liver, and involved **45** patients. The **47 RA** related systemic complications accompanied associated diseases of the liver in **23** of **115** patients.

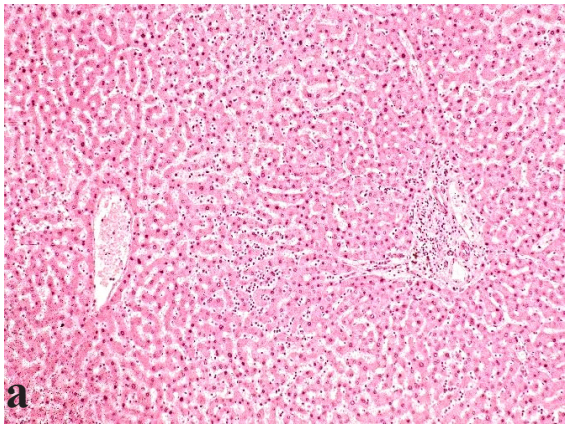
The relationship between **RA** related complications and associated diseases of the liver was significant, but inverse with negative colligation's coefficient (c*=--0.7087, χ^2=20.9146, p <**0.000005**).

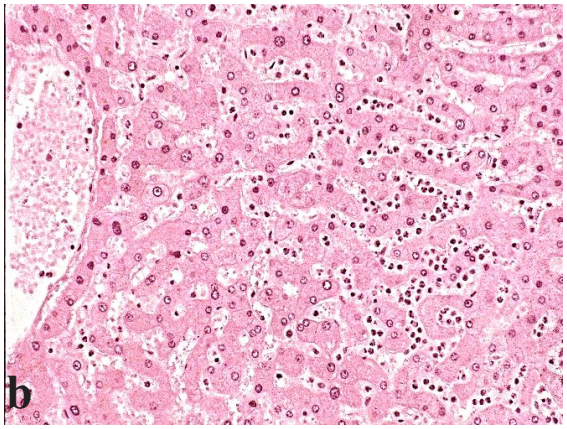
Atrophy (**Atr**) of converging liver cell plates, an accompanying phenomenon of **RA** related complications or associated diseases of the liver, was detected in 105 (69.078 %) of 152 patients, including 22 patients with bridging atrophy (**BrAtr**) (20.95 % of 105, and 14.47 % of 152 patients).

Atr (with or without **BrAtr**) showed no significant relationship neither with **RA** related complications nor with associated diseases of the liver.

In our patient's population only **9** (**5.92** % of 152) had an intact liver without complications or associated diseases.

Figures 7-16 demonstrate associated diseases of the liver by traditional stainings, viewed by light microscopy, and ocasionally under polarized light, respectively.





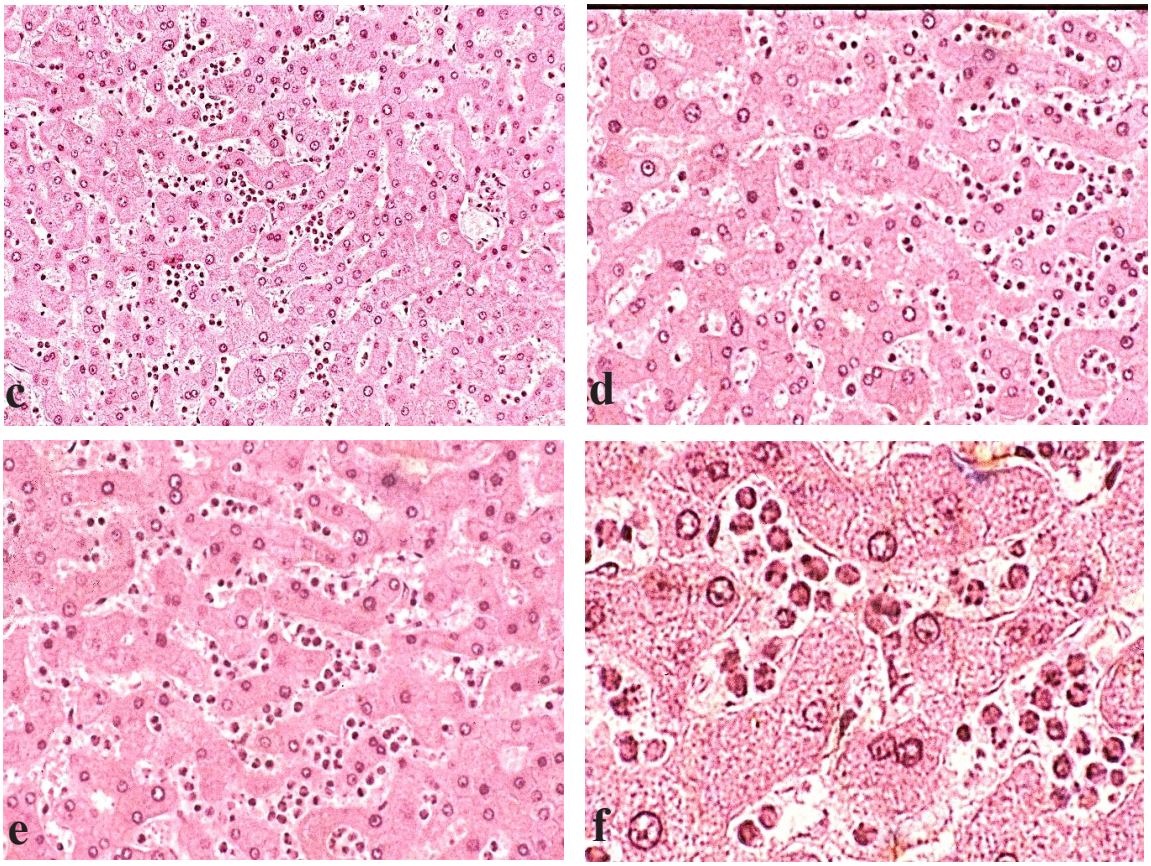


Figure 7a-f. *Rheumatoid arthritis, acute eosinophilic hepatitis, in association with systemic rheumatoid vasculitis, without acute bacterial septic infection in three of 4 patients (285-89)*

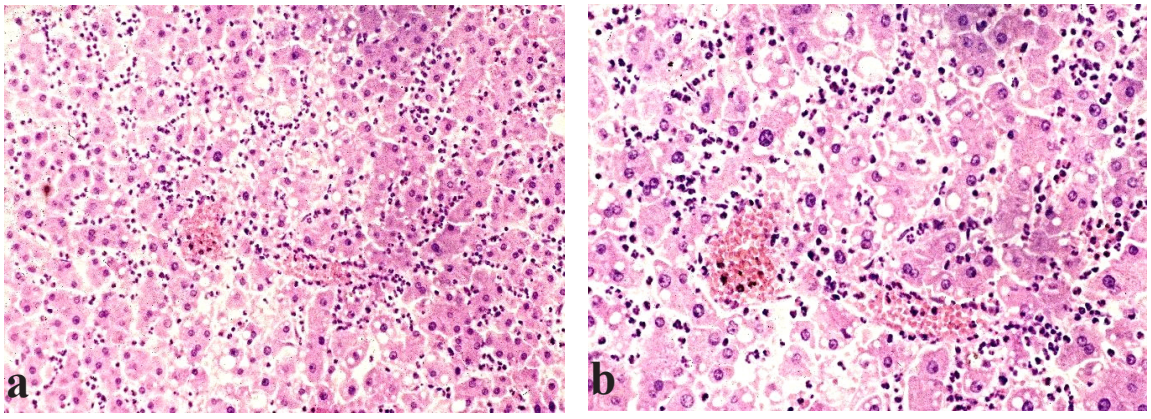
Acute eosinophilic hepatitis is characterized by eosinophilic leucocytic cellular infiltration of the liver, without histological evidence of chronicity i.e., without fibrous portal expansion. The limiting plates of the lobules and the structure of the liver are intact.

(**a**) expressed eosinophilic leucocytic cellular infiltration, HE, x50,

(**b** and **c**) same as Figure (a) x125,

(**d** and **e**) same as Figure (a) x200,

(**f**) same as Figure (a) x600



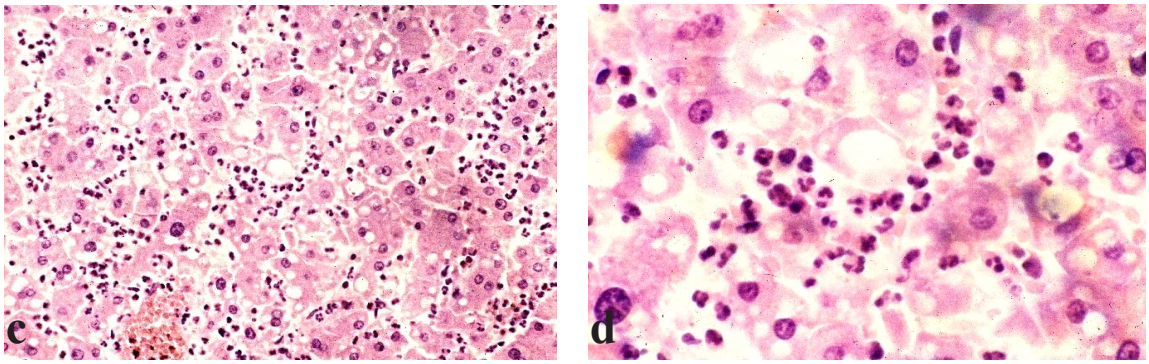


Figure 8a-d. *Rheumatoid arthritis, acute eosinophilic hepatitis, in association with acute bacterial septic infection, without systemic rheumatoid vasculitis in one of 4 patients (266-78)*

Acute eosinophilic hepatitis is characterized by leucocytic cellular infiltration of the liver, without histological evidence of chronicity i.e., without fibrous portal expansion. The limiting plates of the lobules and the structure of the liver are intact.

(**a**) Leukocytic cellular infiltration, the overwhelming majority of leukocytes are eosinophilic HE, x125, (**b** and **c**) same as Figure (a) x200, (**d**) same as Figure (a) x600

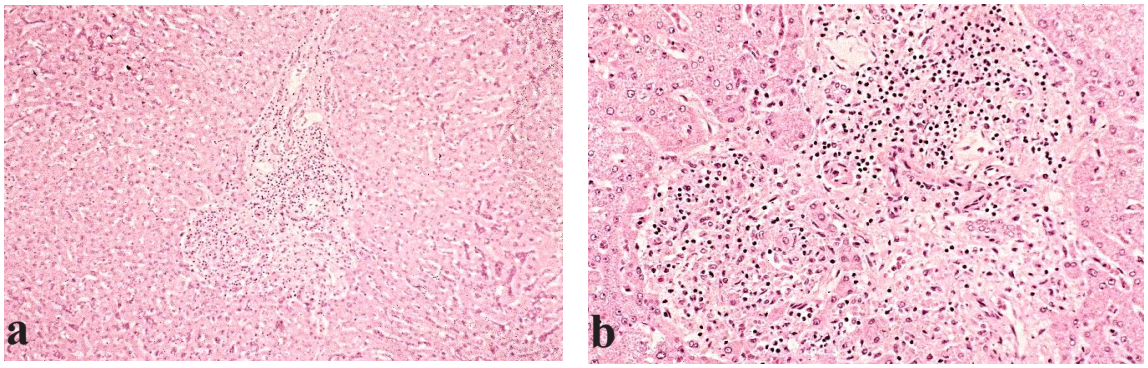
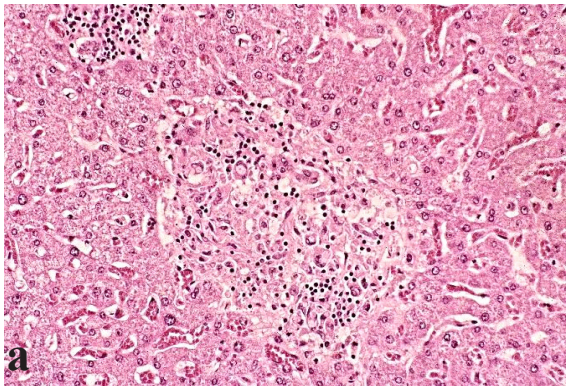


Figure 9a-b

Rheumatoid arthritis, granulomatous cholangitis, early stage.

The portobiliar cellular infiltration is accentuated around the remnants of biliary ducts; the arterioles are more or less preserved. The portobiliar inflammation is accompanied by moderate fibrous portal expansion, the limiting plates of the lobules are intact and there is no cirrhotic transformation.

(**a**) Mononuclear cellular infiltration with scattered eosinophils, HE, x50, (**b**) same as Figure (a) x125



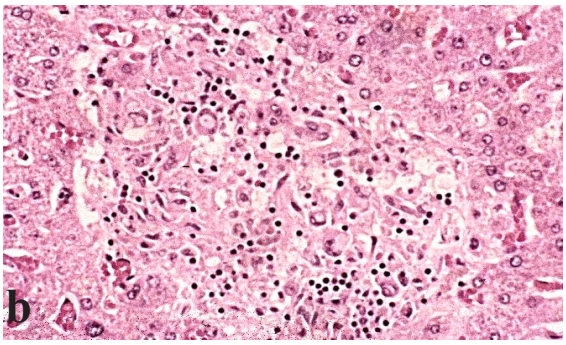


Figure 10a-b. *Rheumatoid arthritis, granulomatous cholangitis, advanced stage.*

Fibrous portal expansion with destroyed biliary ducts.

Dominant mononuclear cell infiltration with histiocytes and multinucleated giant cells, the limiting plates of the lobules are more or less damaged, but cirrhotic transformation of the liver is not detectable.

(**a**) Inflammatory infiltration with damaged portal triads, HE, x125, (**b**) same as Figure (a) x200

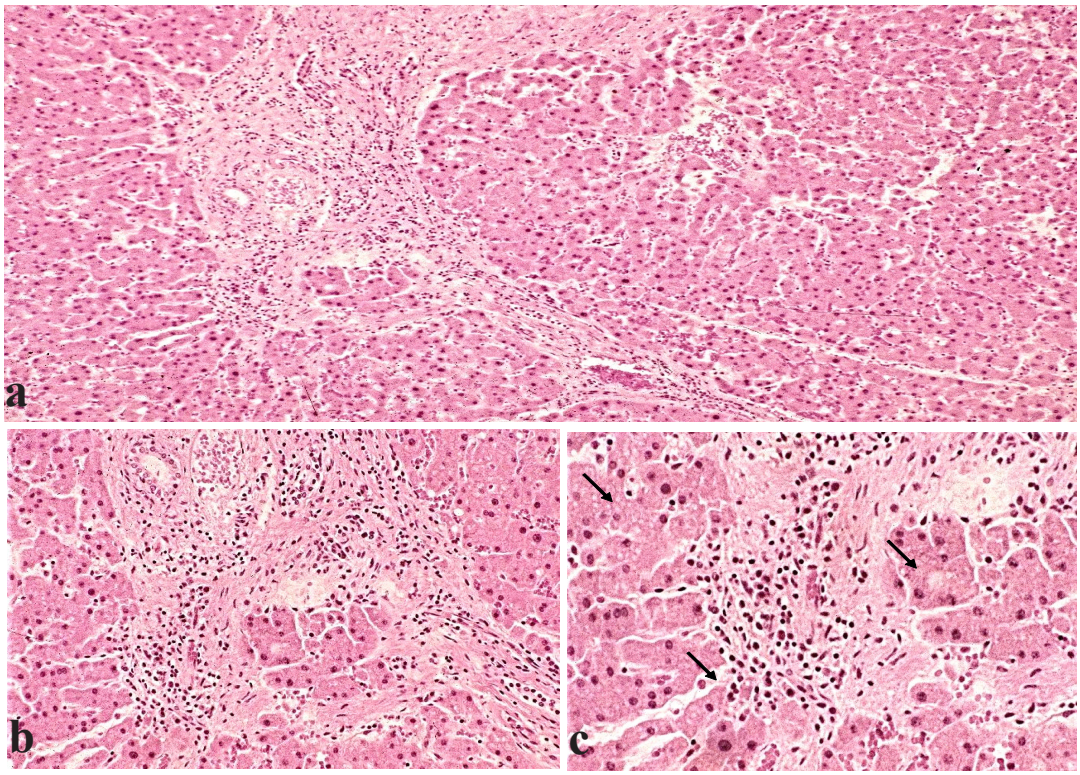


Figure 11a-c. *Rheumatoid arthritis, chronic active hepatitis, without general cirrhotic transformation*

Portal tract with inflammatory infiltration (neutrophils, lymphocytes, plasma cells, macrophages, and fibroblasts) and scattered piece meal necrosis of the limiting plates.

The portal inflammatory infiltration is accompanied by fibrous portal expansion and bridging fibrosis, intralobular cell-degeneration (acidophilic bodies of Councilman, balloon cells), and focal liver cell necrosis, without structural remodeling (cirrhotic transformation).

(**a**) HE, x50, (**b**) same as Figure (a), dislocation of liver cell group, x125, (**c**) same as Figure (a), black arrows indicate piece meal necrosis of the limiting plates, acidophilic necrotic and vacuolated liver cells x200

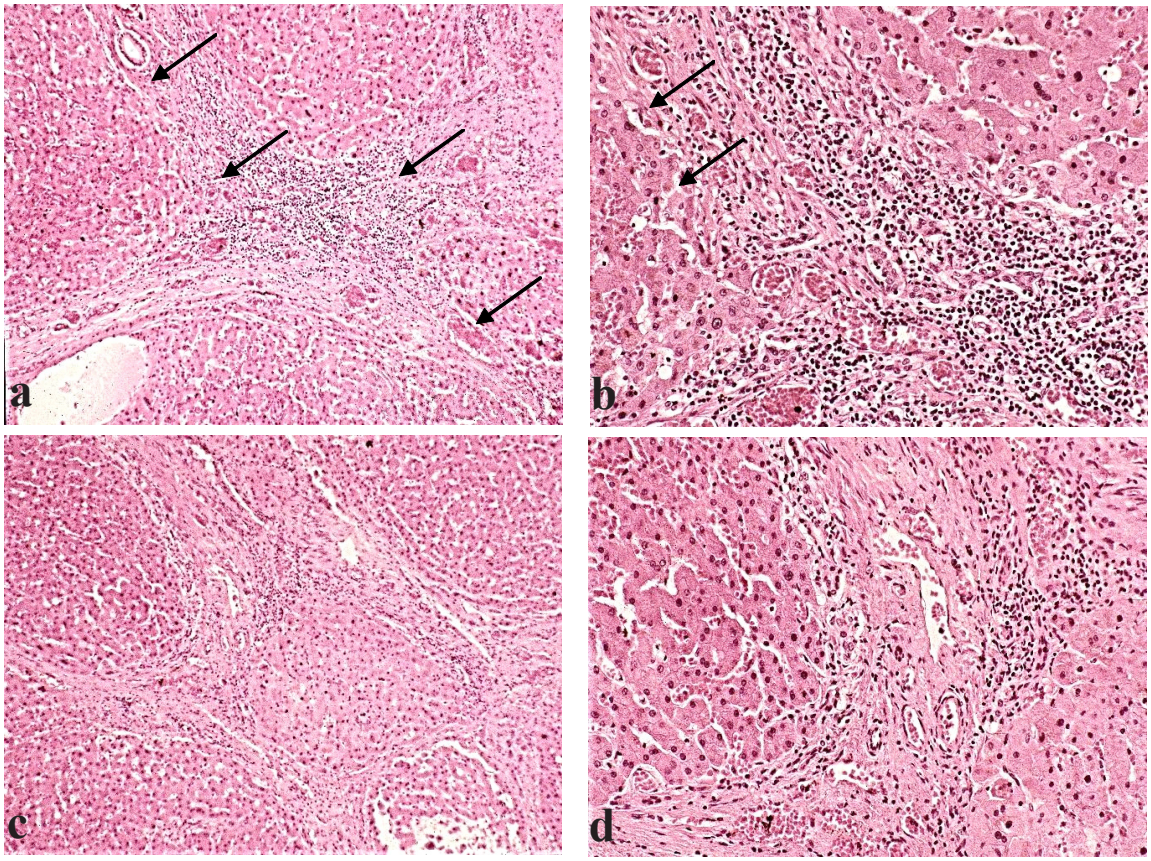


Figure 12a-d. *Rheumatoid arthritis, chronic active hepatitis, with cirrhotic nodular transformation.*

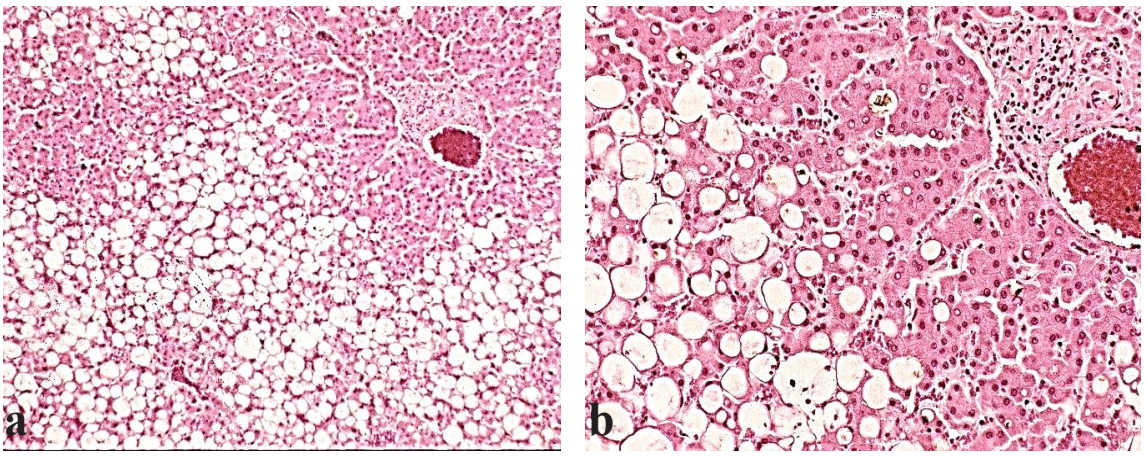
Inflammatory infiltration of portal tract is dominated by neutrophils, limiting plates are piece meal necrotic (black arrows), accompanied by cirrhotic transformation.

(**a**) HE, x50,

(**b**) same as Figure (a), limiting plate is piece meal necrotic (black arrows), x125,

(**c**) HE, x50,

(**d**) same as Figure (c), The portobiliary inflammatory infiltrate is accompanied by fibrous portal expansion and bridging fibrosis; black arrows indicate pseudolobe formation (cirrhotic nodular transformation), x125



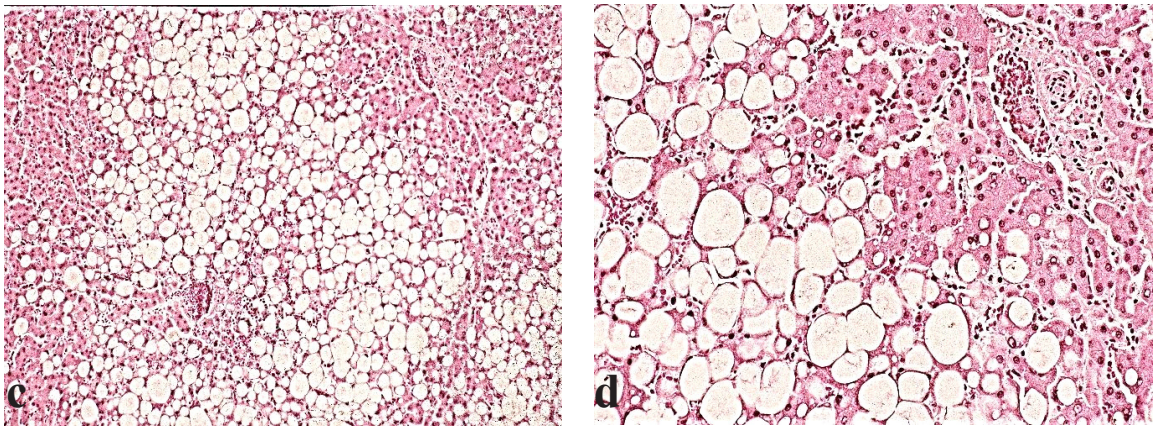


Figure 13a-d. *Rheumatoid arthritis, alcoholic steatosis, without cirrhotic transformation*

Inflammatory infiltrate in portal tracts is absent or minimal, reticulin framework is intact, there are no fibrous septa.

Alcoholic steatosis with centrilobular accumulation of fat (intracytoplasmic large vacuoles of signet ring' appearance, and/or with small ones resulting in a cobweb-like network). Alcoholic steatosis may involve only a few hepatocytes or entire lobules.

(**a**) HE, x50, (**b**) same as Figure (a) x125,

(**c**) HE, x50, (**c**) same as Figure (c) x125

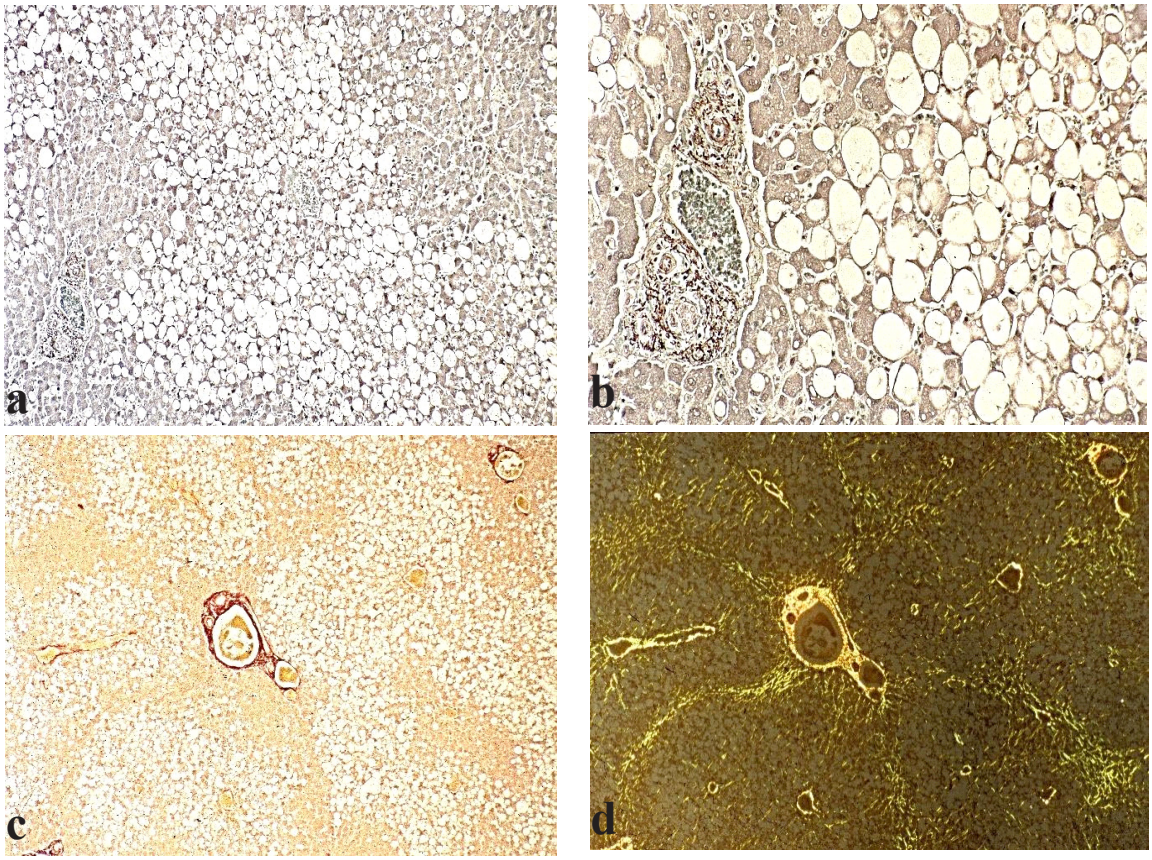


Figure 14a-d. *Rheumatoid arthritis, alcoholic steatosis, without cirrhotic transformation*

Reticulin framework is intact (a-b); fibrous portal expansion or collagen fiber septa are absent (c-d).

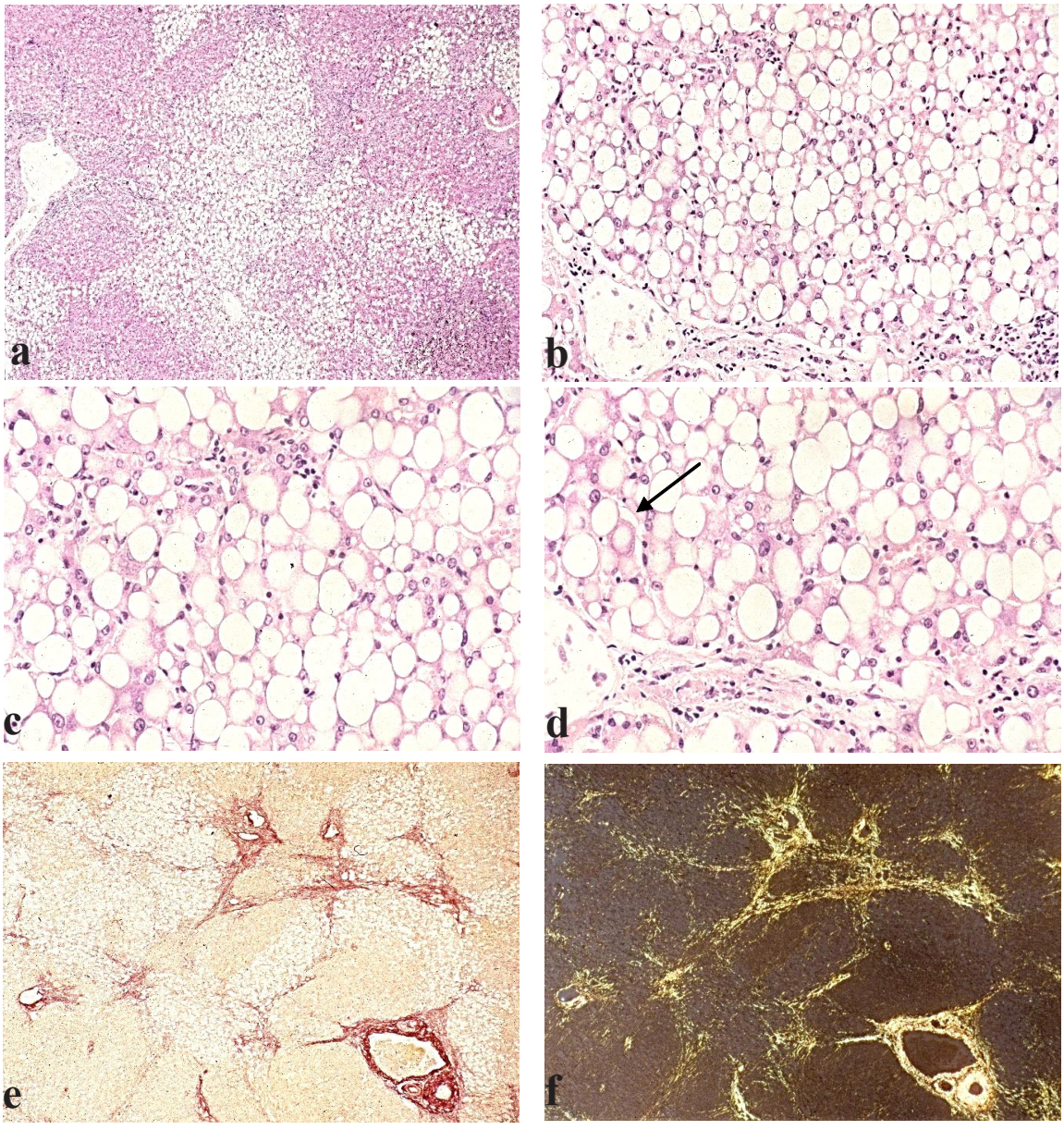
(**a**) Light green-orcein combined staining [1], x50, (**b**) same as Figure (a) x125,

(**c**) Sirius red F3BA staining [2, 3], x50, (**c**) same as Figure (c) x50

[1] **Unna PG**: "Notiz, betreffend die Tänzersche Orceinfärbung des elastischen Gewebes". *Monatschrift für praktische Dermatologie*, 1891; 12: 394–396. In: Patológiai technika (Editor: Krutsay M). Medicina, Budapest 1999 pp:186-187.

[2] **Sweat F, Puchtler H, Rosenthal SI**: "Sirius red F3BA as a stain for connective tissue". *Archives of Pathology*, 1964; 78:69-72

[3] **Constantine VS, Mowry RW**: "Selective staining of human dermal collagen. II. The use of Picrosirius red F3BA with polarization microscopy". *Journal of Investigative Dermatology*, **1968**; 50: 419-423. https://doi.org/10.1038/jid.1968.68



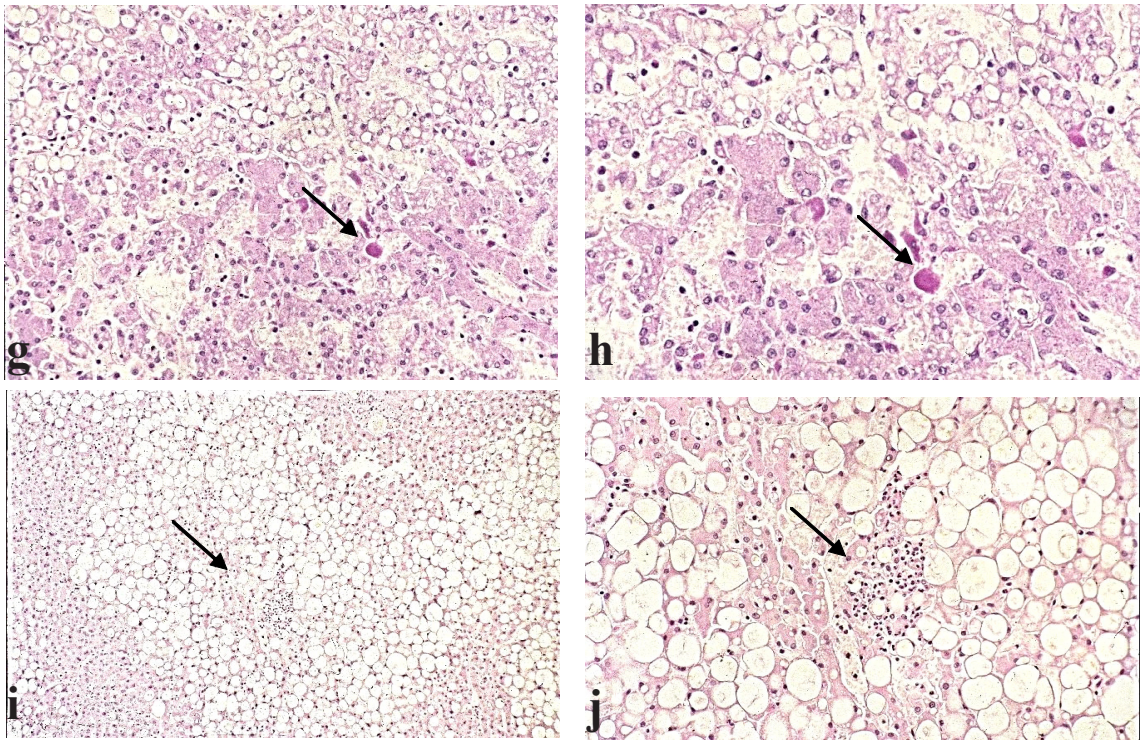


Figure 15a-j. *Rheumatoid arthritis, alcoholic hepatitis without cirrhotic transformation*

Characterized by acute, subacute or chronic inflammatory infiltration in portal tracts, occasionally with lipogranulomas (**a-d**).

Reticulin framework may be compact mainly in the central region of the lobules (centrilobular sclerosis), accompanied with more or less prominent fibrous septa (**e-f**).

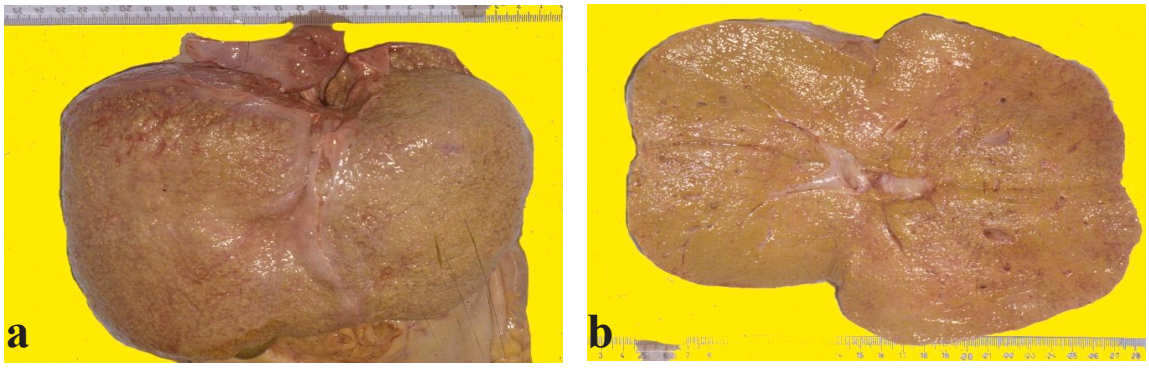
The hepatocytes have small and/or large intracytoplasmic vacuoles resulting in a cobweb-like network, some hepatocytes have blurred cell boundaries, Mallory bodies (**g-h**), Satellitosis' (neutrophil accumulation around the degenerated parenchymal cells) may also occur (**i-j**).

(**a**) HE, x50, (**b**) same as Figure (a) x125,

(**c**) HE, x50, (**d**) same as Figure (c) x125

(**e**) Sirius red F3BA staining, x50, (**f**) same as Figure (e) x50

(**g**) Mallory bodies usually are spheroid or irregular in shape, occasionally ring like (see black arrow in: **d**), HE, x125, (**h**) same as Figure (g) x200, (**i**) Satellitosis (see: black arrows), HE, x50, (**j**) same as Figure (i) x125



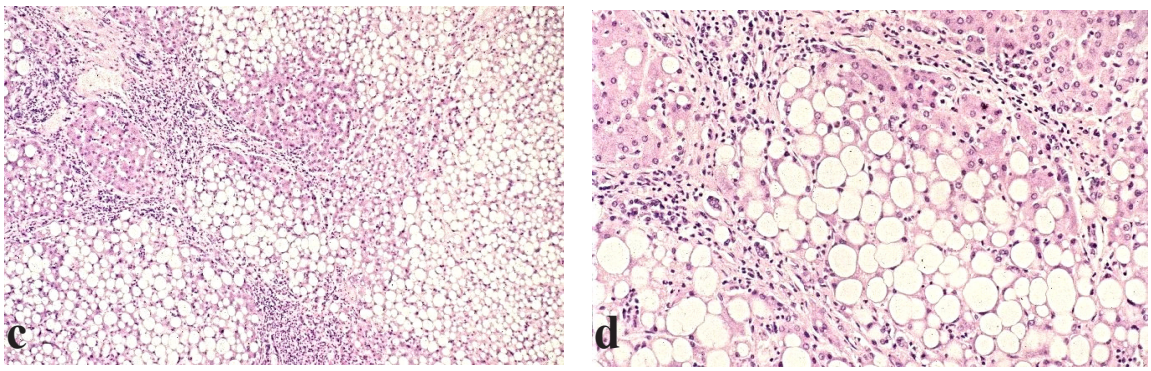


Figure 16a-d. *Rheumatoid arthritis, alcoholic cirrhosis*

All aforementioned histological and cytological signs of alcoholic steatosis or alcoholic hepatitis with cirrhotic nodule formation (degeneration, regeneration of hepatocytes and pseudolobule formation).

(**a**) Macrophotograph, surface,

(**b**) Macrophotograph, same as Figure (a), cut surface

(**c**) HE, x50, (d**b**) same as Figure (c) x125

Table 1 summarizes the demographics, onset and duration of disease of total population with and without complication of **RA** or associated diseases of the liver.

Table1. **Sex, mean age with SD, range, onset and disease duration (in years) of 152 RA patients with and without complication of RA or associated diseases of the liver**

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)	**152**	**65.81±13.06**	**16 – 88**	**51.43±17.20**	**14.30±10.61**
Female	108	65.54±11.85	16 – 87	50.99±15.89	14.54±10.78
Male	44	66.45±15.62	19 – 88	52.56±20.15	13.69±10.12
with sRhV	**32 of 152**	**67.47±10.68**	**32 – 83**	**57.07±14.86**	**11.90±10.44**
Female	20	66.95±11.11	32 – 82	59.47±10.15	10.63±7.46
Male	12	68.25±9.84	53 – 83	52.91±19.92	14.09±13.91
without sRhV	**120 of 152**	**65.37±13.59**	**16 – 88**	**49.72±17.49**	**15.03±10.55**
Female	88	65.22±11.99	16 – 87	48.81±16.36	15.54±11.27
Males	32	65.78±17.25	19 – 88	52.40±20.25	13.52±7.89
with hRhV	**12 of 32**	**71.00±6.20**	**58 – 82**	**60.67±9.66**	**10.33±8.30**
Female	8	70.63±6.84	58 – 82	56.88±9.27	13.75±8.24
Male	4	71.75±4.60	65 – 78	68.25±4.66	3.50±0.87
without hRhV	**20 of 32**	**65.35±12.14**	**32 – 83**	**54.67±17.07**	**12.94±11.53**
Female	12	64.50±12.63	32 – 80	61.36±10.34	8.36±5.88
Male	8	65.50±11.20	53 – 83	44.14±20.00	20.14±14.24
with sAAa	**32 of 152**	**63.25±15.64**	**19 – 88**	**48.17±18.41**	**16.00±9.51**
Female	27	65.48±10.54	32 – 83	49.28±15.48	16.20±10.08
Male	5	51.20±28.18	19 – 88	41.25±30.07	14.75±4.44
without sAAa	**120 of 152**	**66.49±12.19**	**16 – 87**	**52.37±16.71**	**13.81±10.86**

Female	81	65.56±12.25	16 – 87	51.62±15.99	13.93±10.97
Male	39	68.41±11.83	20 – 87	53.97±18.05	13.56±10.61
with hAAa	**26 of 32**	**61.31±16.39**	**19 – 88**	**47.83±19.83**	**14.39±9.34**
Female	21	63.71±10.65	32 – 83	49.21±16.57	14.32±10.07
Male	5	51.20±28.18	19 – 88	41.25±30.07	14.75±4.44
without hAAa	**6 of 32**	**71.67±7.34**	**66 – 82**	**49.50±11.34**	**22.17±7.40**
Female	6	71.67±7.34	66 – 82	49.50±11.34	22.17±7.40
Male	0	–	–	–	–
with AbSI	**23 of 152**	**61.78±9.04**	**41 – 83**	**47.75±12.63**	**13.30±9.52**
Female	15	60.33±9.78	41 – 83	47.92±14.38	11.54±10.24
Male	8	64.50±6.63	52 – 73	47.43±8.47	16.57±6.93
without AbSI	**129 of 152**	**66.53±13.53**	**16 – 88**	**52.10±17.83**	**14.49±10.79**
Female	93	66.38±11.94	41 – 83	51.49±16.07	15.03±10.79
Male	36	66.89±7.66	19 – 88	53.79±21.89	13.00±10.63
with AbSH	**9 of 23**	**63.22±9.99**	**52 – 83**	**53.29±12.26**	**8.00±4.00**
Female	5	64.60±11.32	52 – 83	57.00±13.58	5.75±2.59
Male	4	61.50±7.66	52 – 70	48.33±7.85	11.00±3.56
without AbSH	**14 of 23**	**60.86±8.24**	**41 – 73**	**44.77±11.80**	**16.15±10.38**
Female	10	58.20±8.11	41 – 68	43.89±12.80	14.11±11.27
Male	4	67.50±3.35	64 – 73	46.75±8.84	20.75±5.80
with EoH	**4 of 152**	**65.25±10.87**	**55 – 83**	**53.50±22.16**	**11.75±15.74**
Female	1	83.00±0.00	83.0	80.0±0.0	3.0±0.0
Male	3	59.33±4.19	55 – 65	44.67±18.52	14.67±17.21
without EoH	**148 of 152**	**65.82±13.12**	**88 – 16**	**51.36±17.01**	**14.38±10.39**
Female	107	65.37±11.78	87 – 16	50.67±15.68	14.66±10.77
Male	41	66.98±16.02	88 – 19	53.27±20.14	13.61±9.20
with RH	**62 of 152**	**67.47±11.78**	**20 – 88**	**52.43±16.91**	**14.47±11.80**
Female	47	68.11±10.27	32 – 87	53.89±15.30	14.11±11.75
Male	15	65.40±15.39	20 – 88	47.00±21.00	15.82±11.88
without RH	**90 of 152**	**64.67±13.76**	**16 – 87**	**50.75±17.36**	**14.19±9.72**
Female	61	63.56±12.58	16 – 83	48.70±15.97	14.88±9.94
Male	29	67.00±15.71	19 – 87	55.00±19.27	12.76±9.08
with ChrAH	**6 of 152**	**68.17±9.77**	**48 – 77**	**60.00±3.03**	**12.20±5.42**
Female	3	65.33±12.50	48 – 77	61.50±0.50	12.50±2.50
Male	3	71.00±4.32	65 – 75	59.00±3.56	12.00±6.68
with ChrPH	**19 of 152**	**67.79±8.30**	**50 – 79**	**55.44±12.06**	**12.25±10.97**
Female	10	66.40±9.62	50 – 79	54.50±9.27	11.38±12.35
Male	9	69.33±6.16	59 – 79	56.38±14.25	13.13±9.32
without ChrAH or **ChrPH**	**127 of 152**	**65.40±13.72**	**16 – 88**	**50.44±18.02**	**14.70±10.69**
Female	95	65.45±12.03	16 – 87	50.40±16.44	14.89±10.69
Male	32	65.22±17.81	19 – 88	50.56±22.47	14.08±10.66
with AlcSt	**60 of 152**	**65.82±11.76**	**32 – 87**	**51.90±17.13**	**13.52±11.12**

Female	45	64.44±12.30	32 – 87	50.51±15.69	13.43±11.16
Male	15	69.93±8.74	53 – 87	56.18±19.90	13.82±10.99
with AlcH	**10 of 60**	**66.60±9.10**	**51 – 87**	**56.83±12.92**	**9.83±7.58**
Female	8	64.13±6.73	51 – 74	51.60±5.99	11.00±7.80
Male	2	76.50±10.50	66 – 87	83.00±0.0	4.00±0.0
without AlcSt or **AlcH**	**92 of 152**	**65.80±13.85**	**16 – 88**	**51.17±17.23**	**14.72±10.30**
Female	63	66.32±11.45	16 – 84	51.26±15.88	15.18±10.51
Male	29	64.66±17.92	19 – 88	50.96±20.05	13.64±9.71
with PBC	**2 of 152**	**73.00±2.00**	**71 – 75**	**57.00±6.00**	**16.00±8.00**
Female	2	73.00±2.00	71 – 75	57.00±6.00	16.00±8.00
Male	0	–	–	–	–
with cirrhosis *	**8 of 152**	**70.50±8.72**	**48 – 77**	**58.67±4.50**	**15.00±5.35**
Female	6	69.33±9.78	48 – 77	59.25±4.82	14.25±6.18
Male	2	74.00±1.00	73 – 75	57.50±3.50	16.50±2.50
without cirrhosis *	**144 of 152**	**65.55±13.21**	**16 – 88**	**51.07±17.51**	**14.27±10.80**
Female	102	65.31±11.92	16 – 87	50.62±16.11	14.55±10.94
Male	42	66.10±15.90	19 – 88	52.26±20.68	13.53±10.37
without complications or allied disorders	**9 of 152**	**70.78±10.98**	**50 – 85**	**56.11±17.41**	**14.67±8.49**
Female	6	65.83±10.14	50 – 80	48.67±16.71	17.17±7.86
Male	3	80.67±3.09	78 – 85	71.00±4.32	9.67±7.41

Glossary to Table 1

RA – Rheumatoid **A**rthritis

sAAa – systemic **AA a**myloidosis

hAAa – hepatic **AA a**myloidosis (amyloid A deposits in the liver)

sRhV – systemic **Rh**eumatoid **V**asculitis of autoimmune origin

4hRhV –hepatic **Rh**eumatoid **V**asculitis (RhV in the liver)

AbSI –**A**cute **b**acterial **S**eptic **I**nfection of lethal outcome

AbSH –**A**cute **b**acterial **S**eptic (serous) **H**epatitis

EoH –**Eo**sinophilic **H**epatitis

RH –**n**onspecific **R**eactive **H**epatitis

ChrAH – **Chr**onic **A**ctive **H**epatitis

ChrPH – **Chr**onic **P**assive (non agressive) **H**epatitis

PhC – **P**ost**h**epatitic **C**irrhosis

AlcSt – **Alc**oholic **St**eatosis (alcoholic fatty change of the liver)

AlcH –**Alc**oholic **H**epatitis

SD – Standard **D**eviation

Remarks to Table 1

*In Table 1 only the total number of patients with cirrhotic transformation of the liver are listed. Different causes of cirrhosis [acute hepatitis (**PhC**: n=4 of 6), chronic alcoholism (**AlcC**: n=1 of 10), subacute liver necrosis (**PnC**: n=1 of 2) or primary biliary cirrhosis (**PBC**: n=2 of 152)] are not mentioned.

PhC – **P**ost**h**epatitic **C**irrhosis

AlcC –**Alc**oholic **C**irrhosis

PBC – **Pr**imary **B**iliary **C**irrhosis

aLN – **a**cute "yellow" **L**iver **N**ecrosis of toxic (drug induced) origin

saLN – **s**uba**c**ute "red" **L**iver **N**ecrosis of toxic (drug induced) origin

Demographics of patients with acute or subacute liver necrosis are not listed in Table 1 due to lack of the data.

Because of the small number and/or lack of the data only the total number of patients with cirrhosis is listed; cirrhosis due to acute hepatitis (**PhC**: n=4 of 6), chronic alcoholism (**AlcC**: n=1 of 10) or subacute liver necrosis (**PnC**: n=1 of 2) are not mentioned separately.

1. Demographics of patients with rheumatoid arthritis related complications

(sRhV, **hRhV**, **sAAa**, **HAAa**, **AbSI**, and **AbSH) –** (Tables 1 and 2).

1.1 Demographics of patients with rheumatoid vasculitis

Comparing the **age, sex**, and **duration of RA** there was **no significant** difference in the **mean age** of **female** and **male** patients at death (n=152) **with sRhV** (n=32) or **hRhV** (n=12), and **without sRhV** (n=120) or **hRhV** (n=20).

RA started later in **female** patients **with sRhV**, than in **female** patients **without sRhV** (59.47 years versus 48.81; **p< 0.0011**).

RA started also later in **male** patients **with hRhV**, than in **male** patients **without hRhV** (68.25 years versus 44.14; **p< 0.026**), and in these male patients the **duration of RA** was shorter (3.5 years versus 20.14; **p< 0.029**).

1.2 Demographics of patients with AA amyloidosis

There was **no significant difference** in the **mean age** at death (63.25 ys versus 66.49 ys; p< 0.290 – NS), **onset** of **RA** (48.17 ys versus 52.37 ys; p< 0.284 – NS), and **duration** of **RA** (16.00 ys versus 13.81 ys; p< 0.303 – NS), between **RA** patient cohorts **with sAAa** (n=32) and **without sAAa** (n=120), **with sAAa** (n=32) and **with hAAa** (n=26), furthermore **with hAAa** (n=26) and **without hAAa** (n=6), neither between **females** and **males** (except in the age of patients **with hAAa** and **without hAAa**; the patients **with hAAa** died earlier, than the patients **without hAAa** (61.31 ys versus 71.67 ys; **p <0.040**).

1.3 Demographics of patients with acute bacterial septic infection

RA patients died earlier **with** acute bacterial septic infection (**AbSI**), than the patients **without AbSI** (61.78 ys versus 66.53 ys; p <**0.043**), and the **mean age** of **women with AbSI** was also significantly lower at death, than the mean age of **women without AbSI** (60.33 ys versus 66.38 ys; p <**0.049**).

Comparing the **onset of RA** (47.75 ys versus 52.10 ys; p <0.205 – NS), and **duration of RA** (13.30 ys versus 14.49 ys; p <0.628 – NS) the differences were **not significant** between patient cohorts **with** and **without AbSI**.

There was **no significant difference** in **mean age** of patients (63.25 ys versus 66.49 ys; p< 0.290 – NS), **onset of RA** (48.17 ys versus 52.37 ys; p< 0.284 – NS), and **duration** of **RA** (16.00 ys versus 13.81 ys; p< 0.303 – NS) between **female** or **male** patients **with AbSI** (n=23) and **with AbSH** (n=9) or **with AbSH** (n=9) and **without AbSH** (n=14), except **duration of RA**, which was significantly shorter in patient **with AbSH** than that of in patients **without AbSH** (8.0 ys versus 16.15 ys; **p <0.029**).

2. Demographics of patients with associated diseases of the liver

(EoH, **RH**, **ChrAH**, **ChrPH**, **alkoholic changes**, **aLn**, **saLn** or **PBC) –** (Tables 1 and 2).

2.1 Demographics of patients with eosinophil hepatitis

The difference was not significant in **mean age** of **RA** patients at death, **onset of RA**, and **duration** of **RA with** eosinophil hepatitis (**EoH**) and **without EoH**.

2.2 Demographics of patients with nonspecific reactive hepatitis

There was **no significant difference** in **mean age** of patients at death (67.47 ys versus 64.67 ys; p< 0.184 – NS), **onset of RA** (52.43 ys versus 50.75 ys; p< 0.587 – NS), and **duration** of **RA** (14.47 ys versus 14.19 ys; p< 0.887 – NS) between patient cohorts **with** reactive hepatitis (**RH**) and **without RH**, except in mean age of **female** patients **with RH**, which was higher at death than the mean age of female patients **without RH** (68.11 ys versus 63.56 ys; p< **0.043**).

2.3 Demographics of patients with chronic active or passive hepatitis

The difference was not significant in **mean age** of **RA** patients at death **with** chronic active hepatitis (**ChrAH**) and **without hepatitis** (68.17 ys versus 65.40 ys; p< 565 – NS), neither between **females** (65.33 ys versus 65.45 ys; p< 991 – NS) and **males** (71.00 ys versus 65.22 ys; p< 227 – NS).

The **RA** started later in patients **with ChrAH**, than **without hepatitis** (60.00 ys versus 50.44 ys; p< **0.0005**), and this significant difference of **onset of RA** was more pronounced in **females** (61.50 ys versus 50.40 ys; p< **0.00000**).

There was **no significant difference** in **mean age** of patients at death (68.17 ys versus 65.40 ys; p< 0.308 – NS), **onset of RA** (60.00 ys versus 55.44 ys; p< 0.173 – NS), and **duration** of **RA** (12.20 ys versus 12.25 ys; p< 0.426 – NS) between patients **with ChrPH** (n=19) and **without hepatitis** (n=127), neither between **females** or **males**.

2.4 Demographics of patients with alcoholic changes of the liver

Comparing the **age, sex**, and **duration of RA** of **total population** (152) **with** patient cohorts of **alcoholic steatosis** (**AlcSt**) (n=60), **alcoholic hepatitis** (**AlcH**) (n=10) or **without alcoholic changes of the liver** (n=92) the differernces were **not significant**, neither between **females** or **males**.

There was **no significant difference** in **mean age** of patients at death (65.82 ys versus 65.80 ys; p< 995 – NS), **onset of RA** (51.90 ys versus 51.17 ys; p< 0.821 – NS), and **duration** of **RA** (13.52 ys versus 14.72 ys; p< 0.555 – NS) between patients **with alcoholic steatosis** (**AlcSt**) (n=60) and **without alcoholic changes of the liver** (n=92), neither between **females** or **males**.

2.5 Toxic liver necrosis with or without cirrhosis

Demographics of patients with acute or subacute liver necrosis were not analyzed because of the small number, and lack of the data; boths patients were female

2.6 Demographics of patients with primary biliary cirrhosis

Comparing the **age, sex**, and **duration of RA** of **two** female patients with **primary biliary cirrhosis** (**PBC**) and the **total number of patients** (n=152), the differences were not significant, furthermore they were not significant between patient cohorts **with PBC** (n=2) and **without PBC** (n=150).

2.7 Demographics of patients with cirrhotic transformation of the liver

There was no significant difference in **mean age** at death (70.50 ys versus 65.55 ys; p< 189 – NS) or **duration** of **RA** (15.00 ys versus 14.27 ys; p< 0.786 – NS) between patients **with cirrhosis** (**CT**) (n=8) and **without cirrhosis** (n=144).

The **males with cirrhosis** died earlier, than **males without cirrhosis** (74.00 ys versus 66.10 ys; p< **0.006**).

RA started significantly later in patients **with cirrhosis** (58.67 ys versus 51.17 ys; p< **0.011**) compared to the patients **without cirrhosis**, and this difference in females was also significant (59.25 ys versus 50.62 ys; p< **0.040**).

Table 2 summarizes the "p" values of demographics, onset and disease duration of **RA** betwen patient cohorts with and without complication of **RA** or associated diseases of the liver.

Table2. **Statistical links of female and male patients with and without complication of RA or associated diseases of the liver**

Rheumatoid vasculitis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with sRhV n=32**	**0,453**	**0,080**	**0,271**
Female n=**108** of 152 versus n=20 of 32	0,617	0,006	0,070
Male n=**44** of 152 versus n=12 of 32	0,641	0,961	0,934
with sRhV n=32 versus **with hRhV n=12**	**0,196**	**0,376**	**0,625**
Female n=**20** of 32 versus n=8 of 12	0,323	0,550	0,401
Male n=**12** of 32 versus n=4 of 12	0,399	0,044	0,037
with hRhV n=12 versus **without hRhV n=20**	**0,103**	**0,246**	**0,492**
Female n=**8** of 12 versus n=12 of 20	0,200	0,363	0,164
Male n=**4** of 12 versus n=8 of 20	0,318	0,026	0,029
with sRhV n=32 versus **without sRhV dis n=120**	**0,362**	**0,029**	**0,164**
Female n=**20** of 32 versus n=88 of 120	0,548	0,0011	0,031
Male n=**12** of 32 versus n=32 of 120	0,569	0,947	0,905
AA amyloidosis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with sAAa n=32** of 152	**0,399**	**0,397**	**0,407**
Female n=**108** of 152 versus n=**27** of 32	0,407	0,981	0,397
Male n=**44** of 152 versus n=5 of 32	0,397	0,482	0,981
with sAAa n=32 versus **with hAAa n=26 of 32**	**0,655**	**0,950**	**0,552**
Female n=**27** of 32 versus n=**21** of 26	0,578	0,989	0,552
Male n=**5** of 32 versus n=**5** of 26	1,000	1,000	1,000
with hAAa n=26 vs. **without hAAa n=6 of 32**	**0,040**	**0,804**	**0,075**
Female n=**21** of 26 versus n=**6** of 6	0,076	0,965	0,081
Male n=**5** of 26 versus n=**0** of 6	–	–	–
with sAAa n=32 versus **without sAAa n=120 of 152**	**0,290**	**0,284**	**0,303**
Female n=**27** of 32 versus n=**81** of 120	0,976	0,532	0,359
Male n=**5** of 32 versus n=**39** of 120	0,291	0,520	0,721
Acute bacterial septic infection and septic hepatitis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with AbSI n=23**	**0,075**	**0,270**	**0,677**
Female n=**108** of 152 versus n=15 of 23	0,083	0,503	0,357
Male n=**44** of 152 versus n=8 of 23	0,578	0,303	0,403
with AbSI n=23 versus with AbSH 9 of 23	**0,726**	**0,360**	**0,064**
Female n=**15** of 23 versus n=5 of 9	0,520	0,355	0,101
Male n=**8** of 23 versus n=4 of 9	0,581	0,897	0,186
with AbSH n=9 versus without AbSH 14 of 23	**0,582**	**0,186**	**0,029**
Female n=**5** of 9 versus n=**10** of 14	0,348	0,206	0,078
Male n=**4** of 9 versus n=**4** of 14	0,280	0,843	0,068
with AbSI n=23 versus without AbSI 129 of 152	**0,043**	**0,205**	**0,628**

Female n=**15** of 23 versus n=93 of 129	**0,049**	0,442	0,291
Male n=**8** of 23 versus n=36 of 129	0,536	0,249	0,322
Eosinophilic hepatitis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with EoH n=4**	**0,935**	**0,882**	**0,798**
Female n=**108** of 152 versus n=1 of 4	–	–	–
Male n=**44** of 152 versus n=3 of 4	0,116	0,612	0,944
with EoH n=4 versus without EoH 148 of 152	**0,934**	**0,878**	**0,791**
Female n=**1** of 4 versus n=**107** of 148	–	–	–
Male n=3 of 4 versus n=**41** of 148	0,099	0,583	0,939
Reactive hepatitis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with RH n=62**	**0,370**	**0,721**	**0,929**
Female n=**108** of 152 versus n=47 of 62	0,179	0,325	0,844
Male n=**44** of 152 versus n=15 of 62	0,826	0,468	0,615
with RH n=62 versus without RH 90 of 152	**0,184**	**0,587**	**0,887**
Female n=**47** of 62 versus n=**61** of 90	**0,043**	0,119	0,743
Male n=**15** of 62 versus n=**29** of 90	0,755	0,314	0,477
Chronic active hepatitis			
Chronic Passive (nonagressive) hepatitis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with ChrAH n=6**	**0,620**	**0,0011**	**0,496**
Female n=**108** of 152 versus n=3 of 6	0,962	**0,0000**	0,599
Male n=**44** of 152 versus n=3 of 6	0,224	0,066	0,677
RA pts. n=152 versus **with ChrPH n=19**	**0,381**	**0,259**	**0,500**
Female n=**108** of 152 versus n=10 of 19	0,805	0,386	0,529
Male n=**44** of 152 versus n=9 of 19	0,380	0,559	0,887
with ChrAH n=6 versus without hepatitis 127 of 152	**0,565**	**0,00050**	**0,426**
Female n=**3** of 62 versus n=**95** of 127	0,991	**0,00000**	0,503
Male n=**3** of 6 versus n=**32** of 127	0,227	0,123	0,717
with ChrPH n=19 versus without hepatitis 127 of 152	**0,308**	**0,173**	**0,426**
Female n=**10** of 62 versus n=**95** of 127	0,788	0,321	0,486
Male n=**9** of 6 versus n=**32** of 127	0,295	0,422	0,821
with ChrAH n=6 versus ChrPH n=19	**0,939**	**0,203**	**0,990**
Female n=**3** of 62 versus n=**10** of 19	0,918	0,087	0,838
Male n=**3** of 6 versus n=**9** of 19	0,679	0,669	0,857
Alcoholic steatosis (Alcoholic fatty liver)			
Alcoholic hepatitis			
Level of significance p< 0.05	**Age**	**Onset of disease**	**Disease duration**
RA pts. n=152 versus **with AlkSt n=60**	**0,997**	**0,875**	**0,686**
Female n=**108** of 152 versus n=45 of 60	0,618	0,883	0,622
Male n=**44** of 152 versus n=15 of 60	0,303	0,619	0,975

RA pts. n=152 versus **with AlkH n=10**	**0,810**	**0,402**	**0,253**
Female n=**108** of 152 versus n=8 of 10	0,624	0,864	0,426
Male n=**44** of 152 versus n=2 of 10	0,510	–	–
with AlcSt n=60 vs. without alcoholic changes 92 of 152	**0,995**	**0,821**	**0,555**
Female n=**45** of 60 versus n=**63** of 92	0,429	0,830	0,465
Male n=**15** of 60 versus n=**29** of 92	0,207	0,495	0,965
with AlcH n=10 of 60 vs without alcoholic changes 92 of 152	**0,934**	**0,397**	**0,189**
Female n=**8** of 10 versus n=**63** of 92	0,469	0,928	0,358
Male n=**2** of 10 versus n=**29** of 92	0,451	–	–
with AlcSt n=60 versus **with AlkH n=10**	**0,821**	**0,461**	**0,359**
Female n=**45** of 60 versus n=8 of 10	**0,920**	**0,794**	**0,597**
Male n=15 of 60 versus n=2 of 10	0,643	**–**	**–**
PBC			
RA pts. n=152 versus **with PBC n=2**	**0,111**	**0,519**	**0,867**
Female n=**108** of 152 versus n=2 of 2	0,099	0,493	0,885
Male n=44 of 152 versus 0 of 2	–	–	–
with PBC n=2 versus without PBC 150 of 152	**0,108**	**0,513**	**0,865**
Female n=2 of 2 versus n=106 of 152	0,094	0,485	0,883
Male n=0 of 2 versus 44 of 152	–	–	–
Total number of cirrhotic taransformation of the liver			
RA pts. n=152 versus **with CT n=8**	**0,210**	**0,014**	**0,794**
Female n=**108** of 152 versus n=6 of 8	0,435	0,047	0,943
Male n=**44** of 152 versus n=2 of 8	0,007	0,373	0,447
with CT n=8 versus without CT 144 of 152	**0,189**	**0,011**	**0,786**
Female n=**6** of 8 versus n=102 of 144	0,410	**0,040**	0,940
Male n=**2** of 8 versus n=42 of 144	**0,006**	0,355	0,426

Glossary to Table 2

sRhV – systemic **Rh**eumatoid **V**asculitis of autoimmune origin

hRhV – hepatic **Rh**eumatoid **V**asculitis

sAAa – systemic **AA a**myloidosis (**s**ystemic **A**myloid **A** protein **a**myloidosis)

hAAa – hepatic **AA a**myloidosis (**AA** protein deposition in the liver)

AbSI –Acute **b**acterial **S**eptic **I**nfection of lethal outcome

AbSH –Acute **b**acterial **S**eptic (serous) **H**epatitis

RH –nonspecific **R**eactive **H**epatitis

ChrAH – Chronic **A**ctive **H**epatitis

ChrPH – Chronic **P**assive (non agressive) **H**epatitis

AlcSt – Alcoholic **St**eatosis (alcoholic fatty change of the liver)

AlcH –Alcoholic **H**epatitis

PBC – **Pr**imary **B**iliary **C**irrhosis

CT – Cirrhotic **T**ransformation of the liver (total number of cirrhosis: n=8) due to acute hepatitis (**PhC**: n=4 of 6), chronic alcoholism (**AlcC**: n=1 of 10), subacute liver necrosis (**PnC**: n=1 of 2) or primary biliary cirrhosis (**PBC**: n=2 of 152)

3. Interactions between rheumatoid arthritis related complications and/or coexistent associated diseases of the liver

3.1 Interactions between coexistent complications of rheumatoid arthritis

Systemic vasculitis was associated with systemic amyloidosis in **5** (3.29 % of 152), and with septic infection in **one** (0.66 % of 152) patient; the relationship was inverse between **sRhV** and **sAAa**: c*= -0.2211, χ^2=0.718, p <0.3967 – NS, furthermore between **sRhV** and **AbSI**: c*= -0.7487, χ^2=3.4429, p <0.0635 – NS.

Systemic amyloidosis was accompanied by septic infection in **3** (1.97 % of 152) patients, and the relationship was inverse as well (c*=-0.3182, χ^2=0.555, p <0.456 – NS).

Rheumatoid vasculitis in the liver (**hRhV**) was not associated with **hAAa** or **AbSH**; the reralitonship was inverse between **hRhV** and **hAAa** (c*=-1.00, χ^2=1.5382, p <0.215 – NS) or between **hRhV** and **AbSH** (c*=-1.00, χ^2=0.0720, p <0.789 – NS).

Amyloid A deposits of the liver (**hAAa**) were accompanied by septic hepatitis (**AbSH**) in **2** (**1.32** % of 152) patients the; the reralitonship was not significant between **hAAa** and **AbSH** (c=0.1724, χ^2=0.0013, p <0.971 – NS).

Table 3.1 summarizes the possible relationships between coexistent complications of rheumatoid arthritis.

Table3.1. **The statistical links ("p" values of significance) between RA related complications in 152 RA patients**

Prevalence of coexistent complications & assoc. disease	**hRhV** **n=12**	**sAAa** **n=32**	**hAAa** **n=26**	**AbSI** **n=23**	**AbSH** **n=9**
sRhV n=32 of 152	c =1,000 χ^2=43,836 **p< 0.0000**	c =-0,2211* χ^2=0,7184 p< 0.3967	c =-0,3925* χ^2=1,0875 p< 0.2970	c =-0,7487* χ^2=3,4429 p< 0.0635	c =-1,0000* χ^2=1,3823 p< 0.2397
hRhV n=12 of 152		c =-0,1538* χ^2=0,0004 p< 0.9845	c =-1,000* χ^2=1,5382 p< 0.2149	c =-1,000* χ^2=1,2198 p< 0.2694	c =-1,000* χ^2=0,0720 p< 0.7885
sAAa n=32 of 152			c =1,000 χ^2=111,9587 **p< 0.0000**	c =-0,3182* χ^2=0,5552 p< 0.4561	c =0,0367 χ^2=0,1107 p< 0.7393
hAAa n=26 of 152				c =-0,1825* χ^2=0,0681 p< 0.7940	c =0,1724 χ^2=0,0012 p< 0.9712
AbSI n=23 of 152					c =1,000 χ^2=46,8605 **p< 0.0000**

Glossary to Table 3.1

sRhV – systemic **Rh**eumatoid **V**asculitis of autoimmune origin

hRhV –blood vessels of the liver involved by **RhV**

sAAa – **s**ystemic **AA a**myloidosis (**s**ystemic **A**myloid **A** protein **a**myloidosis)

hAAa – **h**epatic **AA a**myloidosis (**AA** protein deposition in the liver)

AbSI –**A**cute **b**acterial **S**eptic **I**nfection with lethal outcome

AbSH –**A**cute **b**acterial **S**eptic (serous) **H**epatitis

***** – Asterisk indicates negative value of association's coefficient (inverse relationship)

3.2 Interactions between complications of rheumatoid arthritis and coexistent associated diseases of the liver

Eosinophilic hepatitis (**EoH**) was associated with **sRhV** in **3** (**1.97** %), and with **hRhV** in **1** (**0.66** %) of 152 patients; **EoH** was combined with **sAAa**, **hAAa**, **AbSI** or **AbSH** only in **1-1** (**0.66** %) of 152 patients.

The relationship was significant between **EoH** and **sRhV** (c=0.8497, χ^2=4.2461, **p <0.0393**) or **hRhV** (c=0.6140, χ^2=0.1232, p <0.7256 – NS), and was not between **EoH** and **sAAa**, **hAAa**, **AbSI** or **AbSH**.

Nonspecific reactive hepatitis (**RH**) was associated with **sRhV** in **11** (**17.74** %), and with **hRhV** in **4** (**6.45** %) of 62 patients with **sAAa** in **10** (**16.13** %), and with **hAAa** in **9** (**14.51** %) of 62 patients with **AbSI** in **8** (**12.90** %), and with **AbSH** in **1** (**1.61** %) of 62 patients.

The correlations were not significant between **RH** and **sRhV**, **hRhV**, **sAAa**, **hAAa**, **AbSI** or **AbSH**, even the relationships were invers; the coefficients of colligation were negative.

Chronic active hepatitis (**ChrAH**) was associated with **sRhV** in **2** and with **hRhV** in **one** of 6 patients; the correlations were not significant between **ChrAH** and **sRhV** (c=0.5946, χ^2=0.6686, p <0.414 – NS) or **ChrAH** and **hRhV** (c=0.4211, χ^2=0.0017, p <0.968 – NS).

Chronic passive hepatitis (**ChrPH**) coexisted with **sRhV** in **7** and with **hRhV** in **3** of 19 patients; the correlations were not significant between **ChrPH** and **sRhV** (c=0.4318, χ^2=3.2571, p <0.071 – NS) or **ChrPH** and **hRhV** (c=0.4419, χ^2=0.8272, p <0.363 – NS).

ChrAH was not associaterd with **sAAa** or **hAAa** in any patient; the correlations were inverse and not significant between **ChrAH** and **sAAa** (c*=-1.0, χ^2=0.6080, p <0.436 – NS) or **ChrAH** and **hAAa** (c*=-1.0, χ^2=0.3389, p <0.560 – NS).

ChrPH coexisted with **sAAa** in **1** of 19 patients and with **hAAa** in **another one**; the correlations were inverse and not significant between **ChrPH** and **sAAa** (c*=-0.6909, χ^2=2.2619, p <0.133 – NS) or **ChrPH** and **hAAa** (c*=-0.6129, χ^2=1.2991, p <0.254 – NS).

ChrAH was not associaterd with **AbSI** or **AbSH**; the correlations were not significant even negative between **ChrAH** and **AbSI** (c*=-1.0, χ^2=0.2248, p <0.635 – NS) or **ChrAH** and **AbSH** (c*=-1.0, χ^2=0.0652, p <0.798 – NS).

ChrPH associaterd with **AbSI** in **3** and with **AbSH** in **1** of 19 patients; the correlations were not significant between **ChrPH** and **AbSI** (c=0.0288, χ^2=0.0659, p <0.797 – NS) or **ChrPH** and **AbSH** (c*=-0.0706, χ^2=0.1518, p <0.697 – NS).

Alcoholic fatty liver disease (**AlcSt**) was associated with **sRhV** in **14** and with **hRhV** in **3** of 60 patients; the correlations were not significant between **AlcSt** and **sRhV** (c=0.1116, χ^2=0.31024, p <0.577 – NS) or **AlcSt** and **hRhV** (c*=-0.3465, χ^2=0.5793, p <0.446 – inverse, NS).

Alcoholic fatty liver disease (**AlcSt**) associated with **sAAa** in **7** and with **hAAa** in **5** of 60 patients; the correlations were significant but negative (inverse) between **AlcSt** and **sAAa** (c*=-0.4771, χ^2=5.2543, **p <0.0218**) or **AlcSt** and **hAAa** (c*=-0.5298, χ^2=5.3494, **p <0.0203**).

Alcoholic fatty liver disease (**AlcSt**) was associated with **AbSI** in **12** and with **AbSH** in **4** of 60 patients; the correlations were not significant between **AlcSt** and **AbSI** (c=0.2960, χ^2=1.8295, p <0.176 – NS) or **AlcSt** and **AbSH** (c=0.1083, χ^2=0.0989, p <0.753 – NS).

Alcoholic hepatitis (**AlcH**) was associated with systemic rheumatoid vasculitis (**sRhV**) in **1** of 10 patients, and with acute bascerial septic infection (**AbSI**) in another **one** (**10.0** %).

AlcH was not associated with **hRhV**, **sAAa**, **hAAa**, or **AbSH**.

The correlations were inverse with negative colligation coefficients and not significant between **AlcH** and **sRhV**, **hRhV sAAa**, **hAAa**, **AbSI** or **AbSH**.

AlcC was not associated with **sRhV**, **hRhV sAAa**, **hAAa**, **AbSI** or **AbSH**, and the relationships were inverse between them.

PBC were associated with **sRhV** in two patients and one of these two with **hRhV** as well; the relationships were not significant between them. **PBC** was not associated with **sAAa**, **hAAa**, **AbSI** or **AbSH**; the relationship was inverse between them.

Acute liver necrosis (**aLN**) or **PnC** was not associated with **sRhV**, **hRhV**, **sAAa**, **hAAa**, **AbSI** or **AbSH**.

The correlations were inverse with negative colligation coefficients between **aLN** and **sRhV**, **hRhV sAAa**, **hAAa**, **AbSI** or **AbSH**.

Cirrhotic transformation (**CT**) was associated with systemic rheumatoid vasculitis (**sRhV**) in **3** (**37.50** %), and with rheumatoid vasculitis of the liver (**hRhV**) in **1** (**12.5** %) of 8 patients.

The correlations were not significant between total number of **CT** (n=8) and **sRhV** or **hRhV**.

Cirrhotic transformation was not associated with **sAAa**, **hAAa**, **AbSI** or **AbSH**.

The relationships were not significant and were inverse with negative colligation coefficients between total number of **CT** and **sAAa**, **hAAa**, **AbSI** or **AbSH**.

Table 3.2 summarizes the possible interactions between complications of rheumatoid arthritis and associated diseases of the liver.

Table3.2. **The statistical links ("p" values of significance) between RA related complications and associated diseses of the liver in 152 RA patients**

Prevalence of coexistent complications / assoc. disease	**sRhV n=32**	**hhV n=12**	**sAAa n=32**	**hAAa n=26**	**AbSI n=23**	**AbSH n=9**
EoH n=4 of 152	c =0,8497 χ^2=4,2462 **p< 0.0393**	c =0,6140 χ^2=0,1232 p< 0.7256	c=0,1143 χ^2=0,1808 p< 0.6707	c=0,2424 χ^2=0,614 p< 0.8042	c=0,3125 χ^2=0,0333 p< 0.8817	c=0,7073 χ^2=0,3192 p< 0.5721
RH n=62 of 152	c =-0,1705* χ^2=0,6905 p< 0.4060	c =-0,1717* χ^2=0,0016 p< 0.9675	c =-0,3381* χ^2=2,6918 p< 0.1009	c =-0,2558* χ^2=1,3039 p< 0.2535	c =-0.1489* χ^2=0,4049 p< 0.5246	c =-0.7429* χ^2=2,9477 p< 0.0859
ChrAH n=6 of 152	c=0,5946 χ^2=0,6686 p< 0.4135	c=0,4211 χ^2=0,6686 p< 0.4135	c =-1,0000* χ^2=0,6080 p< 0.4355	c =-1,0000* χ^2=0,3389 p< 0.5604	c =-1,0000* χ^2=0,2248 p< 0.6354	c =-1,0000* χ^2=0,0652 p< 0.7983
ChrPH n=19 of 152	c=0,4318 χ^2=3,2571 p< 0.0711	c=0,4419 χ^2=0,8272 p< 0.3630	c =-0,6909* χ^2=2,2619 p< 0.1325	c =-0,6129* χ^2=1,2991 p< 0.2543	c=0,0288 χ^2=0,0658 p< 0.7974	c =-0,0706* χ^2=0,1518 p< 0.6967
AlcSt n=60 of 152	c=0,1116 χ^2=0,3102 p< 0.5775	c =-0,3465* χ^2=0,5793 p< 0.4465	c =-0,4771* χ^2=5,2543 **p< 0.0218**	c =-0,5798* χ^2=5,3794 **p< 0.0203**	c=0,2960 χ^2=1,8295 p< 0.1761	c=0,1083 χ^2=0,0989 p< 0.7531
AlcH n=10 of 60	c =-0,4308* χ^2=0,2359 p< 0.6271	c =-1,0000* χ^2=0,1233 p< 0.7254	c =-1,0000* χ^2=1,6596 p< 0.1976	c =-1,0000* χ^2=1,1062 p< 0.2929	c =-0,2699* χ^2=0,0074 p< 0.9312	c =-1,0000* χ^2=0,0163 p< 0.8984
AlcC n=1 of 10	c =-1,0000* χ^2=0,5075 p< 0.4762	c =-1,0000* χ^2=2,4542 p< 0.1172	c =-1,0000* χ^2=0,5075 p< 0.4762	c =-1,0000* χ^2=0,7681 p< 0.3807	c =-1,0000* χ^2=0,9530 p< 0.3289	c =-1,0000* χ^2=3,5110 p< 0.0609

aLN or saLN n=2 of 152	c =-1,0000* χ^2=0,0190 p< 0.4762	c =-1,0000* χ^2=0,9154 p< 0.3665	c =-1,0000* χ^2=0,0190 p< 0.4762	c =-1,0000* χ^2=0,0890 p< 0.7653	c =-1,0000* χ^2=0,1536 p< 0.6950	c =-1,0000* χ^2=1,3283 p< 0.2498
PBC n=2 of 152	c =1,0000 χ^2=3,3860 p< 0.0657	c =0,8400 χ^2=0,7009 p< 0.4024	c =-1,0000* χ^2=0,0190 p< 0.8903	=-1,0000* χ^2=0,0890 p< 0.7653	c =-1,0000* χ^2=0,1536 p< 0.6950	c =-1,0000* χ^2=1,3283 p< 0.2498
CT total n=8 of 152	c =0,4082 χ^2=0,5283 p< 0.4673	c =0,2667 χ^2=0,0314 p< 0.8593	c =-1,0000* χ^2=1,1132 p< 0.2913	c =-1,0000* χ^2=0,7017 p< 0.4021	c =-1,0000* χ^2=0,5187 p< 0.4713	c =-1,0000* χ^2=0,0016 p< 0.9676

Glossary to Table 3.2

sRhV – systemic **Rh**eumatoid **V**asculitis of autoimmune origin

hRhV –blood vessels of the liver involved by **RhV**

sAAa – **s**ystemic **AA a**myloidosis (**s**ystemic **A**myloid **A** protein **a**myloidosis)

hAAa – **h**epatic **AA a**myloidosis (**AA** protein deposition in the liver)

AbSI –**A**cute **b**acterial **S**eptic **I**nfection of lethal outcome

AbSH –**A**cute **b**acterial **S**eptic (serous) **H**epatitis

EoH – **Eo**sinophilic **H**epatitis

RH –**n**onspecific **R**eactive **H**epatitis

ChrAH – **Chr**onic **A**ctive **H**epatitis

ChrPH – **Chr**onic **P**assive (non-agressive) **H**epatitis

AlcSt – **Alc**oholic **St**eatosis (alcoholic fatty change of the liver)

AlcH –**Alc**oholic **H**epatitis

AlcC –**Alc**oholic **C**irrhosis

aLN –**a**cute **L**iver **N**ecrosis

saLN –**s**uba**c**ute **L**iver **N**ecrosis

PBC – **Pr**imary **B**iliary **C**irrhosis

CT – Cirrhotic **T**ransformation of the liver (total number of cirrhosis) due to acute hepatitis (**PhC**: n=4 of 6), chronic alcoholism (**AlcC**: n=1 of 10), subacute liver necrosis (**PnC**: n=1 of 2) or primary biliary cirrhosis (**PBC**: n=2 of 152)

***** – Asterisk indicates negative value of association's coefficient (inverse relationship)

3.3 Interactions between associated diseases of the liver

The correlations were strongly positive and significant between the total number of cirrhotic transformation (**CT**) and cirrhosis due to chronic active hepatitis (**PhC** due to **ChrAH**: c=0.9782, χ^2=35.2839, **p <0.0000**), chronic alcoholism (**AlcC** due to **AlcH**: c=1.0, χ^2=4.04047, **p <0.0444**), subacute liver necrosis (**PnC** due to **saLN**: c=1.0, χ^2=4.04047, **p <0.0444**) or biliary cirrhosis (**PBC**: c=1.0, χ^2=19.7670, **p <0.0000**).

Furthermore, the correlations were positive and significant between chronic passive hepatitis (**ChrPH**) and alcoholic fatty liver (**AlcSt**) (c=0.5971, χ^2=7.6157, **p <0.0057**) or alcoholic fatty liver (**AlcSt**) and alcoholic hepatitis (**AlcH**) (c=1.0, χ^2=13.8134, **p <0.0002**) (Table 3.3).

Associated diseases of the liver did not exist together, and were separate entities. The relationships were mainly inverse (with negative colliquation coefficients) between associated diseases of the liver.

Table 3.3 summarizes the interactions between coexistent associated diseases of the liver.

Table3.3. **The statistical links ("p" values of significance) between associated diseses of the liver in 152 RA patients**

Prevalence of coexistent	**RH**	**ChrAH**	**ChrPH**	**AlkSt**	**AlkH**	**AlkC**	**PBC**	**CT**
complications & assoc. disease	**n=62**	**n=6**	**n=19**	**n=60**	**n=10** of 60	**n=1** of 10	**n=2**	**n=8**
EoH n=4 of 152	c =-0,3556* χ^2=-0,0184 p< 0.8921	c =-0,8101 χ^2=-0,7925 p< 0.3733	c =-1,000* χ^2=0,0000 p< 1.0000	c =-0,3308* χ^2=0,0067 p< 0.9348	c =-1,000* χ^2=0,2343 p< 0.6283	c =-1,000* χ^2=8,8147 **p< 0.0030**	c =-1,000* χ^2=3,9575 **p< 0.0467**	c =-1,000* χ^2=0,4315 p< 0.5113
RH n=62 of 152		c =-1,000* χ^2=2,7245 p< 0.0988	c =-1,000* χ^2=13,0908 **p< 0.0003**	c=-0,3088* χ^2=3,4160 p< 0.0646	c =-1,000* χ^2=5,6770 **p< 0.0172**	c =-1,000* χ^2=0,0354 p< 0.8508	c =-1,000* χ^2=0,2092 p< 0.6474	c =-1,000* χ^2=4,17117 **p< 0.0411**
ChrAH n=6 of 152			c =-1,000* χ^2=0,0991 p< 0.7528	c =-0,5445* χ^2=0,5477 p< 0.4592	c =-1,000* χ^2=0,0312 p< 0.8596	c =-1,000* χ^2=5,6306 **p< 0.,0176**	c =-1,000* χ^2=2,3690 p< 0.1237	c =0,9722 χ^2=32,2839 **p< 0.0000**
ChrPH n=19 of 152				c =0,5971 χ^2=7,6157 **p< 0.0057**	c =-1,000* χ^2=0,5505 p< 0.4581	c =-1,000* χ^2=1,2942 p< 0.2552	c=0,7600 χ^2=0,2895 p< 0.5905	c=0,0000 χ^2=0,3015 p< 0.5828
AlkSt n=60 of 152					c=1,0000 χ^2=13,8134 **p< 0.0002**	c=1,0000 χ^2=0,0467 p< 0.8289	c =-1,000* χ^2=0,1777 p< 0.6733	c =-0,3385* χ^2=0,2390 p< 0.6249
AlkH n=10 of 152						c=1,0000 χ^2=3,0879 p< 0.0789	c =-1,000* χ^2=1,1189 p< 0.2901	c=0,3636 χ^2=0,0014 p< 0.9692
AlkC n=1 of 152							c =-1,000* χ^2=18,3642 **p< 0.,0000**	c=1,0000 χ^2=4,0404 **p< 0.0444**
saLn n=1 of 152								c=1,0000 χ^2=4,0404 **p< 0.0444**
PBC n=2 of 152								c=1,0000 χ^2=19,7670 **p< 0.0000**

Glossary to Table 3.3

EoH – Eosinophilic **H**epatitis

RH –nonspecific **R**eactive **H**epatitis

ChrAH – Chronic **A**ctive **H**epatitis

ChrPH – Chronic **P**assive (non agressive) **H**epatitis

AlcSt – Alcoholic **St**eatosis (alcoholic fatty change of the liver)

AlcH –**Alc**oholic **H**epatitis

AlcC –**Alc**oholic **C**irrhosis

PnC –**P**ost**n**ecrotic **C**irrhosis

PBC – **Pr**imary **B**iliary **C**irrhosis

CT – Cirrhotic **T**ransformation of the liver (total number of cirrhosis) due to acute hepatitis (**PhC**: n=4 of 6), chronic alcoholism (**AlcC**: n=1 of 10), subacute liver necrosis (**PnC**: n=1 of 2) or primary biliary cirrhosis (**PBC**: n=2 of 152)

***** – Asterisk indicates negative value of association's coefficient (inverse relationship)

Discussion

RA is a chronic progressive systemic autoimmune disease characterized by repeated acute exacerbations of inflammation of different joints and various organs (heart, lungs, kidneys, serous membranes: peritoneum, pleura, pericardium, etc.).

Numerous data of the early literature data raise the existence of a special rheumatoid liver disease. Volhard and Basler (1939) defined a "rheumatoid liver cirrhosis" [13], Schmengler (1952) spoke about "rheumatoid hepatitis" [14], and Enomoto et al. (1963) mentioned "specific rheumatoid hepatitis" [15].

Kendall et al. (1970) also considered the "rheumatoid liver" is a separate entity [16]. Siegmeth (1976) mentioned "specific rheumatoid hepatitis" in one of his studies [17], but ignored it as a specific entity [18], like others did [19-26].

There is a lack of consensus about the involvement of the liver is an integral part of **RA** or should it be considered only as consequence of the treatment [27].

In our autopsy population a distinct liver disease specific for RA was not identified.

Various liver lesions such as granulomas or vasculitis-related lesions may be problematic or are not considered specific for RA.

Roberts and Coblyn (1983) describe a "granulomatous hepatitis of rheumatoid origin" excluding etiologies of granulomas, such as fungal or bacterial infections, sarcoidosis, drugs etc. [28].

In our **RA** autopsy population hepatic granulomas were found only in association with active disseminated miliary tuberculosis in 3 of 6 cases [29].

Hepatic rheumatoid vasculitis may result in liver cell atrophy and noncirrhotic nodular regenerative hyperplasia of the liver [30].

In rheumatoid arthritis or in Felty's syndrome (characterized by the triad of rheumatoid arthritis, leukopenia and splenomegaly) portal hypertension and hepatocellular atrophy may also be accompanied with liver cell hyperplasia and nodular regeneration [31-32], but these are not accepted as specific liver lesions. Beside autoimmune diseases, other reasons of portal hypertension, such as hepatotoxic drugs, circulatory disturbances, hemopathies, or carcinomas may lead to diffuse (noncirrhotic) nodular regenerative hyperplasia of the liver [33].

In rheumatoid arthritis single or multiple typical rheumatoid nodules may be present in the liver [34].

Rheumatoid noduls represent the more serious form of vasculitis [35].

Rheumatoid vasculitis ("hepatic arteritis") may cause spontaneous hepatic rupture with lethal outcome [36].

Rheumatoid vasculitis affecting the liver (**hRhV**), in our opinion, can be considered a phenomenon of a systemic complication rather than a separate liver disease, like amyloid A deposition of the liver (**hAAa**) or "serous hepatitis" of generalized septic infection (**AbSH**).

In our autopsy population we found two patients with granulomatous cholangitis (Figure 10ab). According to our interpretation these correspond to primary biliary cirrhosis (**PBC**) asssociated to rheumatoid arthritis. **PBC** is a sovereign autoimmune entity, which may accompany to **RA** as a secondary autoimmune disease.

Emmanuel et al. (1919) describes persistent eosinophilia of unknown origin in rheumatoid

arthritis, excluding common causes of eosinophilia [37].

Our **RA** patients with acute eosinophilic hepatitis (**EoH**) did not have eosinophilia in the blood, allergy was not mentioned in the medical history, and other reasons of eosinophilic were not identified at meticulous post mortem analysis.

The close connection (positive and significant correlation) between **EoH** and **sRhV** may reflect to a possible non-specific origin.

Hepatitis is an entity of various etiologies infections [38]. The recent literature accepts the existance of autoimmune hepatitis (**AIH**, autoimmune chronic active hepatitis or autoimmune chronic hepatitis) as a separate immune-mediated entity, resulting by combination of autoimmunity, environmental factors, and a genetic predisposition.

AIH is not specific for **RA**; may be present in various autoimmune diseases, e.g. systemic lupus erythematosus (hence the former name „lupoid hepatitis"), celiac disease, vasculitis, autoimmune thyroiditis, etc. Overlaps with primary biliary cholangitis and primary sclerosing cholangitis has been observed [39-40].

Patients may be asymptomatic, or may produce the symptoms of chronic cryptogenic (latens) hepatitis (fatigue, right upper abdominal pain, anorexia, nausea, jaundice, joint pain, rash) or may present with acute liver failure.

Hypergammaglobulinemia with increased immunoglobulin G level is an obligatory laboratory finding in **AIH**; the elevated serum aminotransferase levels, in the presence or absence of specific circulating autoantibodies (antinuclear, antineutrophil and antismooth muscle antibody) are characteristic as well [40].

The histology of **AIH** is identical with chronic active or passive hepatitis, characterized by interface inflammatory infiltrates of neutrophils, CD4 positive T-cell, plasma cells, eosinophils, apoptotic or necrotic liver cells, rosettes of regenerating hepatocytes, and fibrosis, with or without cirrhosis [41].

Regarding of our autopsy population the histology of chronic active or passive hepatitis may correspond to **AIH**, but the **onset** or **duration of RA** did not influence the presence of chronic active or passive hepatitis, even when **RA** started later in patient cohorts with **ChrAH**, than in patients without **ChrAH**.

Gammaglobulin levels and gamma GT values were elevated, like in any of liver diseases. Specific circulating autoantibodies (antinuclear, antineutrophil and antismooth muscle antibodies were not determined; our patients died between 1969-1992.

The risk of **ChrAH** increased in the late stage of **RA** (Tables 1 and 2), which is improbable in **AIH**; an **RA** related **AIH** could be manifest itself in an earlier stage of the basic disease.

Demographics of our patient cohort do not suggest a special liver disease in our autopsy population with **RA**.

Aside the gender there was no significant difference in mean age of the patients at death with or without complications of **RA** except acute bacterial septic infection, and amyloid A deposition in the liver. The patients died earlier **with AbSI** than the patients **without AbSI** (61.78 y vs 66.53, **p <0.043**), and **with hAAa** than **without hAAa** (61.31 y vs 71.67, **p <0.040**).

AbSI complicated by **AbSH** increased the risk of early death; duration of **RA** was significantly lower in patients with **AbSH** than without it (8.00 y vs 16.15, **p <0.029**).

Apart from these differences there was no significant difference in **onset** or **duration** of **RA** between patient cohorts **with** or **without RA related complication** or **associated diseases of the liver**. **RA** related complications or associated diseases of the liver existed in the patients of all ages independently of onset or duration of **RA**; **onset** or **duration** of **RA** *do not influence the prevalence of* **RA** related complications or associated diseases of the liver (Tables 1 and 2).

Our results suggest that the **RA** related systemic complications and associated diseases of the liver are independent entities.

Given the total number of involved patients the negative colligation's coefficient showed an inverse relationship between **RA** related systemic complications and associated diseases of the liver (c^***=-**0.7640, χ^2=20.6357, p <**0.000006**).

The negative colligation's coefficient showed also an inverse relationship between hepatic manifestation of **RA** related complications and associated diseases of the liver (c*=--0.7087, χ^2=20.9146, p <**0.000005**).

The **RA** related systemic complications or their manifestation in the liver separately did not influence the prevalence of associated diseases of the liver, and vice versa; the links were not significant, even in some cases they were inverse with negative colligation's coefficients. The link between rheumatoid vasculitis and eosinophilic hepatitis is an exception; the positive and significant correlation between **sRhV** and **EoH** propounds a possible relation between these entities (Tables 3.1 – 3.3).

From a prognostic point of view, the **RA** related complications (with or without their manifestation in the liver) led to death in 60 (37.27%) of 161 patients (**sRhV** in 19, **sAAa** in 17, and **AbSI** in 24 cases). They should be considered the most serious life-threatening systemic complications of **RA**, and the diagnosis of these is a great challenge for the rheumatologist especially in early (latent) stages of **sRhV**, **sAAa** or **AbSI** [1].

In contrast of **RA** related complications, the associated diseases of the liver did not prove to be serious life-threatening diseases in **RA** patients; only acute or subacute liver necrosis (**aLN** or **saLN**) led directly to death in two patients (one of them died of hepatorenal insufficiency, the other one died in postnecrotic cirrhosis complicated by massive internal bleeding). Viral etiology was exluded, and **aLN** or **saLN** was regarded as a result of aggressive therapy.

The remainder of patients died of other causes, including patients with more or less pronounced cirrhotic transformations, e.g.: circulatory failure, cardiorespiratory insufficiency, bronchopneumonia, emboli etc.

Conclusions

A distinct liver disease specific for **RA** was not found in our autopsy population.

RA related systemic complications and associated diseases of the liver are independent entities.

We found that the patients' life expectancy is declining with acute bacterial septic infection or hepatitis (**AbSI** or **AbSH**), and with amyloid A deposition in the liver (**hAAa**), and these patients die earlier.

The risk of **ChrAH** (with or without **CT**) increases in the late stage of **RA**.

Apart from these exceptions **RA** related complications or associated diseases of the liver may develop in both sexes, and at any time in the course of **RA**; **onset** or **duration** of **RA** do not influence the prevalence of **RA** related complications or associated diseases of the liver

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