Should liver biopsy be systematic during surgery for ulcerative colitis?

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SUMMARY

Aim — The aim of this study was to evaluate the prevalence of primary sclerosing cholangitis and other histological liver abnormalities in patients operated on for ulcerative colitis and to discuss the advantages of performing a systematic liver biopsy during surgery.

Methods — From 1996 to 2001, 21 consecutive patients underwent a restorative proctocolectomy or a reoperation after proctocolectomy for ulcerative colitis. These patients systematically underwent liver biopsy during the procedure.

Results — One patient presented with primary sclerosing cholangitis (4.7%). This patient was clinically and biologically asymptomatic. Four patients had steatosis, 8 had non-specific inflammation such as non-alcoholic steatohepatitis in patients taking long-term corticosteroid therapy or on parenteral nutrition, granulomatous hepatitis, or hepatic amylosis [2]. More exceptionally, it may be associated with other disease such as thyroiditis, sarcoidosis, or inflammatory rheumatic disease.

Conclusion — Peroperative liver biopsy identify primary sclerosing cholangitis or other liver diseases in an early diagnosis and help evaluate their stage in order to start appropriate treatment.

Sclerosing cholangitis is a chronic inflammation with fibrosis of the intra- and extra-hepatic biliary ducts. The course of the disease is slow and unpredictable, the most serious complication being malignant degeneration to cholangiocarcinoma which is difficult to detect at an early stage. Histological diagnosis of primary sclerosing cholangitis is a difficult task because lesions predominate in the segmentary and septal bile ducts. Non-specific lesions may appear in the interlobar and portal ducts. Furthermore, lesions can be focal and scattered and missed on liver biopsy [1]. Sclerosis cholangitis is often associated with inflammatory bowel disease and ulcerative colitis is the commonest association, found in up to 75% of cases.
peroperative liver biopsy. The purpose of this study was to
determine the clinical pertinence of this systematic liver biopsy.

Patients and methods

Between 1996 and 2001, 21 consecutive patients (10 women and
11 men), aged 16 – 70 years (mean 43) at the time of liver biopsy, with
histologically proven ulcerative colitis, and scheduled for colorectal
resection were included in this prospective study.

A data sheet was established for each patient to record medical
history and severity of the bowel disease (Trueelove criteria) at admission
to surgery. Standard liver tests were obtained for all patients; comple-
mentary information (daily alcohol intake, viral serology, iron status,
metabolic status, auto-antibodies titers) was ordered if the standard tests
were abnormal. Body mass index (BMI) and duration of corticosteroid
therapy or parenteral nutrition were also recorded when appropriate.

A cold-scalpel deep subcapsular macrobiopsy was taken at the
anterior border of liver segments III or IV followed by suture or
electrocoagulation. The liver biopsy was performed at the onset of the
surgical procedure to enable peroperative surveillance of adequate
coagulation. Standard stains were used for histological analysis.

Results

Patient characteristics (table I)

Mean duration of ulcerative colitis was 11.5 years. Four
patients (19%) (patients n° 1, 2, 3, 4), with steroid-dependent
disease and major steroid-related side effects, underwent surgery
for an acute exacerbation. Two patients underwent surgery for
proven or suspected cancer (degenerated cecal polyp, patient n°
5; suspected degeneration of numerous adenomatous polyps,
patient n° 6). The indication for surgery in the other 15 patients
(71.5%) was an acute exacerbation of steroid-resistant disease.
Fourteen of these 15 patients (93.3%) had steroid-resistant
pencolitis (steroid dose 1 mg/kg/d). According to the Trueelove
and Witts criteria, these patients had moderate to severe
exacerbations (5 patients had 4 to 5 criteria). Eleven underwent
surgery after failure of intravenous cyclosporin. Cyclosporin was
not attempted in two patients (n°10 and 11) with poor clinical
status. In one patient with steroid-resistant disease, surgery was
indicated because of three zones of inflammatory stenosis and
microrectitis with very low rectal compliance at manometry
(patient n° 20). Finally, the last of these 15 patients had been
referred to our unit several years after a colectomy performed in
an other institution for an acute exacerbation of steroid-resistant
disease (patient n° 21). Consequently, 18 of the 21 patients
(86%) had been taking steroids for a mean duration of 43 months
(range : 3 weeks to 30 years) at the time of liver biopsy. Seven of
the 21 patients (33%) were on parenteral nutrition (mean
duration 22 days) at the time of surgery ; one of these 7 was also
given enteral nutrition for 15 days. Finally, 12 of the 21 patients
(57%) had a normal body mass index (18-25) at the time of liver
biopsy, 2 were overweight (BMI 25-30), 1 was obese (BMI >30),
and 6 were in a state of malnutrition (BMI <18). None of the patients had clinical signs of advanced-stage liver
disease.

Preoperative liver tests were normal in 18 of the 21 patients
(86%). Elevated serum gamma-glutamyl transferase (10X nor-
mal) and serum aminotransferase (2X normal) was related to
excessive alcohol intake in patient n° 3. In patient n° 13,

<table>
<thead>
<tr>
<th>n</th>
<th>Gender</th>
<th>Age</th>
<th>Indication for surgery</th>
<th>Duration of corticosteroid therapy</th>
<th>Cyclosporin</th>
<th>Liver tests</th>
<th>Truelove</th>
<th>Duration of inflammatory colitis</th>
<th>Parenteral nutrition</th>
<th>Body mass index</th>
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<td>15 yr</td>
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<td>5/5</td>
<td>5 yr</td>
<td>18 days + enteral</td>
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<td>6 yr</td>
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<td>2 m</td>
<td>no</td>
<td>&lt; 18</td>
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<td>35</td>
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<td>Perturbed</td>
<td>5/5</td>
<td>2 yr</td>
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<td>&lt; 18</td>
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<td>Perturbed</td>
<td>4/5</td>
<td>8 yr</td>
<td>2 weeks</td>
<td>&gt; 25</td>
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<td>yes (resistance)</td>
<td>Normal</td>
<td>3/5</td>
<td>7 yr</td>
<td>no</td>
<td>Normal</td>
</tr>
<tr>
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<td>3/5</td>
<td>14 yr</td>
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<td>Normal</td>
</tr>
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<td>Normal</td>
<td>4/5</td>
<td>6 yr</td>
<td>3 weeks</td>
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<td>3/5</td>
<td>4 yr</td>
<td>2 weeks</td>
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<tr>
<td>19</td>
<td>F</td>
<td>18</td>
<td>Steroid resistance</td>
<td>6 m</td>
<td>yes (resistance)</td>
<td>Normal</td>
<td>4/5</td>
<td>6 m</td>
<td>1 m</td>
<td>&lt; 18</td>
</tr>
<tr>
<td>20</td>
<td>M</td>
<td>70</td>
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<td>3 yr 4 m</td>
<td>no</td>
<td>Normal</td>
<td>2/5</td>
<td>35 yr</td>
<td>no</td>
<td>Normal</td>
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<td>21</td>
<td>M</td>
<td>25</td>
<td>Steroid resistance (a)</td>
<td>14 m</td>
<td>no</td>
<td>Normal</td>
<td>4/5</td>
<td>7 yr</td>
<td>no</td>
<td>Normal</td>
</tr>
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</table>
moderate (2X normal) and transient elevation of serum amino-
transferases was attributed to parenteral nutrition as the search
for another cause was negative. Parenteral nutrition was also
considered to be the cause of elevated serum ALAT (2X normal),
gamma glutamyl transaminase (3.5X normal) and phosphatase
alkaline (1.4X normal) in patient n°14.

Technique and early and late post-operative
morbidity

Eighteen of the 21 patients (86%) were referred for total
coloprotecmy with J-pouch ileoanal anastomosis. Two of the
21 patients underwent secondary proctectomy after colectomy
performed in another institution. The last patient underwent two
procedures to fashion a new J pouch after developing a pelvic
abscess on a complex fistula.

The mean hospital stay after surgery was 17 days. There
were no operative deaths. Thirteen patients developed early
complications. The rate of medical and surgical morbidity was
38%. None of the complications could be attributed to the liver
biopsy.

Pathology examination of the liver biopsies (Table II)

Eight of the liver biopsies (38%) were considered normal. Four exhibited steatosis (19%): 2 discrete and 2 more pro-
nounced (figure 1). Eight biopsies (38%) exhibited either non-
specific inflammatory lesions such as discrete chronic portitis,
small duct cholangitis (figures 2 and 3), or lymphoplasmocyte
infiltrate in the portal spaces. All of these lesions were moderate
and were attributed to parenteral nutrition, surgery, corticoste-
roid treatment, or the underlying disease. One biopsy showed
early signs of sclerosing cholangitis (figures 4, 5, 6) with
extensive septal fibrosis, altered portal spaces exhibiting dense
perivascular concentric fibrosis, neovascularization, and fibro-
hyaline thickening of the arteries with a polymorphous leukocyte
infiltration crossing at the interface in focal areas and involution
of the ductal structure which was replaced by fibrous laminar
cylinders. This sclerosing cholangitis was diagnosed in a
47-year-old woman who had ulcerative colitis for 16 years
before become steroid-dependent. Coloprotecmy was perfor-
moved after the discovery of a degenerated polyp of the cecum at a
regular follow-up coloscopy. The preoperative liver tests were
normal in this patient.

Discussion

This homogeneous series of consecutive patients allows a
prospective analysis of the liver pathology findings associated
with severe ulcerative colitis.

Liver tests are frequently abnormal in patients with ulcerative
colitis (8-50%), especially in case of extensive intestinal involve-
ment [4]. Non-specific histological anomalies are also observed
in 50% of the patients but not necessarily in association with
abnormal liver tests. Portal inflammation or steatosis are the most
common features [5]. Special attention must be given to the small
bile ducts which often present histological anomalies in ulcerative
colitis. The histological pattern is the same as observed in
sclerosing cholangitis but, when performed, retrograde cholan-
giography or biliary MRI are normal [1]. For some authors [6],
the small duct lesions would be a different expression of
sclerosing cholangitis.

We identified one patient with sclerosing cholangitis among
our 21 patients with ulcerative colitis (4.7%). Sclerosing cho-
langitis is asymptomatic at diagnosis in about 50% of the cases [7].
In a Swedish series reported by Broome et al. [8], 44% of the

<table>
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<tbody>
<tr>
<td>1</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Mixed steatosis – 50%</td>
</tr>
<tr>
<td>3</td>
<td>Mixed steatosis – 50%</td>
</tr>
<tr>
<td>4</td>
<td>Discrete chronic portitis without cholangitis, rare intralobar microgranulomas</td>
</tr>
<tr>
<td>5</td>
<td>Grade 3 sclerosing cholangitis, extensive septal fibrosis, neovascularization and fibrohyaline thickening of the arteries, rare foco of neudactal proliferation with cholangiolitis</td>
</tr>
<tr>
<td>6</td>
<td>Normal</td>
</tr>
<tr>
<td>7</td>
<td>Normal</td>
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<tr>
<td>8</td>
<td>Normal</td>
</tr>
<tr>
<td>9</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>Macrocyte steatosis – 5% - mild to moderate polymorphonuclear neutrophil infiltration, cholangitis in certain portal spaces, hyperplasia of the Kupffer cells</td>
</tr>
<tr>
<td>11</td>
<td>Non-specific chronic portitis, one focus of focal nodular hyperplasia</td>
</tr>
<tr>
<td>12</td>
<td>Perisinusoidal fibrosis, sinusoidal ectasia, fibrosis of the suprahepatic veins, rare non-specific chronic portitis, lipofuchsin overload of the hepatocytes</td>
</tr>
<tr>
<td>13</td>
<td>Mixed steatosis, 30 – 50%</td>
</tr>
<tr>
<td>14</td>
<td>Microcyte steatosis, 10%, polymorphonuclear neutrophil infiltration of certain portal spaces, small duct cholangitis, hyperplasia of the Kupffer cells</td>
</tr>
<tr>
<td>15</td>
<td>Polymorphonuclear neutrophil infiltration in certain portal spaces without cholangitis but with moderate periportal partial necrosis, a few intralobar granulomas</td>
</tr>
<tr>
<td>16</td>
<td>Discrete non-specific chronic portitis, mixed steatosis &lt; 20%</td>
</tr>
<tr>
<td>17</td>
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<td>18</td>
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<tr>
<td>19</td>
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<tr>
<td>20</td>
<td>Macrocyte steatosis &lt; 20%, moderate chronic portitis in certain portal spaces without cholangitis, a few intralobar granulomas</td>
</tr>
<tr>
<td>21</td>
<td>Mild to moderate polymorphonuclear neutrophil infiltration of the portal spaces with discrete small duct cholangitis, hyperplasia of the Kupffer cells</td>
</tr>
</tbody>
</table>
Fig. 1 50% Steatosis (HES × 250).
Fig. 2 Small bile duct cholangitis (HES × 250).
Fig. 3 Small bile duct cholangitis (HES × 250).
Fig. 4 Sclerosing cholangitis (HES × 100).
Fig. 5 Sclerosing cholangitis (HES × 250).
Fig. 6 Sclerosing cholangitis (trichroma × 25).
305 patients with sclerosing cholangitis had no clinical signs at diagnosis and 22% of the initially asymptomatic patients became symptomatic after a median follow-up of 69 months. The diagnosis of sclerosing cholangitis can be retained when 2 of the 4 following criteria, including at least one radiological or histological criterion (cholestasis), radiological criterion (anomaly of the intra and/or extrahepatic bile ducts), histological criterion (fibrous or obstructive cholangitis), and association with another disease, particularly inflammatory bowel disease involving the colon.

To our knowledge, no other team has attempted to determine the prevalence of sclerosing cholangitis, particularly liver involvement, on the basis of systematic peroperative liver biopsy in a population of operated ulcerative colitis patients.

A Danish group [4] assessed the prevalence of sclerosing cholangitis from 1976 to 1987 among a population of 305 patients with ulcerative colitis. This population presented elevated serum alkaline phosphatase levels and diagnosis was based on the results of retrograde cholangiography or percutaneous needle biopsy. The prevalence of sclerosing cholangitis was 3.6% (11/305), which correlates well with other studies (1-4%) [9, 10], as well as with our own findings. It should be noted however that this Danish population only included patients who underwent exploration because of abnormal liver tests (elevated alkaline phosphatase) while it is known that sclerosing cholangitis associated with ulcerative colitis may be observed in patients with normal alkaline phosphatase levels [5]. The 3.6% prevalence may thus be an underestimation.

Several studies tend to show that sclerosing cholangitis is readily associated with minimally active ulcerative colitis when an extensive proportion of the bowel is involved [2, 4, 9, 11]. In our series, all patients had extensive ulcerative colitis, generally in a very active phase. This recruitment bias did not appear to influence prevalence.

In the study reported by Bergquist et al., which included 604 patients with sclerosing cholangitis followed for a mean 28 years, the incidence of cholangiocarcinoma was 1.5% [12], pointing out the importance of early detection. In another study of 1207 patients with ulcerated colitis followed between 1948 and 1982, the prevalence of cholangiocarcinoma was 0.5% [2].

Patients with ulcerative colitis and sclerosing cholangitis have a higher risk of colorectal cancer [12, 13]. In a retrospective study from Baltimore conducted between 1979 and 1991 in 33 patients with ulcerative colitis and sclerosing cholangitis, the incidence of colorectal cancer of dysplastic polyps was 37% [14]. This rate is similar to the highest incidence of cancer reported for patients with severe pancolitis without cholangitis. The one patient in our series with sclerosing cholangitis underwent surgery after the discovery of in situ carcinoma. The relative quiescence of ulcerative colitis in patients with sclerosing cholangitis leads to late diagnosis of the bowel disease, often established after several years. Regular colonoscopic surveillance, as is recommended for patients with severe pancolitis, is advisable. When the diagnosis of cholangitis is established, a regular colonoscopy surveillance program should be initiated early.

Liver transplantation is the only therapeutic option that can be proposed for patients with end-stage sclerosing cholangitis. Small duct cholangitis, a recently described entity, appears to have a better prognosis than sclerosis cholangitis. In a study conducted in Great Britain and Norway, 33 patients with small duct cholangitis and 260 patients with sclerosing cholangitis (only in the setting of ulcerative colitis in some cases) were followed; small duct cholangitis progressed to sclerosing cholangitis in 4 of these patients. None of the 33 patients with small duct cholangitis developed cholangiocarcinoma, compared with 11% of the patients with sclerosing cholangitis [15]. A recent study showed that high-dose ursodeoxycholic acid (20 mg/kg/d) can improve liver test results, slow down progression of biliary lesions, and inhibit progression towards fibrosis, both in sclerosing cholangitis and in small duct cholangitis.

Likewise, patients with marked hepatic steatosis should be followed closely due to the risk of fibrosis. Patients should be advised to lose weight with a well adapted diet and measures should be taken to correct fat and carbohydrate disorders. Any toxic medications should be discontinued or prescribed at a lower dose.

**Conclusion**

Peroperative liver biopsy can provide pertinent information for patients with severe ulcerative colitis undergoing surgery. The biopsy specimen is large enough for good quality pathology examination. Systematic peroperative liver biopsy would enable a study of the prevalence of sclerosing cholangitis and other liver diseases, for example small duct cholangitis or steatosis, in this population. It would also enable earlier diagnosis and staging necessary for optimal treatment.

**REFERENCES**


