Overlap Syndromes

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Definition of Overlap Syndromes (OLS)

There is no unequivocal definition of an OLS

The OLS can be defined as: coexistence of two autoimmune liver diseases in one patient

a) simultaneously

b) successively
Autoimmune Liver Diseases

- **Classic form of AIH**
  Peculiar features of classic AIH (acute, insidious, fluctuating, relapsing etc.)

- **Variant forms of AIH**
  - AIH + AMA
  - AIH + cholestasis
  - AIH + ulcerative colitis
  - AIH + bile duct injury
  - AIH without ANA, SMA, LKM
  - AIH resistant to immunosuppressants

- **Classic form of PBC**
  Peculiar features of classic PBC (missing histol. features, piecemeal necros. etc)

- **Variant forms of PBC**
  - PBC – AMA negative
  - PBC without biochemical cholestasis

- **Classic and variant forms of PSC** (diff.antibody spectr., small duct PSC)

- **PBC/AIH-OLS**
- **PSC/AIH-OLS**
- **PBC/PSC-OLS**

3 diseases (AIH, PBC, PSC):
18 peculiar/variant forms

*What does overlap syndrome mean?*
Atypical Manifestations of Autoimmune Hepatitis

**Overlap Syndromes** (two diseases in one liver)

- AIH/PBC
- AIH/PSC
- AIH/PBC = AIC
- AIH/HepC, B ?

**Outlier Syndromes** (cannot be classified)

- AIC (AMA negative PBC ?)
- Cryptogenic chronic hepatitis

**Changing diagnosis** (switch over time)

- PBC → AIH
- AIH → PSC
Prevalence of Serological and Morphological Features Common to Chronic Liver Diseases

- Hepatic Liver Disease
  - Chronic Hepatitis C: 10%
  - Autoimmune hepatitis: 13%
- Cholestatic Liver Disease
  - Primary Biliary Cirrhosis (PBC): 8%
  - Primary Sclerosing Cholangitis (PSC): 6%
  - Autoimmune Cholangitis (AIC): 10%

PBC: primary biliary cirrhosis
PSC: primary sclerosing cholangitis
AIC: autoimmune cholangitis

Tools for diagnosing an Overlap Syndrome

- Etiology ?
- Immunogenetics ?
- Biochemical/serological characteristics ?
- Liver histology ?
- Response to treatment ?
Pathogenes, Toxins, HLA-Type

Etiology of OLS's

PBC - AIH/PBC-,

PSC - AIH/PSC-

OLS

AIH

AIH/PBC-, AIH/PSC - OLS
# Genetics of Autoimmune Liver Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA-association</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH type 1</td>
<td>DR3</td>
<td>early onset, severe disease</td>
</tr>
<tr>
<td></td>
<td>DR4</td>
<td>older-onset, extrahep.manifestations, good response to therapy, protective in children?</td>
</tr>
<tr>
<td>DR2</td>
<td></td>
<td>alleles in Japan</td>
</tr>
<tr>
<td>DR4</td>
<td></td>
<td>see above</td>
</tr>
<tr>
<td>AIH type 2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PSC/IBD</td>
<td></td>
<td>stage III, IV 24%, stage I, II 5%, marginally significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>has to be confirmed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>strong with B8-DR3, neg. with DR4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>little genetic overlap between genes</td>
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</tbody>
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Immunogenetical Characterization of the Overlap Syndrome AIH/PBC

- A genetic susceptibility influences the disease course
- When AIH characteristics HLA B8-, DR3 or DR4 present, OLS develops a more hepatitic picture
- Spillover of the autoimmune bile duct inflammation to the lobules
- Therapy consequences?

Overlap Syndrome - AIH/PBC

- Histology: criteria of PBC+AIH
- Serology: AMA-M₂ (PDC-E₂)

**Definition:**

- **AIH:** ALT 4-times, IgG 2-times, SMA, histology
- **PBC:** AP 2-times, or GGT 5-times, AMA, histology

- IgG rather low, IgM higher concentrations
- ANA, SMA lower titers than in AIH

- **HLA:** DR3, DR4

### Primary Biliary Cirrhosis/Autoimmune Hepatitis Overlap Syndromes

<table>
<thead>
<tr>
<th>Variant I (AIH/PBC)</th>
<th>Variant II (AIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology:</strong> PBC+AIH</td>
<td><strong>Histology:</strong> PBC (not AIH)</td>
</tr>
<tr>
<td><strong>Serology:</strong> AMA-M₂</td>
<td><strong>Serology:</strong> AMA negative</td>
</tr>
<tr>
<td><strong>HLA:</strong> DR3, DR4; (DR8 neg.)</td>
<td><strong>HLA:</strong> DR3, DR4; (DR8 neg.)</td>
</tr>
<tr>
<td>(= OLS)</td>
<td>(= OLS or AMA-neg.PBC ?)</td>
</tr>
</tbody>
</table>

- IgG rather low, IgM higher conc.
- ANA, ASMA < AIH

- IgG rather low, IgM higher conc.
- ANA, ASMA > than in PBC

Definition of Autoimmune Cholangitis (AIC)

AIC is a variant of PBC

- No histological differences
- PDC-E2 expression on bile duct cells
- Carboanhydrase II-AB (not always) present
- Course of the disease identical with that of PBC
- Positive response to UDCA therapy

Kim WR et al. Hepatology 1997;26:22-26
Definition of Autoimmune Cholangitis (AIC)

**AIC is a distinct liver disease**

- AST and IgM lower than in AMA-positive PBC
- Carboanhydrase II-AB present
- ANA, SMA > 1:160
- AB against glycogen-phosphorylase
- AB against nuclear envelop
- PBC-spec. AB against 2-oxoglutar.-dehydrogenase complex (and PDC-E2) absent,
- Lymphocytes of the liver express Vβ.1 TCR
- HLA risk factors different from PBC (DR3,4; but DR8 absent)

Overlap Syndrome – AIH/PSC

- ERC, MRC picture like in PSC
- Histology: mostly PSC (sometimes AIH)
- Association with IBD less frequent (30 – 60%) than in PSC
- High concentrations of IgG (AP, GGT)
- SMA, ANA, p-ANCA
- AP in children in 50% normal

AIH/PSC Overlap Syndrome

Age 39 yrs., male  AP 866 U/l, GGT 238 U/l
ANA 1:160, IgG increased, AMA neg.
Ulcerative colitis since 6 yrs
Histology: PSC+AIH
Hepatitis C/B – Autoimmune Hepatitis Overlap Syndrome

**Does it exist?**

In patients with chronic HCV infection

- ANA: 9 – 38%
- p-ANCA: 10%
- ASMA: 5 – 91%
- AAA: 8%
- HMG1,2 AB: 11%
- LKM1,3: 0 -10% (different epitopes from AIH)

Hypergammaglobulinemia

- Moderate/severe interface hepatitis, lob.infiltrates, granulom.

In patients with Autoimmune hepatitis

- HCV-AB: 44 – 77% (EIA)
- : 12 – 35% (RIBA)
- HCV RNA: 19%

Histol.characteristics of HCV-hepatitis

**But:** No female preponderance, weak assoc. with DR3, DR4

Treatment of the AIH/PBC-Overlap Syndrome

130 consecutive pts with PBC

Definition of OLS: AP > 2N or GGT > 5N, SMA, AMA positive, ALT > 5N, IgG> 2N or ASMA Bile duct lesions, piecemeal necrosis

OLS: n = 12 (9.2%)

UDCA n = 5: incomplete response

Cortic. n = 6: incomplete response

UDCA + corticoids was superior to UDCA- or cortic.- monotherapy

Treatment Outcome in Patients with **AIH/PSC Overlap Syndrome** – Treatment with **Glucocorticoids**

225 patients with AIH investigated

**Overlap**
- AIH/PBC : 5%
- AIH/PSC : 6%
- AIH/AIC : 5%

**Poor treatment outcome**
- AIH/PSC : 78%
- the others : 17%

**Death or LTX**
- AIH/PSC : 33%
- vs. AIH : 8% (p=0.05)

Treatment of Overlap-Syndromes

**AIC (AMA neg. PBC)**
UDCA **13 – 15 mg/kg/d**

**AIH/PBC:**
UDCA, glucocorticoids (when ALT ≥ 5-10-fold)

**AIH/PSC:**
UDCA **15-25 mg/kg/d**, (+ glucocorticoids ?)

**AIH/HepC**:
AIH > HepC (ANA > 1 : 320): glucocorticoids
HepC > AIH (ANA < 1 : 320): IFN + Riba

Changing Diagnosis and Overlap Syndrome in Chronic Autoimmune Liver Diseases

Three diseases

18 peculiar/variant forms

*and changing diagnosis!*

What does „true“ overlap syndrome mean?
Summary and Conclusions

Overlap Syndromes

Old concepts

Rediscovered

Difficult to define and to diagnose

But require new therapy concepts

Increase the insight into autoimmune liver disease