Clinical case: primary sclerosing cholangitis

Prof. N.B. Gubergrits (Donetsk, Ukraine)
Every evil, which could be foreseen, is so hard to prevent.

Pierre Boiste, French philologist
**PSC** pathogenesis

- **Autoimmune disease**
- **Inflammatory reaction on infectious agents**
- **Cholangiopathy**
- **Genetically determined disease**

**Pro**

- 100 fold increase of risk in first degree relatives
- Association with MHC- and non-MHC-alleles

**Contra**

- Association with HLA haplotypes is weak and optional
- Results of studies are contradictory

T.J. Weismüller et al., 2008
PSC – genetically conditioned

Monozygotic twins

PSC + NUC

DR B1*1301

Genetic basis of combination of diseases does not determined yet

3-6%

55-80%

S. Norris et al., 2001; P.T. Donaldson et al., 2002
Patient K., 25 years old (2001)

- Complaints on fever up to 40°C, jaundice, itching, weakness, loss of 12 kg in 6 months, myalgia, arthralgia
- At the age of 18 years he had been diagnosed to have NUC affecting sigmoid colon and rectum, mild activity
- A year ago – periods of elevated temperature up to 37.5°C, episodes of jaundice
- Anemia (RBC – 2.3 T/L, Hb – 68-39 g/L), leukocytosis (15-23 G/L), shift left (stab neutrophils – 18-27%), ESR – 42-65 mm/h
- Alkaline phosphatase – up to 12 norms, γ-GT – up to 8 norms, ALT – 2.0-2.5 norms, total bilirubin – 52-64 mcmol/L
- p-ANCA – determined
- ERCP was not conducted due to severe state of the patient
Patient K., 25 years old (2001)
Liver biopsy
Patient K., 25 years old (2001)
Liver biopsy
Patient K., 25 years old (2001)

Diagnosis

Primary sclerosing cholangitis complicated with bacterial cholangitis. Secondary biliary cirrhosis of the liver, stage A by Child-Pugh with significant morphological activity.

Severe anemia of mixed etiology (iron-deficiency and hemolytic).

NUC with involvement of sigmoid colon and rectum, mild course, remission. Severe malassimilation syndrome.
Patient K., 25 years old (2001)

Treatment

- Ursofalk – 750 mg/day
- Salofalk – 1 suppository/night
- Creon – 100000 U F.I.P. daily
- Gentamycin – 240 mg/day
- Aminoglycosides (in case of resistant flora)
- Ureidopenicillins
- Metronidazole (in case of anaerobic bacteria)

Iron containing drugs, transfusion of red blood cells

Analgesics

The main treatment purpose – to eliminate bacterial cholangitis

<table>
<thead>
<tr>
<th>Prof. U. Leuschner recommendations</th>
<th>Applied treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalosporins of III-IV generation, β-lactams</td>
<td>Zinacef 1,5 g/day. Ceftriaxon 1,5 g/day.</td>
</tr>
<tr>
<td>Ureidopenicillins</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides (in case of resistant flora)</td>
<td>Gentamycin – 240 mg/day</td>
</tr>
<tr>
<td>Metronidazole (in case of anaerobic bacteria)</td>
<td>Metragil – 1,5 g/day.</td>
</tr>
</tbody>
</table>
Pancreatic insufficiency in PSC

Hepathogenic

Deficiency of biliary acids into intestinal lumen
(J.E. Dominguez-Munoz, 2005)

Primary

30% of patients with PSC have changes of pancreatic ducts on ERCP
(U. Leuschner, 2001)

NUC patients have pancreas changes on autopsy in 53% of the cases, reduction of fecal elastase – 30-50%
(M. Barthet et al, 2006)

Osteoporosis, steatorrhea - 25-35%
(U. Leuschner, 2001)
Patient K., 25 years old (2001)

SEPSIS

Fatal outcome
**Patient B., 25 years old (2001)**  
*Monozygotic twin-brother of patient K.*

- Complaints on frequent stool up to 3-4 per day, mucus and sometimes blood streaks in stool
- There’s no cholestatic complaints
- Diagnosis of NUC was made earlier than in brother (in 15 years old), disease was more severe – exacerbations 2-3 times a year, bleedings were more frequent and heavy
- Alkaline phosphatase – 7 norms, γ-GT – 6 norms, ALT – 1,7 norms, bilirubin – norms
- Fecal elastase-1 – 158 mcg/g
- p-ANCA – determined
- DR B1*1301
RRS: apparatus introduced on 25 cm. Mucosa is significantly hyperemic and edematous along the whole length. Multiple erosions, mucus on the intestinal wall.
Patient B., 25 years old (2001)

**RRS**: apparatus introduced on 25 cm. Mucosa is significantly hyperemic and edematous along the whole length. Vascular pattern is smoothed or absent. Increased contents of mucus into intestinal lumen. There are no ulcers and erosion.

**Вывод**: NUC, mild activity.
Patient B., 25 years old (2001)

Biopsy of mucosa of rectosigmoid transition
Patient B., 25 years old (2001)

Punch biopsy of the liver
Patient B., 25 years old (2001)

Punch biopsy of the liver
Patient B., 25 years old (2001)
Punch biopsy of the liver
Patient B., 25 years old (2001)

ERCP
Sclerosing cholangiopancreatitis

Primary sclerosing cholangitis

- Association with NUC
- Pancreas is not enlarged
- Glucocorticoids are ineffective

Sclerosing cholangitis in autoimmune pancreatitis

- Association with NUC is rare
- Pseudotumorous pancreatitis
- Glucocorticoids are of high efficacy

H. Ohara et al., 2007
Patient B., 25 years old (2001)

**Diagnosis**

Primary sclerosing cholangitis.
NUC involving left side of the large intestine, moderate activity, exacerbation stage.
Chronic pancreatitis with mild excretory insufficiency of the pancreas.
Ursodeoxycholic acid in PSC

- 4 placebo controlled studies – significant decrease of activity of alkaline phosphatase, γ-GT and transaminases, reduction of itching and general weakness
  - in 3 studies – decrease of bilirubin blood level
  - in 3 studies – reduction of inflammatory infiltrates in periportal tracts on the background of the same degree of biliary ducts changes
- Optimal UDCA dose in PSC – 15-20 mg/kg
- Dose <10 mg/kg is ineffective
- Treatment should be permanent (lifelong)
- Interruption in treatment leads to relapses
UDCA dosage in PSC

- 86 bile samples obtained from 56 patients with PSC were studied.
- UDCA dosage – 10-32 mg/kg.
- Saturation of bile with UDCA increased depending upon dose elevation, but in dose 22-25 mg/kg there's forming plateau of concentration, i.e. further increase of the dose is inexpedient.
- So dose 22-25 mg/kg is optimal for PSC, as maximally possible bile concentration of UDCA is followed with maximally possible treatment effect.

D. Rost et al., 2004
UDCA high doses in PSC
Ludwig scale takes into account histological changes of the liver (activity of inflammation and level of fibrosis)

- Duration of the treatment – 2 years
- All UDCA doses were tolerated satisfactorily
- Improvement of biochemical indices – in case of all 3 doses

S.N. Cullen et al., 2006
**UDCA high doses in PSC**

- Mayo Risk Score includes age, prothrombin time, bilirubin and albumin blood levels, presence of edema and ascites.
- Study lasted 2 years
- UDCA dosage – 25-30 mg/kg/day

![Bar chart showing stages of PSC at the beginning and after 2 years](chart.png)
**PSC — precancerous pathology**

- Incidence of cholangiocarcinoma in PSC — 6-20%, colorectal cancer — 9% (over 10 years) — 50% (over 25 years)

U. Leuschner et al., 2001; C. Schramm et al., 2005

- Risk of cholangiocarcinoma in PSC is increased in 161 times, risk of colorectal cancer — in 10 times, risk of pancreatic cancer — in 14 times

- Incidence of cholangiocarcinoma in PSC — 6-20%, colorectal cancer — 9% (over 10 years) — 50% (over 25 years)

U. Leuschner et al., 2001; C. Schramm et al., 2005
UDCA – prophylaxis of cancer

✓ Combination of UDCA and endoscopic dilatation lets to decrease incidence of cholangiocarcinoma to 2.8% (A. Stiehl et al., 2002)

✓ Absence of UDCA therapy – an independent predictor of cholangiocarcinoma development, while application of UDCA significantly decreases its risk (B. Brandsaeter et al., 2004)

✓ Long therapy with UDCA (more than 6 years) decreases risk of cholangiocarcinoma depends upon duration of the treatment (G. Rudolph et al., 2007)

✓ Application of UDCA in dose 8-10 mg/kg during 3 years reduces frequency of relapses of large intestine adenomas for 12% and frequency of determination of high grade dysplasia – for 39% (D.S. Alberts et al., 2005)
Survival rate of patients with PSC

A. Stiehl. et al., 1997

Duration of observation (months)

Patients' survival rate (%)

UDCA in combination with endoscopic dilatation

Patients w/o treatment

n=61 55 41 33 24 20 14

Duration of observation (months)
Budesonide in PSC

- Only pilot studies were conducted.
- 21 patients with PSC were examined – budesonide 9 mg/day during a year.
  - Significant decrease of alkaline phosphatase and AST activity was reached.
  - There was no significant change in bilirubin level.
  - Budesonide effect remains even over 3 months after drug withdrawal.
- Systemic corticosteroids are undesirable due to osteoporosis aggravation.

P. Angulo et al., 2000; U. Leuschner et al., 2001
Patient B., 25 years old

Treatment (2001-2009)

- Ursofalk – 25 mg/kg/day constantly
- Salofalk – 1 g/day constantly
- Budenofalk – 6 mg/day constantly
- Creon – 100000 U F.I.P. per day constantly

Results (2009)

- No jaundice and itching
- There were no severe exacerbations of NUC (periods of frequent stools without blood in feces 1-2 times a year)
- Alkaline phosphatase – 1,5-3 norms, γ-GT – 2,5-3 norms, ALT – up to 1,5 norms, bilirubin – normal
- Mild reduction of fecal elastase-1 remains
Patient B., 25 years old
Punch biopsy of the liver (2005)
Patient B., 25 years old

Punch biopsy of the liver (2005)
Every evil, which could be foreseen, is so hard to prevent.

Pierre Boiste, French philologist

...but nevertheless we tried!