ADVANCES IN CLASSIFICATION, PROGNOSTICATION AND TREATMENT OF IMMUNOCHOLANGITIS

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VOORUITGANG IN CLASSIFICATIE, PROGNOSTIEK EN BEHANDELING VAN IMMUUNCHOLANGITIS

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE ERASMUS UNIVERSITEIT ROTTERDAM OP GEZAG VAN DE

Rector magnificus

Prof. dr. ir. J. H. van Bemmel

EN VOLGENS BESLUIT VAN HET COLLEGE VOOR PROMOTIES

DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP

WOENSDAG 22 NOVEMBER 2000 OM 09:45 UUR

DOOR

FRANK PAUL VLEGGAAR

GEBOREN TE DORDRECHT

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Chapter 1

GENERAL INTRODUCTION

F.P. Vleggaar

Immunocholangitis is a collective for chronic inflammatory disorders affecting the biliary tree, presumably with an autoimmune-mediated pathogenesis. Destruction and distortion of bile ducts, leading to impaired bile flow, are key features of immunocholangitis. In general, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are considered to be the main diseases of immunocholangitis.

PBC, a chronic cholestatic liver disease, is one of the most common vanishing bile duct disorders (1). Gradual loss of interlobular and septal bile ducts, histologically described as chronic non-suppurative destructive cholangitis (2), leads to chronic cholestasis, fibrosis and biliary cirrhosis which may ultimately cause liver failure, necessitating transplantation (3). Since 1988, PBC has been the third leading indication for liver transplantation in Europe (European Liver Transplant Association (ELTA) registration).

Typical symptoms of patients with PBC are pruritus, fatigue, arthralgia and dryness of the eyes and mouth (3). A large proportion of patients, especially those with early stage PBC are however often asymptomatic. Physical examination may reveal jaundice, scratch marks, xanthelasma and xanthoma, in particular in the event of marked cholestasis.

PBC is a relatively rare disorder in comparison with chronic viral hepatitis and alcoholic liver disease. It affects primarily middle-aged (40-60 years) women (male:female ratio 1:9). In the 1970's, reported prevalences ranged from only 18 to 54 cases per one million inhabitants (4-6). Since then, substantially higher prevalence rates have been reported (6, 7). Recent studies in Wales (8) and the Newcastle area (9) revealed a prevalence of 200-250 PBC patients per one million inhabitants in 1994, suggesting a more than tenfold increase in less than 20 years! Whether these data reflect a true increase in the number of cases is uncertain. The development of more sophisticated epidemiological case finding methods, increased awareness of PBC as a possible cause of chronic liver disease and routine assessment of serum liver tests for medical examinations (i.e. for insurance) may all have contributed to the identification of more, in particular asymptomatic, cases. Moreover, the diagnosis of asymptomatic subjects might result in higher prevalence rates because of longer survival.

PSC is a cryptogenic chronic cholestatic liver disease characterised by progressive stricturing and obliteration of intrahepatic and/or extrahepatic bile ducts (10), leading to fibrosis and biliary cirrhosis which may cause hepatic decompensation. Since 1988, PSC has been the sixth leading indication for transplantation (ELTA registration). The signs and symptoms of PSC resemble those of PBC.

PSC is regarded as an even more rare disease than PBC, but reliable epidemiological data on prevalence and incidence are lacking. Data from Sweden suggest a prevalence of 60-80 patients per one million inhabitants (11). There is a strong association with inflammatory bowel disease (IBD). It has been found that approximately four percent of patients with IBD have concomitant PSC (12). Conversely, 50-70% of patients with PSC also have IBD (13, 14). PSC has a male predominance (male:female ratio 2:1). The median age at diagnosis is 35 years.

Classification of immunocholangitis

Primary biliary cirrhosis and its variants

The diagnosis of PBC is based on the presence of serum antimitochondrial antibodies (AMA), serum liver tests indicating cholestasis and a liver biopsy showing chronic non-suppurative destructive cholangitis (15). In a small minority of cases (5-10%), the last two criteria are present but serological testing for AMA is negative. These patients have so-called AMA-negative PBC (16). An elevated IgM level, quite common in PBC patients, further supports this diagnosis.

As a rule PBC and autoimmune hepatitis (AIH) are generally easily differentiated on the basis of clinical, biochemical, serological and histological findings. In a minority of cases, however, PBC and AIH may develop either simultaneously or consecutively (17, 18). Recognition of this variant of PBC, the PBC-AIH overlap syndrome, is not only important from the standpoint of classification, since it can have therapeutic implications: patients with this disorder may benefit from immunosuppressive therapy (19). PBC-AIH overlap was found in 9% of PBC patients in a study performed in France (19).

The histological patterns of PBC have been divided into four consecutive stages (2). PBC stage I stands for portal hepatitis with little or no interface hepatitis, stage II is periportal hepatitis with interface hepatitis and ductular proliferation, stage III is characterized by fibrous septa or bridging necrosis and stage IV is biliary cirrhosis. In general, jaundice is only encountered in the cirrhotic stage (20), probably as a consequence of both hepatocellular insufficiency and bile duct loss. Jaundice in non-cirrhotic PBC is rare. In contrast to what is observed in patients with the idiopathic adulthood ductopenia syndrome (21), it appears that the degree of intrahepatic bile duct loss is usually not severe enough to cause jaundice. In *chapter 2*, we report on a subgroup of PBC patients suffering from severe cholestatic, icteric disease for which no causative extrahepatic or intrahepatic factors other than profound ductopenia could be identified. These cases and a large group

of equally non-cirrhotic PBC patients were included in a histomorphological study to define the ductopenia-fibrosis relationship and to test the hypothesis that these patients exhibit extreme paucity of bile ducts in relation to the amount of fibrosis.

Sclerosing cholangitis and its variants

Endoscopic retrograde cholangiography (ERC) is a key step in the diagnostic evaluation of potential PSC patients and remains the "gold standard" for diagnosis (22). Typical findings are fibrosis and sclerosis of the biliary tree with localized or multifocal strictures and intermediate segments of normal, diverticulum-like outpouchings or ectatic ducts (23).

The vast majority of patients with PSC show extrahepatic or intrahepatic biliary abnormalities on cholangiography. In a small minority of patients with IBD and elevated cholestatic serum liver tests, cholangiography shows a normal biliary tree whereas liver biopsy reveals pericholangiolar layered (onion-skin) fibrosis, which is a typical histological feature of PSC. This disorder is regarded as a variant of PSC, known as small-duct PSC (24).

Another variant of PSC is the PSC-AIH overlap syndrome (25, 26). In addition to the cholangiographic and clinical characteristics of PSC, patients with this overlap syndrome have markedly elevated serum transaminase and immunoglobulin G or gammaglobulin levels, in combination with serum autoantibodies, such as antinuclear antibodies and smooth muscle antibodies, and liver histological abnormalities compatible with AIH. The therapeutic response of at least the AIH-component of this disorder to corticosteroids can be excellent. Therefore, clinicians should be well aware of this syndrome, which may be more common than previously thought (*chapter 3*).

Another variant of sclerosing cholangitis occurs primarily in middle-aged men without IBD, usually presenting with jaundice and weight loss. Imaging studies demonstrate focal or diffuse enlargement of the pancreas, strongly suggestive of malignancy. Diabetes mellitus and exocrine pancreatic insufficiency may also be found. Cholangiography reveals the pattern of sclerosing cholangitis. A series of 10 patients with this particular syndrome, so-called "sclerosing pancreato-cholangitis", is described in *chapter 4*, in which the question is posed whether this disease is just an atypical form of ordinary PSC.

It is important to remember that the biliary system possesses a rather limited reportoire of responses to a variety of pathological processes and that the radiological appearance of diffuse stricturing and segmental dilatation of the biliary system may be encountered in

association with a broad array of local and systemic diseases (27). Various immunodeficiency states, i.e. AIDS, may facilitate opportunistic infection of the biliary tree, resulting in sclerosing cholangitis (28). Furthermore, toxic (29) and ischaemic (30) damage to the biliary system may also result in the development of sclerosing cholangitis. In *chapter 5* a group of patients with sclerosing cholangitis due to portal vein thrombosis is described.

Prognosis of immunocholangitis

The determination of a patient's prognosis is an important tool for clinical decision-making. Timing of liver transplantation and selection of patients for the evaluation of new drugs in clinical trials are two examples of important decisions which primarily depend on the patient's future prospects.

Primary biliary cirrhosis

It is generally known that in some patients PBC will follow a fairly benign course over a period of more than 20 years without developing into cirrhosis, whereas in others a progressive course will necessitate transplantation within less than 10 years after diagnosis of PBC. This variable clinical course clearly illustrates the need for a prognostic tool. Mathematical prognostic models, such as the Mayo model (31), use variables that may change in time, such as serum bilirubin and albumin levels, to predict the clinical course and consequently the timing of liver transplantation. However, in the early stages of PBC, when bilirubin and albumin levels are normal, these models cannot predict whether the disease will follow a relatively benign or a progressive course.

Since the relationship between PBC and AMA is close, many studies have focused on the correlation of various aspects of AMA and prognosis. Previous studies found no evidence that AMA titres (32) or the absence of AMA is related to disease progression (33). Four AMA-subtypes have been found to be quite specific for PBC. Prognostic value has been attributed to these AMA-subtypes, which can be linked to the presence of anti-M2, -M4, -M8 and -M9 antibodies (34-37). German PBC patients with serum anti-M4 and/or anti-M8 antibodies were reported to have a progressive course of the disease, leading to cirrhosis and hepatic decompensation, whereas the course in patients without anti-M4 and anti-M8 antibodies was found to be non-progressive for at least 10 years (38-41). In *chapter 6*, we aimed to confirm the prognostic value of AMA-subtypes in a heterogeneous population of Dutch PBC patients.

Primary sclerosing cholangitis

PSC is a progressive disease with an estimated median duration of transplantation-free survival of approximately 12 years (42-44). As in many chronic cholestatic liver diseases, the course of the disease may be characterized by development of biliary cirrhosis, eventually resulting in hepatic decompensation. A number of complications of PSC, however, are quite specific to the disease. The development of dominant bile duct strictures causing cholestatic jaundice is a characteristic feature of PSC (45, 46). Furthermore, PSC patients are more prone to bacterial cholangitis (10) due to the malformed biliary tree. Cholangiocarcinoma is the most feared complication of the disease, since the 2-year survival rate for PSC patients with this malignancy is below 20% (47). Another potentially life-threatening problem in PSC is the development of colorectal cancer, as the vast majority of patients also have long-standing IBD. The risks and clinical impact of these complications are poorly documented. The study described in *chapter 7* was conducted to evaluate the risks of dominant bile duct strictures, suppurative cholangitis, cholangiocarcinoma and colorectal cancer and to define the influence of the first two complications together with the baseline patient characteristics on transplantation-free survival in a cohort of PSC patients. Furthermore, we evaluated whether the new Mayo PSC prognostic model (48) fits our patient population.

Treatment of immunocholangitis

Primary biliary cirrhosis

Since the cause of PBC is unknown, the scientific search for medical treatment has been characterised by a trial-and-error approach. Consequently, a large variety of agents have been tested as potential therapies for patients with PBC. Most of them were ineffective or had serious side effects when studied in well-designed clinical trials (49-53).

Until recently, ursodeoxycholic acid (UDCA) was without doubt considered to be one of the few exceptions. A fairly large number of controlled trials demonstrated convincingly that this treatment improves serum liver tests, including bilirubin level (54-63). Although improvement in (liver transplantation-free) survival should be the main end-point of the evaluation of new treatments for PBC, none of these trials was specifically designed to assess the effects of UDCA therapy on mortality. Therefore, meta-analysis of individual patient data (n=548) from three of the larger trials was performed (64). A significant

improvement in survival without liver transplantation (but not of overall survival) was demonstrated by this combined analysis.

In addition, recent studies have demonstrated convincingly that UDCA slows progression of the disease towards its irreversible terminal phase. First, it should be emphasized that survival of UDCA-treated patients is better than that predicted by the Mayo-model of survival (65). Secondly, UDCA therapy retards histological progression (63) and delays the onset of cirrhosis, according to long-term studies (66).

As a result, the use of UDCA as standard treatment for PBC seemed to be established. Two recently published meta-analyses, however, have cast a reasonable doubt on the benefit of UDCA therapy for PBC (67, 68). Surprisingly, both studies, comprising more than 1200 patients treated in randomised clinical trials, found no difference between UDCA and placebo treatment with respect to the incidence of death, liver-related death, liver transplantation, death or liver transplantation, and the development of complications of chronic liver disease. It should be noted that neither meta-analysis was based on the original individual patient data, only on published data. Furthermore, not all trials included in these analyses used the proposed optimum dosage schedule of 13-15 mg/kg/day. For the higher doses it was shown that these regimens provided the optimal enrichment in biliary UDCA as well as the most significant changes in liver function tests (69).

Apart from the present uncertainty about whether UDCA therapy retards the course of PBC, it is clear that this drug is certainly not potent enough to halt progression of the disease and that a second therapeutic modality is needed. Additional or alternative treatments therefore have to be developed. Assuming that PBC is an immune disease, addition of immunosuppressive drugs to UDCA was an obvious next step. So far, three randomised controlled trials have shown that combined UDCA-corticosteroid treatment exerts more favourable effects on pruritus, serum liver tests and histological disease activity than UDCA-monotherapy (70-72). Since these studies should be considered as pilot studies because of the limited duration of treatment and the small numbers of patients, it remains speculative whether prolonged combined bile acid and immunosuppressive treatment has a beneficial effect on histological and clinical progression and mortality.

Primary sclerosing cholangitis

In contrast to PBC, the number of randomised controlled trials on PSC is fairly limited. Penicillamine (73), methotrexate (74) and colchicine (75) were all found to be ineffective. The first placebo-controlled pilot study on UDCA in PSC showed significant

improvement in serum liver tests and some histological features after one year of treatment (76). Lindor et al. performed a placebo-controlled trial with UDCA among 105 PSC patients. After a median period of two years, biochemical improvement but no clinical or histological benefit could be documented (77). In this respect it should be noted that the number of patients and the median duration of follow-up were limited in comparison to observations in PBC.

Recently, we performed a randomised controlled trial with UDCA-treated PSC patients to evaluate the additional effect of oral prednisone and budesonide therapy. Budesonide is a corticosteroid with high first pass liver clearance which, in theory, allows higher concentrations of active drug to be delivered to the biliary tree (*chapter 8*).

The clinical, biochemical and, most importantly, cholangiographic response to open-label corticosteroid treatment in patients with sclerosing pancreato-cholangitis is described in *chapter 9*.

In view of the results of two case-control studies suggesting that cigarette smoking protects against the development of PSC (78, 79), we wondered whether nicotine patch treatment could treat more than smoking addiction. We therefore performed a double-blind cross-over pilot trial to evaluate the efficacy and safety of transdermal nicotine treatment (*Chapter 10*).

In the subgroup of patients with 'large-duct' PSC, regular endoscopic treatment may be an alternative to pharmacological treatment. Stiehl et al. performed an open prospective study of frequent endoscopic dilatation of major bile duct strictures. They reported that transplantation-free survival was improved compared to survival predicted by the Mayo model (80). This is an interesting observation which needs to be studied within the context of a randomised controlled trial, which remains the gold standard for testing the efficacy of new therapies.

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Part I

Classification of Immunocholangitis

Chapter 2

JAUNDICE IN NON-CIRRHOTIC PRIMARY BILIARY CIRRHOSIS: THE PREMATURE DUCTOPENIC VARIANT

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Submitted

Abstract

The clinical and pathological findings on four females with primary biliary cirrhosis with an unusual and hitherto not well recognized course are reported. Patients suffered severe pruritus and weight loss with progressive icteric cholestasis which did not respond to such treatments as ursodeoxycholic acid and immunosuppressives. In all cases liver histology revealed marked bile duct loss without, however, significant fibrosis or cirrhosis. Further diagnostic studies and repeat biopsies confirmed the absence of liver cirrhosis as well as other potential causes of hyperbilirubinemia. Comparison of the fibrosis-ductopenia relationship for our cases with that for a group of 101 non-cirrhotic PBC patients indicated that in the former the severity of bile duct loss relative to the amount of fibrosis was significantly higher. The proportion of portal triads containing an interlobular bile duct was 3, 4, 6 and 10% compared to 45% (median; range 8.3 - 100%) for controls ($p<0.001$). Three patients received a liver transplant 6-7 years after the first manifestation of PBC because of progressive cholestasis, refractory pruritus and weight loss while the fourth patient is considering this option. In one case cirrhosis had developed at the time of transplantation while the others still had non-cirrhotic disease. These cases suggest that cholestatic jaundice in non-cirrhotic PBC may be secondary to extensive 'premature' or accelerated intrahepatic bile duct loss. Although the extent of fibrosis may be limited initially, progression to cirrhosis appears to be inevitable in the long run. Despite intact protein synthesis and absence of cirrhotic complications, liver transplantation in the pre-cirrhotic stage for preventing malnutrition and improve quality of life should be considered for these patients.

Introduction

Primary biliary cirrhosis (PBC) is a vanishing bile duct disorder (1) of a highly variable, albeit slowly progressive, nature. Immunologically mediated destruction of interlobular and septal bile ducts, resulting in bile duct loss or ductopenia, is considered to be one of the main pathophysiological events leading ultimately to liver fibrosis and biliary cirrhosis (2, 3). The histologic appearances have been divided into four stages, the last (stage IV) representing true cirrhosis (4). In general, jaundice is only encountered in the cirrhotic stage (5), probably as a consequence of both hepatocellular insufficiency and bile duct loss.

Jaundice in non-cirrhotic PBC is rare. In contrast to what is observed, for example, in the idiopathic adulthood ductopenia syndrome (6), it appears that the degree of intrahepatic

bile duct loss usually is not severe enough to cause jaundice. Various – mainly extrahepatic - factors not specifically related to PBC, including hyperthyroidism (7), malignant lymphoma (8, 9), liver metastases, certain drugs (10), hemolysis (11, 12), concomitant autoimmune hepatitis flares (13) and major bile duct obstruction, can cause jaundice in non-cirrhotic PBC.

We report here on a subgroup of PBC patients suffering from severe cholestatic, icteric disease for whom no causative extrahepatic or intrahepatic factors other than profound ductopenia could be identified. Remarkably, this was not associated with histologic evidence of cirrhosis or substantial fibrosis. A histomorphological study of these cases and a large group of non-cirrhotic PBC patients was performed to define the ductopenia-fibrosis relationship and to test the hypothesis that our cases exhibited extreme paucity of bile ducts in relation to the amount of fibrosis.

Cases

Case 1

In 1994, a 39-year-old Chinese woman presented with fatigue, pruritus and jaundice. Her previous medical history was unremarkable. There was no history of either alcohol or drug abuse or familial liver problems. Laboratory investigations showed cholestatic serum liver values (Table I), elevated IgM levels and an antimitochondrial antibody (AMA) titer of 1:10240. Other etiological studies for viral hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency and Wilson's disease were negative. A liver biopsy revealed severe ductopenia (Table I) and non-cirrhotic (stage II) PBC. Subsequent treatment with ursodeoxycholic acid (UDCA) and later with prednisone and azathioprine did not result in improvements in symptoms, serum bilirubin level or other laboratory parameters. Four years later a second biopsy was taken. At that time the serum bilirubin level was 103 µmol/l. Histologic examination showed two bile ducts in a total of 26 portal tracts. The degree of fibrosis had increased significantly and beginning nodularity of the liver parenchyma was noted (PBC stage III). At present, she is considering the possibility of liver transplantation.

Case 2

In 1992, a previously healthy 38-year-old Caucasian woman presented with pruritus and fatigue. A diagnosis of PBC was made on the basis of a positive test for AMA (titer

1:10240), the cholestatic serum liver profile (bilirubin 34 μmol/l), elevated IgM levels and characteristic histology. Other etiological studies for viral hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency and Wilson's disease were negative. UDCA therapy was instituted but did not result in any improvement in the serum liver tests. Treatment with anti-pruritics such as cholestyramine, rifampicin, naltrexone and oxazepam was unsuccessful. In 1997, combined prednisone and azathioprine treatment was given for three months without amelioration of complaints. One year later she was referred to the University Hospital Rotterdam. Jaundice (bilirubin: 77 μmol/l) and marked cholestatic serum liver values were found. Histologic examination of the liver revealed showed non-cirrhotic stage I PBC. In one out of 18 portal tracts one bile duct could be identified (Table I). Severe pruritus and progressive weight loss (13 kg in three years) were the main indications for performing liver transplantation eighteen months later. Histologic examination of a biopsy specimen of the liver explant showed PBC stage I with five intact bile ducts in 32 portal tracts.

Case 3

In 1990, a 38-year-old Caucasian woman presented with pruritus and arthralgia. Her previous medical history was unremarkable. On the basis of cholestatic serum liver values, elevated serum IgM levels, positive AMA serology and the liver biopsy findings a diagnosis of PBC (stage I-II) was made. Other etiological studies for viral and metabolic liver disorders were negative. Treatment with UDCA and prednisone did not result in evident symptomatic or biochemical improvements. Treatments with anti-pruritics such as cholestyramine, rifampicin and naltrexone was unsuccessful. In 1995, the serum bilirubin levels increased to over 150 μmol/l. Severe pruritus and fatigue persisted. A second liver biospy demonstrated non-cirrhotic, stage I-II PBC (Table I). Laparoscopy, abdominal ultrasonography and upper gastrointestinal endoscopy showed no evidence of cirrhosis or portal hypertension. Pruritus persisted and the weight loss was 7 kg when she received a transplant in 1997. The explant showed biliary cirrhosis (PBC stage IV).

Case 4

In 1993, this 47-year-old Caucasian woman was diagnosed with of AMA-negative PBC. The diagnosis was based on serum liver tests indicating cholestasis, elevated serum IgM levels and a liver biopsy showing chronic non-suppurative destructive cholangitis with some portal granulomas. Other etiological studies for viral hepatitis, hemochromatosis, alpha-1-antitrypsin deficiency and Wilson's disease were negative. Ursodeoxycholic acid treatment resulted in aggravation of the pruritus. Subsequently, severe pruritus persisted and failed to respond to cholestyramine, rifampicin and naltrexone. Furthermore, combination treatment with prednisone and azathioprine was given for one year without any symptomatic or biochemical improvement. Shortly after prednisone was discontinued severe jaundice (bilirubin: 129 µmol/l) with aggravating pruritus developed. Periocular and palmar xanthomatous skin abnormalities occurred and her bodyweight decreased from 85 to 55 kg within a period of one year. In 1999 liver transplantation was performed. The liver explant showed non-cirrhotic, stage II-III PBC with striking bile duct loss (Table I).

Patients and methods

The clinical, biochemical and histologic findings for our cases suggested that in these patients the course of the disease deviated from the 'normal' course. Most strikingly, the extent of bile duct loss seemed to be excessive in relation to the amount of fibrosis. To substantiate this impression, the quantified histologic findings on our patients were compared with those for a group of 101 consecutive, untreated PBC patients with non-cirrhotic histology. This population was collected between 1990 and 1998 during a prospective cohort study of PBC in the Netherlands (14). Total serum bilirubin levels in this group were lower than 23 µmol/l at the time of liver biopsy. In both our cases and the reference population liver specimens were obtained percutaneously using tru-cut or Menghini 14-16 Gauge needles. Biopsies were fixed in formalin and processed routinely into paraffin blocks. Sections were stained with hematoxylin and eosin as well as anti-cytokeratin-19 antibodies.

The following features of each specimen were assessed: aggregate length in millimeters, number of portal tracts, number of portal tracts with an interlobular bile duct, degree of fibrosis and Ludwig stage (4). The severity of fibrosis was expressed as a value ranging from 0-4 (15) and 0-5 for biopsies scored between 1990 and March 1994 and between March 1994 and 1998, respectively. The maximum score represents cirrhosis. The

amount of fibrosis was expressed as a fibrosis score, defined as a proportion of the maximum score. One biopsy per patient was included in the statistical analysis.

The proportion of bile ducts was calculated by dividing the total number of portal tracts with an interlobular bile duct by the total number of portal tracts in each biopsy specimen. A ductopenic index was calculated by dividing the total number of portal tracts by the total number of portal tracts containing an interlobular bile duct. Thus, the higher the ductopenic index the more serious the loss of bile ducts. The degree of bile duct loss was also expressed as the biopsy length in millimeters divided by the number of bile ducts.

For the index cases, the possibility of significant bile duct obstruction, which could possibly account for the discrepancy between the clinical features and the non-cirrhotic histology, was assessed by means of endoscopic retrograde cholangiography (ERC) and/or ultrasonography. Hyperthyroidism was evaluated by measurement of the serum thyroid-stimulating hormone (TSH) concentration. To exclude concomitant autoimmune hepatitis, the revised international score (16) was calculated. Hemolysis was assessed by serum lactate dehydrogenase (LD) and hematologic indices. Abdominal ultrasound with measurement of spleen size, upper gastrointestinal endoscopy for detection of esophagogastric varices and visual inspection of the liver during laparoscopy or laparotomy were performed to further exclude the presence of cirrhosis. Statistical analysis was performed with Stata 4.0 for Windows. Correlations were calculated using Pearson's (r) or Spearman's (r_S) tests. A p-level <0.05 was considered statistically significant.

Results

Clinical, biochemical, histologic and radiologic characteristics of the four index patients are shown in Table 1. All were females with a median age of 43 years (range 39-47). Neither spontaneous nor therapy-induced improvements in hyperbilirubinemia or other laboratory parameters were observed.

The mean age of the reference group (n=101) was 56 years (range 37-73); 87% were female and 95% were AMA-positive. Ludwig stages I, II and III were found in 20 (20%), 51 (50%) and 30 (30%) biopsies, respectively.

The median length of the 101 control biopsy specimens was 16 millimeter (range 4-40) and the median number of portal tracts per biopsy was 16 (range 4-44). The median number of portal tracts per millimeter liver tissue was 1.0 (95%-confidence interval 0.98-1.15). The number of portal tracts correlated well with the aggregate length of the biopsy

core (r_S 0.7, $p<0.001$). The four cases did not deviate from the pattern among controls (fig 1).

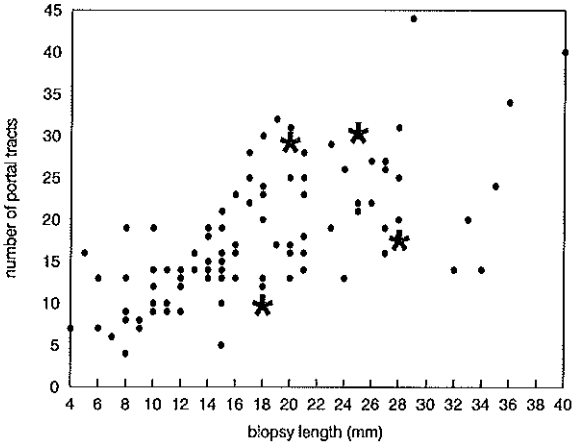

Figure 1. Scatter plot showing the relationship between biopsy length in millimeters and the number of portal tracts. Dots and stars (*) represent controls and cases, respectively.

For our four cases, the proportion of portal tracts containing normal bile ducts was 3, 4, 6 and 10 percent, yielding ductopenic indices of 30, 28, 18 and 10, respectively. For the reference group, the median proportion of portal tracts with a bile duct was 45 percent (range 8.3 to 100%), a significant difference with the cases (Mann-Whitney test: $p<0.001$). The median ductopenic index for the reference group was 2.2 (range 1-12).

The relationship between the degree of ductopenia and fibrosis is shown in figure 2. For the reference group, the ductopenic index was positively correlated with the degree of fibrosis ($r=0.51$ after logarithmic transformation of the ductopenic index to obtain normal distribution; $p<0.001$). This implies that only 26% (i.e. r^2) of the variability in fibrosis may be attributed to an association with the severity of ductopenia. Three out of four cases fall outside the 95%-reference interval (fig 2). Therefore, the degree of bile duct loss was significantly higher in our patients, especially when the slight amount of fibrosis is taken into account (fibrosis score 0.2 in three cases and 0.5 in one). When the number of bile ducts in related to the biopsy length, instead of the number of portal tracts, this ratio is significantly ($p<0.001$) higher for our cases compared to the controls (fig 3). The extreme ductopenia is illustrated by a keratin-19 stained biopsy slide for one of the cases, showing nearly total absence of pre-existent bile ducts (fig 4).

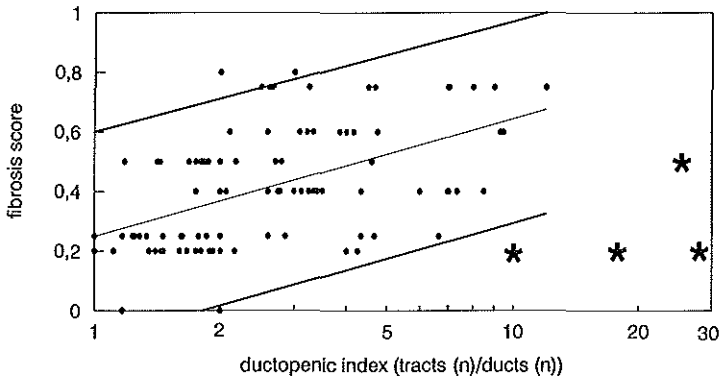

Figure 2. Scatter plot showing the relationship between the ductopenic index (ratio portal tracts (n): ducts (n)) and the fibrosis score. A high index indicates severe ductopenia. Dots and stars (*) represent controls and cases, respectively. The central line indicates the least-squares regression line. The upper linerepresents the 97.5-percentile and the lower line the 2.5-percentile. Note the logarithmically scaled horizontal axis. Three of four cases fall outside the 95%-reference interval of the control biopsy specimens.

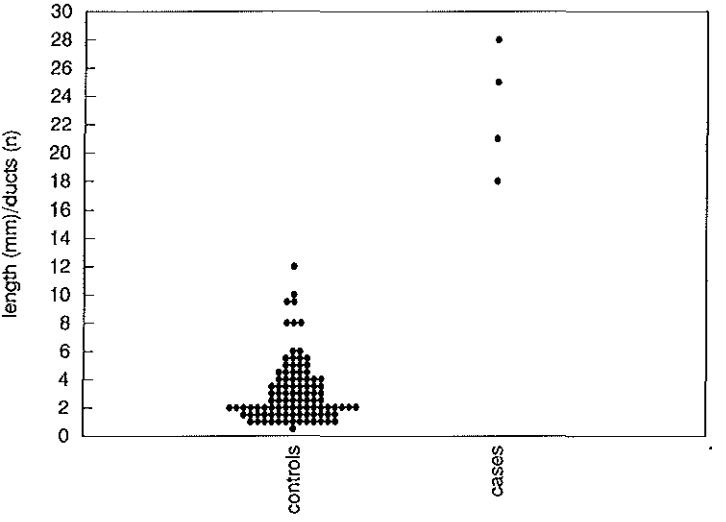

Figure 3. Plot showing the difference in length (mm) / ducts (n) ratio between the controls and cases. A high ratio indicates severe ductopenia.

Other causes that might explain the apparent discrepancy between the severity of cholestasis and hyperbilirubinemia versus the minimal fibrosis in these PBC patients could not be identified. In particular, no evidence of hyperthyroidism, hemolysis, autoimmune

hepatitis (table I), previous use of agents known for their ability to induce cholestasis, or major bile duct obstruction was found. Laparoscopic examination of the liver, performed in three cases, showed normal livers without evidence of cirrhosis. In addition, ultrasonography (n=4) and upper gastrointestinal endoscopy (n=3) did not reveal signs of portal hypertension or evidence of other conditions, including cholelithiasis, liver metastases or lymphoma. Serum values for albumin and antithrombin-III were within normal ranges in all cases, reflecting an intact protein synthesis.

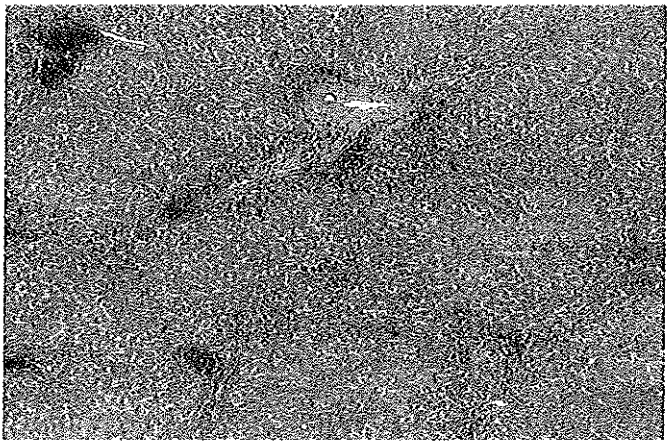

Figure 4A. HE-coloured liver biopsy from case 2 showing at least 4 portal tracts. The amount of fibrosis is very limited and there are no porto-portal or porto-septal connections.

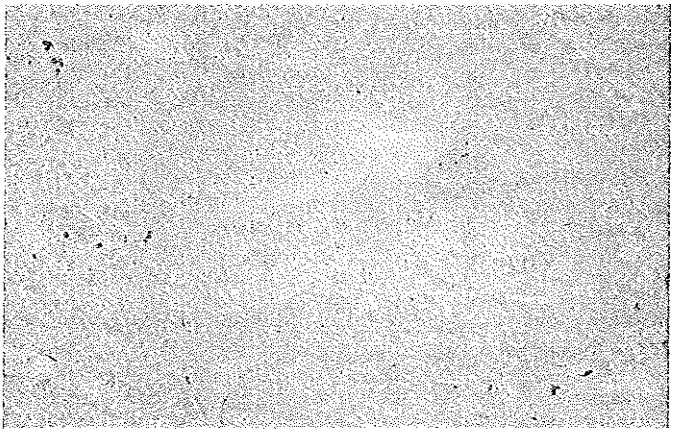

Figure 4B. Anti-cytokeratin-19 (keratin-19)-stained liver biopsy from case 2 showing the same portal tracts as in figure 4A with total absence of pre-existent interlobular bile ducts and only very moderate ductular proliferation (darkish brown coloured cells).

Table I: Clinical characteristics of and diagnostic findings for our cases.

Case	*1*	*2*	*3*	*4*
Age (yrs)	39	43	43	47
Sex	F	F	F	F
Ethnic background	Chinese	Caucasian	Caucasian	Caucasian
Laboratory				
AMA	positive	positive	positive	negative
ANA	positive	positive	negative	positive
bilirubin (µmol/l; N<17)	78	77	168	129
APh (U/l; N<75)	709	926	761	848
ALT (U/l; N<50)	336	287	56	194
IgM (g/l; N<2.8)	4.07	4.13	4.52	9.19
bile salts (µmol/l; N<10)	840	240	400	720
cholesterol (mmol/l; N<6.5)	11.3	8.6	32.6	46.0
TSH (mU/l; N=0.20-4.20)	0.54	0.68	1.23	0.97
LD (U/l; N<480)	308	345	221	364
Histology				
length of biopsy (mm)	21	28	18	25
number of portal tracts	28	18	10	30
number of bile ducts	1	1	1	1*
Radiology				
ERC	n.a.	no stenoses	no stenoses	no stenoses
abdominal ultrasonography	normal	normal	normal	normal
spleen size at US (cm)	n.a.	9-10	12	15
visual liver assessment	n.a.	normal	normal	normal
revised AIH score	+8	+8	+2	+8
upper GI endoscopy	n.a.	no p.h.	no p.h.	no p.h.

Data obtained at the time of liver biopsy as indicated in the text.

n.a.: not available; GI: gastrointestinal; p.h.: portal hypertension; US: ultrasonography; UDCA: ursodeoxycholic acid; *: damaged bile duct; ANA: antinuclear antibodies; APh: alkaline phosphatase; ALT: alanine aminotransferase.

Discussion

The cases described in the present report indicate that among patients with PBC a subgroup can be identified, characterized clinically by severe cholestasis and histologically

by extreme ductopenia which is not accompanied by significant liver fibrosis or cirrhosis. These patients do not seem to respond to treatment with ursodeoxycholic acid or immunosuppressives and the disease evolves in the course of a few years to the stage in which liver transplantation becomes to be the only therapeutic option. The findings for this subgroup are at variance with the usual course of the disease whereby severe cholestasis and jaundice are only encountered in patients with cirrhotic histology.

Jaundice in early histologic stages of PBC has been observed before. Etiologies of this phenomenon, such as hemolysis (11, 12), hyperthyroidism (7) and concomitant autoimmune hepatitis (13), were not specifically related to PBC itself and icterus was reversible upon treatment of the underlying cause (7, 11, 13). No evidence for any of these possibilities was found in our cases.

Histologic evaluation of the liver by means of needle-biopsy may be hampered by the possibility of sampling error. The accuracy of diagnosing cirrhosis, and consequently its absence, by percutaneous needle biopsy alone has been reported to be rather poor (17). However, a combination of this procedure with ultrasonography enhances the sensitivity to nearly 100% (17, 18). Histology was combined with ultrasonography in our four cases. In addition, in three cases macroscopic assessment of the liver as well as upper gastrointestinal endoscopy was performed to further minimize the chances of missing a diagnosis of cirrhosis.

Variability in the total size of the biopsy core influences the yield of portal tracts. The scatter plot (Fig 1) indicates that the biopsies obtained from our patients were comparable to those from the controls. The data show that approximately one portal tract per millimeter needle-biopsy tissue is found, confirming the previously published 1:1 ratio (portal tract:millimeter needle biopsy) for the normal adult human liver (19). Consequently, since cirrhotic PBC was deliberately not included in this study, the ductopenic severity could also be expressed as the proportion of bile ducts per millimeter tissue. Presentation of the data in this way (fig 3) demonstrates the extreme degree of bile duct loss in the jaundiced cases even more convincingly.

Sampling error may also weaken the data on the severity of ductopenia. In this study little overlap in degree of ductopenia between the reference group and our cases was found. However, the difference in degree of bile duct loss between the case and control groups was statistically significant, both when the number of bile ducts was related to the number of portal tracts as well as to the length of the biopsy specimen. Furthermore, a

repeat biopsy in two of the cases (one non-cirrhotic liver explant) confirmed the presence of striking ductopenia.

This study does not allow other than speculations about the etio-pathophysiological differences between patients with the non-cirrhotic severe ductopenia variant and those with the more conventional course. We found that the relationship between ductopenia and fibrosis, although present, is not very convincing. We hypothesize that in exceptional cases a particularly aggressive form of immune-mediated bile duct destruction results in extensive ductopenia within a comparatively short period of time. The relatively young age of our patients at presentation with severe cholestasis points to this possibility. Initially, fibrogenesis seems to lag behind the rate of bile duct destruction. Nevertheless, as indicated by the histologic evolution in our patients, progressive fibrosis eventually does develop.

Previously, Nakanuma et al. suggested extensive bile duct loss as a potential cause of cholestatic jaundice in non-cirrhotic PBC (20) without, however, reporting quantitative histologic data. The present study suggests that the proportion of portal tracts with an intact interlobular bile duct has to be less than 10% in order to produce substantial hyperbilirubinemia. Mild ductopenia, defined as a proportion of portal tracts with an intact interlobular bile duct >50%, was shown not to be associated with a rise in serum bilirubin concentration in adults with 'idiopathic biliary ductopenia' (21). Patent bile ducts in 10 to 50% of portal tracts, as was found in the large majority of patients in the reference group, was not associated with hyperbilirubinemia either. These percentages should not be regarded as absolute limits but rather as broad indications. Also, when assessing the degree of ductopenia the size of the biopsy specimen should always be taken into account. For a reliable assessment of ductopenia a minimum of 20 evaluable portal tracts has been suggested. (22). In clinical practice, however, this is not always feasible.

Already in 1978, Popper hypothesized that in PBC two pathways may lead to cirrhosis (2). One is the consequence of biliary destruction within the portal triads and the other is due to peri-portal interface hepatitis that is uniformly found in PBC, albeit to a variable extent. These two mechanisms may be operative in variable degree in individual patients. Consequently, one could speculate that PBC may have a wide range of phenotypical expressions, varying from a PBC-autoimmune overlap syndrome on the one side to the 'premature ductopenic variant' on the other side of the spectrum. Although it appears that both manifestations eventually may lead to cirrhosis, the name of the disease clearly needs

to be revised. 'Primary intrahepatic cholangitis' (PIC) (23) might be a more appropriate term.

In conclusion, cholestatic jaundice in non-cirrhotic PBC may be secondary to an unusually accelerated intrahepatic bile duct loss. Although the extent of fibrosis in affected patients may be limited initially, progression to cirrhosis seems to be inevitable. Despite intact protein synthesis and the absence of cirrhotic complications, liver transplantation in the pre-cirrhotic stage for treatment of pruritus and (prevention of) progressive weight loss due to malabsorption should be considered for these patients.

Acknowledgement

We would like to thank professor V. Desmet for studying some of the biopsy specimens and for critically reviewing the manuscript.

Appendix

The Dutch multicenter PBC study group: R. Adang, V. Verstappen: St. Maartens Gasthuis Venlo; P. Batenburg: Zuiderziekenhuis Rotterdam; G. van Berge Henegouwen, J. van Hattum: University Hospital Utrecht; P. Biemond, L. Lie: Ziekenhuis St. Franciscus Roosendaal; J. Breed: St. Jans Gasthuis Weert; C. van Deursen: Ziekenhuis De Wever en Gregorius Brunssum; Th. van Ditzhuijsen, I. van Munster: Bosch Medicentrum Den Bosch; O. van Dobbenburgh: Het Nieuwe Spittaal Zutphen; L. Engels: Maasland Ziekenhuis, Sittard; J. Ferwerda: Kennemer Gasthuis Haarlem; J. Groen: Ziekenhuis St. Jansdal, Harderwijk; K. Heering: Groene Hart Ziekenhuis Gouda; P. van Hees: St. Antonius Ziekenhuis, Nieuwegein; E. vd Hoek, J. de Bruijne: Carolus Ziekenhuis Den Bosch; M. Houben, R. Valentijn: Rode Kruis Ziekenhuis Den Haag; J. Kapelle, P. Spoelstra: Medisch Centrum Leeuwarden; M. Kerbert-Dreteler, J. van Lijf: Medisch Spectrum Twente Enschede; I. Klompmaker, E. Haagsma: University Hospital Groningen; G. Koek, W. Hameeteman: University Hospital Maastricht; J. Lambert: Sophia Ziekenhuis Zwolle; P. Leeuwerik: Ziekenhuis Lievensberg Bergen op Zoom; B. Looij: Maasland Ziekenhuis Geleen; A. Luckers: Maasziekenhuis Boxmeer; A. van Milligen de Wit: Elisabeth Ziekenhuis Tilburg; C. van Nieuwkerk: University Hospital Free University Amsterdam; J. den Ouden-Muller, A. van Tilburg: St. Franciscus Gasthuis Rotterdam; S. Peters, P. Tjepkema: IJsselmeerziekenhuizen Lelystad; G. Ras: Ignatius Ziekenhuis Breda; M. Rijk: Ziekenhuis De Baronie Breda; R. Robijn: Ziekenhuiscentrum Apeldoorn; S. Schalm: University Hospital Rotterdam; J. Scherpenisse: Reinier de Graaf Gasthuis Delft; A. Stronkhorst: Catharina Ziekenhuis Eindhoven; T. Tan: Streekziekenhuis Midden-Twente Hengelo; J. Thijs: Ziekenhuis Bethesda Hoogeveen; K. te Velde: Deventer Ziekenhuizen Deventer; M. Vidakovic-Vukic: Lucas Andreas Ziekenhuis Amsterdam; A. van Vliet, R. Beukers, H. Ponssen: Albert Schweitzer Ziekenhuis Dordrecht; R. de Vries, C. Mulder, J. Thies: Ziekenhuis Rijnstate Arnhem; S. vd Werf: Westeinde Ziekenhuis Den Haag; B. Witteman, J. van Bergeijk: Ziekenhuis De Gelderse Vallei Wageningen; R. van Zanten: Twenteborg Ziekenhuis Almelo; R. Zeijen: Schieland Ziekenhuis Schiedam; R. Zwertbroek: Westfries Gasthuis Hoorn; A. Saleh: Elisabeth Hospitaal Willemstad, Curacoa.

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Chapter 3

HIGH PREVALENCE OF AUTOIMMUNE HEPATITIS AMONG PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS

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Journal of Hepatology, in press.

Abstract

Traditionally, autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) are regarded as separate disease entities. We report on a group of patients that suggests the existence of an overlap syndrome of the two conditions and on the prevalence of this syndrome among patients with PSC. Furthermore, the impact of the recently revised AIH scoring system for diagnosing AIH in this context was assessed. Retrospective analysis of consecutive patients of a tertiary referral centre for liver disease with a diagnosis of PSC. Diagnosis of the overlap syndrome was established for nine patients (8%) of a total group of 113 PSC patients. Four patients initially presented with features of AIH and in five cases PSC was diagnosed first. All patients responded to immunosuppressive therapy, in three cases long-term remission was achieved. Three patients underwent liver transplantation after 4 months and 7 and 9 years. The original and revised versions of the AIH scoring system gave essentially the same results in the patients with the PSC-AIH overlap syndrome. Patients with overlapping features of AIH and PSC may be more common than is currently assumed. Recognition of this syndrome is of clinical significance considering the important therapeutical consequences.

Introduction

Autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) are usually regarded as separate disease entities. On the basis of clinical, biochemical, sero-immunological, histological and radiological criteria, a clear distinction between these conditions can readily be made in the majority of cases. However, AIH, PSC and PBC also have many features in common. In particular, autoimmune-mediated necro-inflammatory damage of hepatocytes and bile ducts seems to be of primary pathogenetic importance (1-5).

In other autoimmune diseases the occurrence of patients with overlap syndromes has been clearly established (6). In recent years, syndromes with overlapping features of AIH and PBC have also been recognised increasingly (7-11). Furthermore, the simultaneous presence of AIH and PSC has been described, especially in children (12, 13) but also in a number of adults (14-20). Recent review articles, however, (4, 5, 21, 22) do not refer to this syndrome, illustrating that it is still believed to be rare. Our senior authors (HRvB and SWS) have noticed over a 20-year period a change in the phenomenology of AIH, in particular an increase in incidence in young males, often with cholestatic features and regular occurrence together with PSC. To verify this clinical impression, a retrospective

study was initiated. We report here our single-centre experience with nine patients with an AIH and PSC overlap syndrome.

Patients and Methods

An exhaustive survey was performed to identify all consecutive cases with a diagnosis of PSC in our centre since 1976. The diagnosis was based on cholangiography showing (multi)focal strictures of intrahepatic and/or extrahepatic bile ducts with intervening normal or dilated segments, producing a beaded bile duct appearance. Originally, cholangiograms were studied by a senior radiologist with a special interest in endoscopic retrograde cholangiography (ERC); for the purpose of this study all cholangiograms were reviewed by the first author. PSC was not diagnosed if bile duct abnormalities could possibly be attributed to such causes as previous bile-duct surgery, ischaemia, portal vein thrombosis or sclerosing pancreato-cholangitis (23).

The clinical diagnosis of AIH was based on the finding of at least three-fold elevations in serum transaminase activities, elevated concentrations of IgG or γ-globulins and positive tests for antinuclear antibodies (ANA), smooth muscle antibodies (SMA), perinuclear antineutrophile cytoplasmic antibodies (pANCA) or liver-kidney microsomal antibodies in combination with liver histology showing moderate or severe chronic active hepatitis with interface hepatitis and a predominantly lymphoplasmacytic infiltrate. Patients were assumed not to have AIH if there was evidence for viral hepatitis or some other concomitant liver disease, except for PSC, and if antimitochondrial antibodies (AMA) were present. Immunofluorescence techniques were used to detect autoantibodies. pANCA was detected on granulocytes, ANA on Hep2 cells, AMA on mouse and rat kidney cells and SMA on rat stomach cells.

In order to verify our clinical diagnosis of AIH, the numerical scoring systems for the diagnosis AIH, proposed by an international group of experts during a consensus meeting in 1993 (24) and modified by the same group in 1999 (25), were applied to all patients. In accordance with others who applied this diagnostic system to patients with PSC (26) scores were obtained before therapy.

Data relevant for this study were extracted from patient files and data-banks of the radiological, pathological, biochemical and immunological departments. All patients were followed until December 1998 or until death.

Results

In the period 1976-1998 113 patients with PSC were identified in our center. Nine patients (8%) fulfilled the diagnostic criteria for both AIH and PSC (table 1). The age at presentation of these nine cases with either one of these conditions varied from 7 to 54 (mean 27) years. An overlap syndrome was diagnosed after intervals varying from 6 months to 11.5 (mean 5.8) years. The duration of follow-up ranged from 1 to 16.8 years. Eight patients had concomitant IBD; in the one remaining case colonoscopy was not performed.

Four patients (no 1-4), 2 males and 2 females, mean age 16 (range 7-22) years, were initially diagnosed with AIH (table 1). In all cases the serum transaminase levels were elevated at least ten-fold (mean 18 times the upper limit of normal), IgG or γ-globulin concentrations were raised, SMA and/or ANA were detected and the liver biopsy showed interface hepatitis with a lymphoplasmacytic infiltrate (figure 1). Marked biochemical improvement was observed after treatment with prednisone and azathioprine (table 2). Mainly because a predominantly cholestatic biochemical profile emerged during follow-up, ERC was performed at intervals after the initial diagnosis, varying from 5.9 to 11.5 (mean 8.9) years. Despite an initially favourable therapeutic response to immunosuppressive therapy, patient no 4 had slowly progressive disease necessitating liver transplantation after 7 years. The remaining three patients are alive and are still being followed; long-term complete biochemical remission was achieved in one patient with continued immunosuppressive treatment.

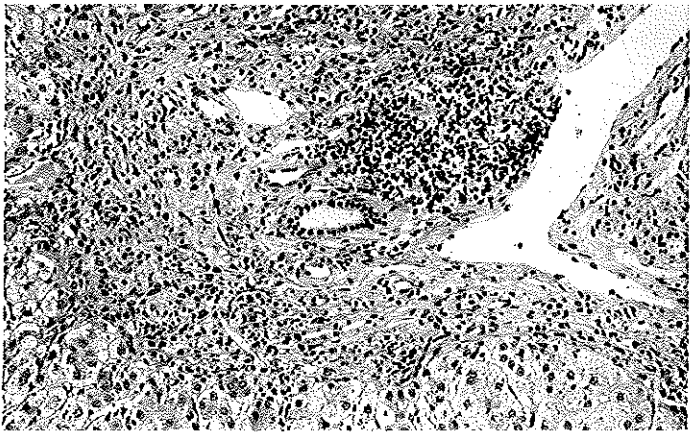

Figure 1. Liver biopsy showing an enlarged portal area with a predominantly lymphoplasmacytic infiltrate with an ill-defined limiting plate and (top) inflammatory cells infiltrating into the adjacent parenchyma (patient no 1). Original magnification x 20.

Five patients (no 5-9), four men and one female with a mean age of 32.6 (range 15-54) years, were initially diagnosed with PSC (table 1). Liver histology showed periocholangiolar fibrosis in two cases; pANCA was detected in three cases and four suffered from concomitant IBD. AIH was diagnosed after a mean interval of 3.3 (range 0.5-5.8) years. One of these patients (no 5) exhibited the classical features of AIH: transaminases elevated ten-fold, IgG 49 g/l, high titres of SMA and histologically severe chronic active hepatitis. PSC had been diagnosed elsewhere six years earlier; in the course of time he exhibited persistently elevated transaminases and had an episode of severe hepatitis which resolved spontaneously. In retrospect, the diagnosis of AIH could have been established six years earlier. Another patient (no 6) developed liver failure with variceal bleeding and ascites when corticosteroids were withdrawn following colectomy for ulcerative colitis. Renewed immunosuppressive treatment resulted in complete clinical and long-term biochemical remission. Another patient (no 7) developed AIH when the corticosteroids, which he had received for 8 weeks in the context of a controlled clinical trial for PSC, were tapered off. These three patients (no 5-7) are alive and are being followed. The fourth patient (no 8) remained jaundiced after hepaticojejunostomy for common bile duct strictures. During immunosuppressive treatment bilirubin, transaminases, APh and immunoglobulins normalised or decreased significantly (table 2). Nine years later, however, he received a liver transplant for progressive disease. The last patient (no 9) was known with PSC for one-and-half years when severe jaundice and hepatic insufficiency developed. The initial diagnostic and therapeutic efforts focussed on the biliary tree. Only after five months immunosuppressive treatment was instituted. Four months later liver transplantation was performed because of insufficient therapeutic response.

Six patients, five with an initial diagnosis of PSC, received UDCA during the course of their disease at various intervals after the date of diagnosis. This treatment appeared to result in slight improvements in the serum liver tests in some cases.

ERC revealed bile duct changes characteristic of PSC in all cases. Mild abnormalities of both intrahepatic and extrahepatic ducts were found in 3 patients while only the intrahepatic ducts were affected in 2 patients. In 2 patients marked intrahepatic bile duct deformities were found, one was associated with intrahepatic stones while the extrahepatic ducts appeared to be normal. Dominant strictures were observed in one patient (no 8). Severe intrahepatic and extrahepatic PSC was found in patient 9 (figure 2).

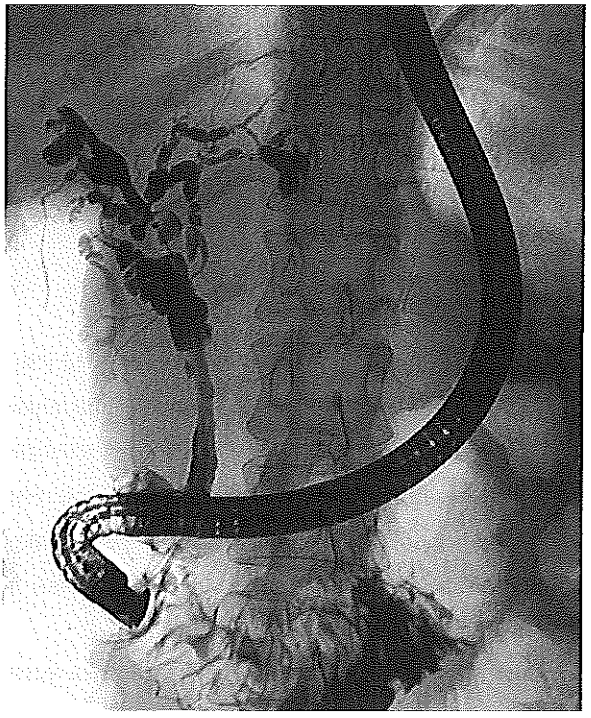

Figure 2. Endoscopic retrograde cholangiogram (patient no 9) showing multiple areas of intrahepatic strictures and ductal dilatation.

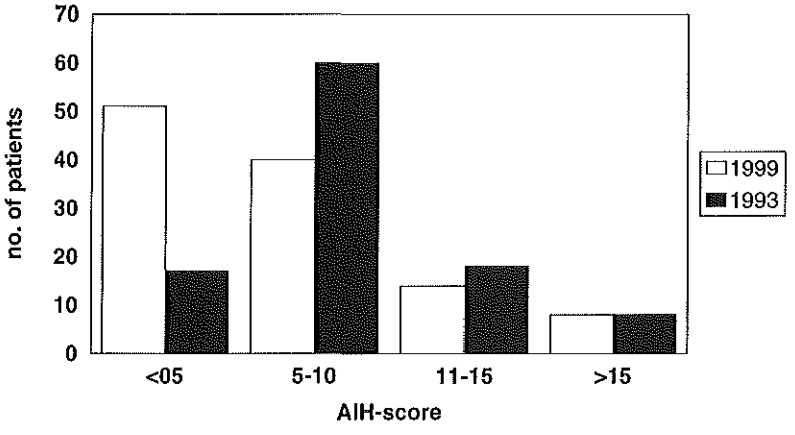

Figure 3. Distribution of the numerical AIH-scores of both the 1993 and 1999 scoring lists in the total group of 113 PSC patients. The black and white bars represent the results according to the 1993 and 1999 lists, respectively.

Comparison of the outcomes of the original and revised AIH scoring systems gave essentially the same results for the cases with a clinical diagnosis of both AIH and PSC (table 1). Both the original and revised version of the scoring list resulted in scores indicating 'definite' AIH in eight cases and 'probable' AIH in one. In the total group of 113 PSC patients, the 1999 scoring list gave lower numerical AIH-scores than the 1993 list (figure 3).

Discussion

In this report nine patients with an overlap syndrome of AIH and PSC are described. In view of the number of cases reported in the literature (table 3) this represents a relatively large series. It is noteworthy that four more patients have been identified with AIH who had marked cholestatic liver function test abnormalities, negative test results for AMA, and histologically chronic active hepatitis with ductular changes, pericholangiolar fibrosis and copper deposits. A definite diagnosis of PSC, however, could not be made because cholangiography was not performed.

Specific referral patterns and increased diagnostic awareness in recent years may have contributed to the number of cases reported here. The prevalence of the overlap syndrome among patients with AIH remains to be established because none of the studies reported, including the present one, included cholangiography in all cases. Among children with AIH a prevalence of 27% was reported, but also in this study cholangiography was not performed uniformly (27). The prevalence of AIH among patients with PSC was assessed by Boberg et al. (26), who applied the 1993 AIH scoring system to a group of 114 PSC patients. Two (2%) patients were classified as 'definite' AIH and 38 (33%) as 'probable' AIH. We found a prevalence of 'definite' AIH of 8% in our group of 113 PSC patients.

Establishment of the diagnosis of AIH is difficult since there is no single diagnostic test or validated set of criteria. This applies specifically for patients with a concomitant liver disease. The diagnostic aspects of AIH were addressed by an international forum of experts during consensus meetings in 1993 (24) and 1999 (25). In our centre we rely mostly on the positive criteria of >3-10 fold elevations of serum transaminases, two-fold elevation of IgG or gammaglobulins, presence of auto-antibodies and compatible liver histology. Negative factors such as alcohol use, positive viral serology, hepatotoxic medication and biliary lesions on biopsy are clearly considered, but we do not attribute a decisive significance to these factors. The reports of the 1993 and 1999 meeting (24, 25) states that patients with biliary changes identified either histologically or by

cholangiography should not be assumed to have AIH. This point of view should be modified in the light of cumulating evidence that true overlap syndromes do occur (28). With these reservations in mind, our patients were evaluated according to the 1993 and 1999 systems. The scoring systems were applied conservatively and resulted in scores indicating 'definite' AIH for eight patients and 'probable' AIH for one. The latter patient, however, exhibited a complete biochemical response to immunosuppressive therapy. The observed response to immunosuppressive therapy in the other cases further strengthens our belief that all of our patients had AIH. Essentially, application of the recently revised AIH numerical scoring system for diagnosing AIH did not affect the results obtained with the 1993 version. Therefore, both systems seem appropriate tools for identifying PSC patients with concomitant AIH. Although we applied both scoring lists to all 113 patients for methodological reasons, we do not feel that this is rational approach in daily practice. In our opinion, application of the scoring list should only be considered in case of clinical evidence of concomitant AIH.

When the clinical features of patients in the present series are compared with those of previously reported adult patients (table 3) with AIH-PSC overlap, several similarities are found: percentage males is 67% versus 66% in the literature, mean age at presentation 27 versus 26 years and prevalence of IBD 89% versus 59%, respectively. With respect to other laboratory, histological and radiological characteristics, these patients seem to be very similar. The presently available cumulative experience indicates that the AIH-PSC overlap syndrome is mainly, but not exclusively, a disorder encountered in children and young adults, with a predominance of males. In the majority of cases the overlap syndrome is associated with ulcerative colitis or Crohn's disease.

The therapeutic response to immunosuppressants, in particular of the AIH-component of the overlap syndrome, can be excellent. Our experience as well as that of others (15, 16, 18) indicates that proper therapy can lead to complete remission of disease activity and indeed may be life-saving. However, our experience seems to be in accordance with that of earlier reports (12, 14, 29, 30) suggesting that the therapeutic benefit for patients with an overlap syndrome may be less than for those with 'genuine' AIH. In fact, two of our patients needed a liver transplant 7-9 years after the start of immunosuppressive therapy. This finding is in contrast to current results for genuine AIH (31). One may speculate that the immunosuppressive treatment does not influence the PSC-component of this overlap syndrome in a major way. In the patient who was transplanted after four months,

immunosuppressive therapy probably was instituted at a stage of irreversible hepatic damage.

The cause of AIH and PSC is unknown. Most findings seem to indicate that these disorders may develop in patients with a genetic susceptibility. Human leucocyte antigen (HLA) studies have shown that both disorders are closely associated with B8, DR3-positive haplotypes (26, 32) and with the DRB3 allele DRB3*0101, which encodes for DR52a (33, 34). The results of detailed HLA typing have not been reported for patients with the overlap syndrome and this therefore requires further study. The many similarities between the clinical, histological, genetic and immunological features of AIH and PSC (26, 35) and the existence of an overlap syndrome may suggest that these conditions represent phenotypic expressions of a common underlying process with aberrant autoreactivity. The role of IBD within this concept is even more speculative. IBD is associated with both PSC (4, 5, 36) and AIH (29) and the majority of overlap patients had IBD. In theory, IBD could be another phenotypic manifestation of a common underlying disease process. On the other hand IBD could be a condition that facilitates the development of AIH and PSC.

In conclusion, we report on nine patients with an overlap syndrome of AIH and PSC, which brings the total number of reported cases to 38. Our experience suggests that this entity may be less rare than currently assumed. Clinicians should be well aware of this syndrome since recognition of these cases can have major therapeutic implications.

Acknowledgement

We gratefully acknowledge the help of P.E. Zondervan and M. Seijbel of the Department of Pathology of the University Hospital Rotterdam.

Table 1: Patient characteristics at presentation and laboratory findings at the time of diagnosis of AIH.

Patient	sex	age	IBD	initial diagnosis	Diagnostic interval AIH-PSC (yrs)	original AIH score	Revised AIH score	histology	IgG (g/l)	γ-glob (g/l)	SMA	ANA	pANCA
1	M	7	UC	AIH	11	16	16	ifh, h	29.4		1:10	>1:640	
2	M	14	UD	AIH	11.5	17	16	ifh, f		49.2	1:40	1:80	
3	F	21	UC	AIH	5.9	19	20	ifh, f		40	neg	1:2560*	1:160
4	F	22	CD	AIH	7.3	19	19	ifh		34	1:320*	1:80*	
5	M	20	UC	PSC	5.6	18	17	pcf, ifh	49.4		1:320	neg	neg
6	M	23	UC	PSC	2.9	16	16	ifh, c	34.8		neg	1:180	1:10240*
7	M	37	no	PSC	5.8	15	13	ifh, f	23.2		neg	1:2560	neg
8	M	54	UD	PSC	0.5	17	17	ifh, f	53.1		1:80	1:40	
9	F	44	UC	PSC	1.5	17	19	pcf, ifh, f	32.6		neg	neg	1:160

IBD: inflammatory bowel disease; UC: ulcerative colitis; CD Crohn's disease; UD undetermined colitis

AIH score: score according to international autoimmune hepatitis group before immunosuppressive treatment (24). A score >15 indicates definite AIH and a score of 10 to 15 probable AIH.

ifh: interface hepatitis, pcf: pericholangiolar fibrosis, f:fibrosis, c:cirrhosis, *data 3-4 years after diagnosis AIH

Table 2: Serum liver tests and IgG/γ-globulins during the first year of immunosuppressive treatment.

patient	bilirubin (µmol/l)			AST (U/l)			APh (U/l)			IgG/γ-globulin (g/l)		
	start	1 month	1 year	Start	1 month	1 year	start	1 month	1 year	start	1 month	1 year
1	52	10	9	364	38	72	458	146	397	29.4	n.a.	n.a.
2	22	19	18	470	30	172	338	223	458	49.2*	n.a.	n.a.
3	123	n.a.	10	918	149	12	35	33	17	40*	n.a.	18*
4	46	11	15	348	82	97	135	80	97	34*	n.a.	n.a.
5	459	148	29	410	81	45	166	151	95	49.4	36	13.9
6	307	450	36	750	332	112	87	100	122	34.8	19	21
7	54	27	11	303	23	14	117	55	120	23.2	12.8	9.9
8	117	20	9	432	99	106	119	90	82	53.1	21.6	28.4
9	467	496	LTx	538	343	LTx	218	210	LTx	32.6	18.9	LTx

reference values: APh <75 U/l; AST <30 U/l; bilirubin <17 µmol/l; IgG <16 g/l; γ-globulins 9-18 g/l

* γ-globulins; LTx: liver transplantation; n.a.: not available

Table 3: Case series of the PSC-AIH overlap syndrome.

Author	Year	n	IBD	Treatment	Therapeutic response
Minuk (14)	1988	2	UC	Prednisone	Poor
Rabinovitz (15)	1992	1	UC	Prednisone/azathioprine	Good
Perdigoto (29)	1992	5	UC	Prednisone/azathioprine	treatment failure (n=4) transplantation (n=2)
Lawrence (16)	1994	1	UC	Cyclosporine	good
Wurbs (17)	1995	1	No	Prednisolone/azathioprine	good
Gohlke (18)	1996	3	UC (n=1)	Prednisolone/azathioprine/UDCA	remission (n=1)
Boberg (26)	1996	2	UC	Corticosteroids (n=1)	death (n=1) transplantation (n=1)
Protzer (19)	1996	4	UC (n=1)	Corticosteroids/azathioprine	good
Luketic (30)	1997	5	UC (n=2)	Corticosteroids/azathioprine	Liver transplantation (n=4)
McNair (20)	1998	5	UC (n=2)	Prednisolone/azathioprine	good biochemical response

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Chapter 4

SCLEROSING PANCREATO-CHOLANGITIS
- A SERIES OF TEN PATIENTS -

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Submitted

Abstract

Ten male patients are described who presented with weight loss, jaundice and pruritus. Pancreatic cancer was suggested by imaging studies showing focal or generalized pancreatic enlargement and compression of the distal common bile duct. In one case pancreatoduodenectomy was performed. Cholangiography, however, also demonstrated intrahepatic biliary stenoses, consistent with sclerosing cholangitis. Exocrine pancreatic insufficiency was found in six patients and diabetes in four. Pancreatic histology showed fibrosis and extensive inflammatory infiltrates. No evidence of concomitant IBD was found. A clear response to immunosuppressive treatment was observed in several patients. Notably, clinical and biochemical remission was observed in 3 patients and in one patient previously documented intrahepatic biliary strictures had disappeared after 3 months. The clinical features, pancreatic involvement, relatively high age at presentation, absence of IBD and response to steroids all plead against a diagnosis of 'ordinary' PSC. The natural course of sclerosing pancreato-cholangitis that may be accompanied by other disorders including Sjogren's disease is highly variable. Since the disease may mimick pancreatic carcinoma and, unlike PSC, may respond to immunosuppressives, recognition of cases is of clinical importance.

Introduction

Intrahepatic and extrahepatic bile duct strictures may result from a broad array of causes, such as biliary ischemia (1), AIDS (2), arterial administration of cytotoxic agents (3), portal vein thrombosis (4) and primary sclerosing cholangitis (PSC) (5). PSC is a disease of unknown etiology, with many findings suggesting an (auto)immune pathogenesis. The majority of patients has concurrent inflammatory bowel disease (IBD) (5). Pancreatic involvement in PSC is considered to be rare (6, 7).

Recently, autoimmunity was proposed as potential cause of a distinct type of idiopathic chronic pancreatitis (8-14). Clinical findings at presentation, in combination with radiological imaging studies showing pancreatic enlargement, led to a high initial suspicion of pancreatic cancer in the majority of reported patients. This type of pancreatitis can be found in the absence (8-12) or presence of other putative autoimmune diseases, such as Sjögren's disease (14-16) and systemic lupus erythematosus (17) and IBD (13, 18-21).

We here report on ten patients who presented with clinical signs suggestive of

pancreatic carcinoma but were found to suffer from idiopathic chronic pancreatitis in association with a PSC-like bile duct disease. From our experience we believe that these patients did not merely have atypical PSC with coincidental pancreatic involvement, but rather had a distinct autoimmune-mediated disease involving the pancreato-biliary tract. This entity may be less rare than is suggested by sporadic literature reports of comparable cases (13, 22-42). Recognition is of major clinical importance, in particular since the disease may mimick pancreatic cancer and, unlike PSC, may respond to conventional immunosuppressive therapy.

Patients and methods

In the period 1992-1999 ten patients with both pancreatic disease, in all clinically mimicking pancreatic carcinoma, and a concurrent or subsequent diagnosis of multiple biliary strictures were identified. Patients were followed until January 2000. Data were obtained from patient charts. All relevant radiological studies and histology specimen were reviewed for the purpose of the study.

Explorative laparotomy, abdominal computed tomography (CT) and/or ultrasonography (US) were used to assess pancreatic anatomy. Pancreatic tissue specimens were obtained by needle biopsy or pancreatoduodenectomy. Endocrine and exocrine pancreatic functions were evaluated by means of measurement of serum glucose level and fecal pancreatic elastase-1 content (ScheBo-Tech GmbH, Wettenberg, Germany), respectively.

Bile duct anatomy was assessed with endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC). Liver histology specimen were obtained by needle biopsy. Colonoscopy was performed to diagnose IBD. Immunofluorescence techniques were used to detect perinuclear antineutrophil cytoplasmic antibodies (pANCA).

Case reports

Case A (patient no. 1)

This 63-year old male patient presented with a history of 6 kg weight loss over 3 months. He had frequent pale, sticky stools and dark urine. His previous medical history was unremarkable. Laboratory examination revealed hyperglycemia (19.1 mmol/l, normal <5.5), cholestasis (APh 539 U/l, normal <130; γGT 635 U/l, normal <50; bilirubin 12

μmol/l), slightly elevated transaminase levels (AST 49 U/l, normal <40; ALT 69 U/l, normal <45) and elevated CA19.9 (330 kU/l). Carcinoma of the pancreas was suspected. US and CT studies (Fig 1) showed a diffusely enlarged "sausage"-like pancreas and a thickened aspect of the common bile duct wall. ERCP demonstrated multiple intrahepatic bile duct strictures, consistent with sclerosing cholangitis, and a narrowed pancreatic duct without strictures. Liver biopsy showed periductal inflammation. Colonoscopy was normal. Treatment with prednisone (60 mg/day), ursodeoxycholic acid (UDCA) and pancreatic enzyme substitution was instituted. Complete normalization of serum liver biochemistry (APh, AST and ALT) and CA19.9 level was observed within three months. Bodyweight increased by 10 kg over a period of six months. After tapering off the prednisone and introduction of azathioprine (2 mg/kg bodyweight), glucose serum levels were within normal limits with dietary measures. Exocrine pancreatic insufficiency, which was not assessed at presentation, appeared to be present after prednisone therapy. During the subsequent two years of follow-up he remained in excellent and stable clinical condition. Repeat ERCP after two years showed diminution of biliary strictures.

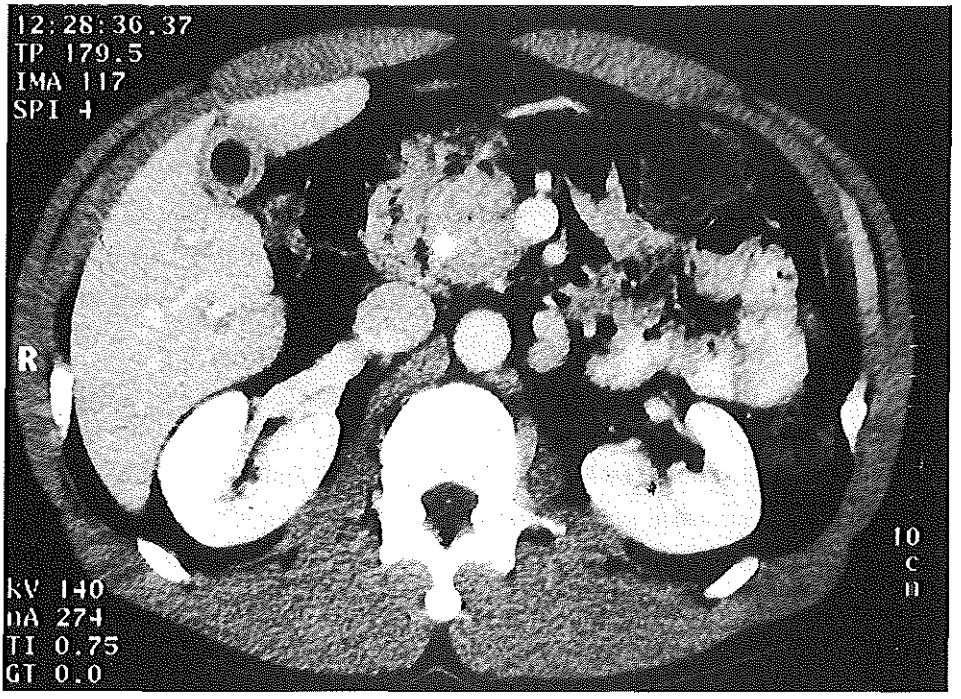

Figure 1. Computed tomography scan of patient no 1 showing enlargement of the pancreatic head region. A biliary endoprosthesis is located in the centre.

Case B (patient no. 3)

This 48-year old male patient was admitted with complaints of pruritus, abdominal pain and 30 kg weight loss. In the past, he had received a corneal graft for keratoconus. Diabetes mellitus was diagnosed and treated with oral medication. One month later painless jaundice developed (bilirubin 126 µmol/l, normal<17; APh 212 U/l, normal <130; γGT 1423 U/l, normal <70; AST 270 U/l, normal <45; ALT 680 U/l, normal <50). ERCP demonstrated marked stenosis of the distal common bile duct. Carcinoma of the pancreatic head or distal bile duct was suspected and a biliary stent was placed. During subsequent explorative laparotomy multiple peritoneal spots, enlarged omental lymph nodes and an enlarged pancreas with a rough surface were found. Microscopy of snap-frozen tissue samples suggested adenocarcinoma. Consequently, the plan to perform a Whipple's resection was abandoned. Definitive histological examination, however, failed to confirm a diagnosis of malignancy. The patient did not consent to a proposed pancreatoduodenectomy and asked for a second opinion elsewhere. Repeated ERCP revealed multiple intra- and extrahepatic bile duct strictures with focal narrowing of the distal common bile duct (Fig 2); the pancreatic duct was narrow and irregular. Liver biopsy demonstrated portal inflammatory infiltrates and moderate lobular fibrosis. Colonoscopy with biopsies was normal and serum pANCA negative. Fecal elastase-1 content (<0.015 mg/g) indicated severe exocrine pancreatic insufficiency. Liver biochemistry normalized spontaneously; pancreatic enzyme suppletion was instituted and a 30 kg weight gain over a period of one and a half year was observed. Subsequently, renal failure and generalized lymphadenopathy developed, accompanied by complaints of migrating polyarthralgia, fatigue and dryness of eyes and mouth. Sjögren's disease was diagnosed based on clinical findings, abnormal Schirmer test results and renal and lip biopsies showing interstitial nephritis and salivary adenitis.

Results

We observed ten patients (Table I) with PSC-like bile duct abnormalities on ERCP (n=9) or PTC (n=1) in combination with an enlarged, malfunctioning pancreas in the period 1992-1999. All patients were males and the age at presentation varied from 19 to 80 (mean 55) years. Weight loss (n=10), jaundice (n=8) and pruritus (n=7) were the main presenting symptoms. One patient had a history of alcohol abuse. None of the patients had clinical evidence of concurrent IBD; colonoscopy was performed in six patients with normal findings. Serum pANCA was negative in all seven cases tested.

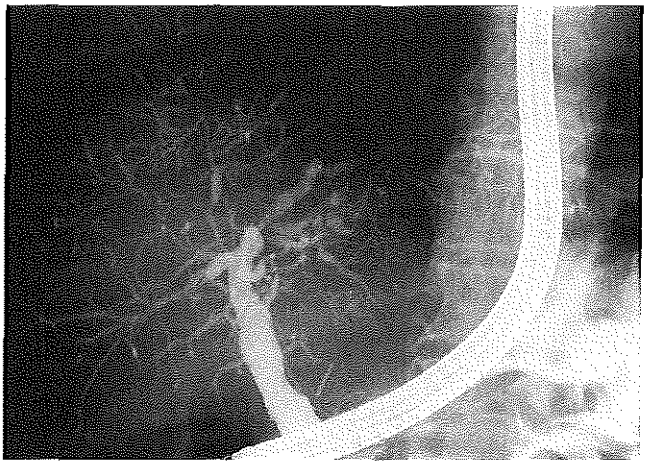

Figure 2. Endoscopic retrograde cholangiography in patient no 3 demonstrating multiple intrahepatic and extrahepatic biliary strictures and focal narrowing of the distal common bile duct.

Pancreas

At presentation, carcinoma of the pancreas was suspected in all patients. CT was performed in 9 patients and demonstrated diffuse pancreatic swelling (n=3) or focal tumor-like (n=3) or diffuse (n=3) enlargement of the pancreatic head region. On US diffuse, sonolucent swelling was found in four cases and a mass confined to the head region in six. Pancreatography, performed in six patients, revealed a narrow, irregular pancreatic duct (n=3) (Fig 3), an irregular duct with focal narrowing, dilatations and ductectasia of side branches (n=2) or a pre-papillary tight stenosis (n=1). Severe exocrine pancreatic insufficiency (fecal elastase-1 content <0.015 mg/g) was found in six of seven patients tested and endocrine insufficiency in four out of ten.

During laparotomy, performed in five patients (no. 3, 7-10), the pancreas proved to be markedly enlarged and firm; on palpation notable firmness of the common bile duct was also noted. Pancreatic tissue was obtained by per-operative needle biopsy (no. 8 and 9) and pancreatoduodenectomy (no. 7). Histological evaluation demonstrated chronic fibrosing pancreatitis with lymphoplasmacellular and eosinophilic infiltrates (Fig 4) and fibrosing inflammation of the common bile duct. Malignancy was not found. Choledochoduodenostomy was performed in one patient (no.10).

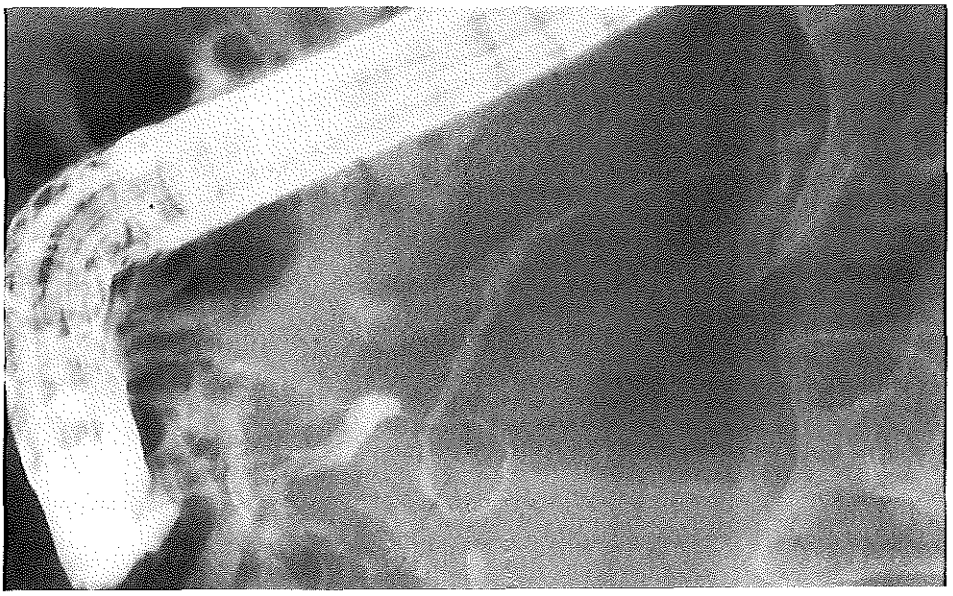

Figure 3. Endoscopic retrograde pancreatography of patient no 3 showing a narrow, irregular pancreatic duct.

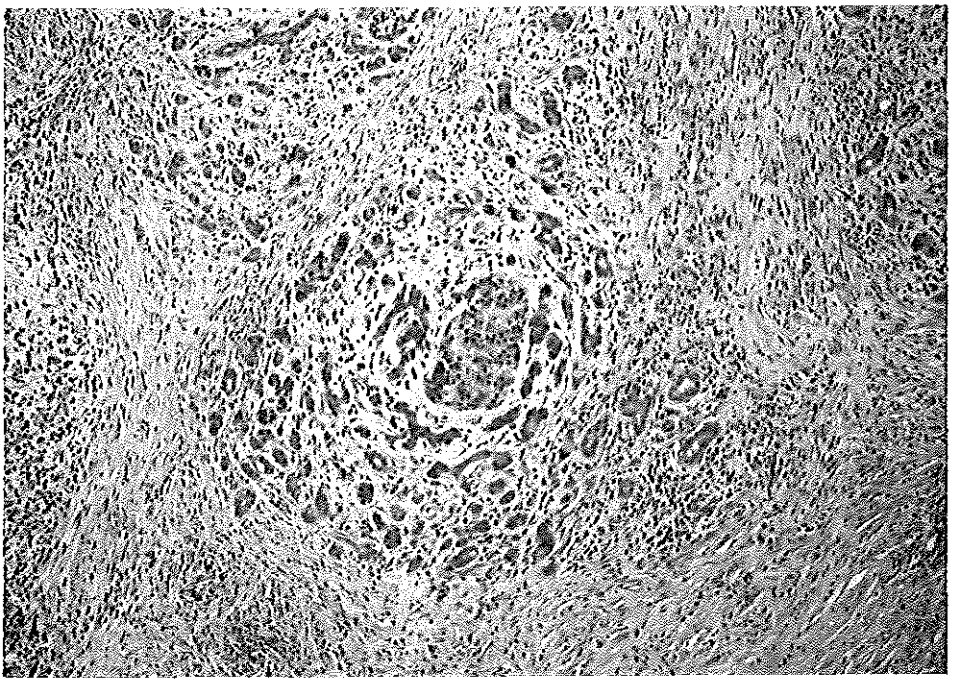

Figure 4. Pancreatic histology of patient no 7 demonstrating fibrosing pancreatitis with eosinophilic and lymphoplasmacellular infiltrate.

Biliary tree and liver

Laboratory examination showed cholestasis in all patients, with hyperbilirubinaemia in 8 (Table I). Cholangiography revealed intrahepatic and extrahepatic bile duct strictures and suggested an enlarged pancreatic head in all cases. Liver histology, available for eight patients, was consistent with chronic cholestasis (Table I). Portal infiltrates were mainly of lymphoplasmacellular and eosinophilic origin. The degree of interface hepatitis varied from absent to slight and the amount of fibrosis from absent to marked. Pericholangiolar "onion-skin" fibrosis was not observed.

Treatment and course of disease

Seven jaundiced patients (no. 2, 3, 4, 6, 7, 9, 10) received temporary biliary stent therapy for stenosis of the distal common bile duct, resulting in decreases of serum bilirubin level and other liver test parameters.

Five patients were treated with immunosuppresives (no. 1, 2, 6, 8, 10). Four (no. 1, 2, 6, 8) received prednisone (30-60 mg/day) tapered to maintenance doses (5-10 mg/day) within 2 months; two patients (no. 1 and 2) also took UDCA and one (no. 6) received concomitant azathioprine 50 mg/day. Complete biochemical remission ensued in all four cases within six months. In one patient (no. 6) the centrally located intrahepatic bile duct strictures and the common bile duct narrowing in the pancreatic head region had disappeared after three months of prednisone, azathioprine and biliary stent therapy. In the other 3 cases (no 1, 2, 8) follow-up cholangiography after two years showed marked improvements. Prednisone treatment was withdrawn after approximately one year in patients 1, 2 and 6. In these cases serum biochemistry remained normal during follow-up. In patient 8, prednisone was also withdrawn after one year. After three months serum levels of APh, γGT, AST and ALT increased again and prednisone therapy was reintroduced, followed by rapid biochemical normalization. In patient 10, prednisone (10 mg/day), azathioprine (50 mg/day) and pancreatic enzyme treatment were started six years after presentation. At that time liver histology showed cirrhosis. During the 2 month follow-up period serum bilirubin level decreased from 60 to 53 μmol/l and serum albumin levels rose from 32 g/l to 37 g/l.

One patient (no. 1) with manifest diabetes mellitus became normoglycemic during corticosteroid therapy. Patients 2 and 6 developed transient diabetes mellitus during corticosteroid treatment. In patient 6, pre-treatment fecal elastase-1 content of <0.015 mg/g

increased to normal values of 0.089 mg/g, 0.159 mg/g and 0.249 mg/g after three, five and twelve months, respectively, of combined prednisone-azathioprine treatment. Pancreatography was not repeated.

UDCA (600 mg/day) treatment in patient 4 did not result in sustained improvement in serum liver biochemistry, whereas in another (no. 5), marked improvements, although no normalization, in serum liver function tests was found after starting treatment with UDCA (750 mg/day). In this patient, a second ERCP performed after two years of UDCA therapy, showed largely the same abnormalities. Patient 10 remained jaundiced despite treatment with UDCA (750 mg/day). In contrast, complete biochemical remission without any medical intervention was observed in patients 3 and 9.

In case 7, initial ERCP showed a stenosis of the common bile duct in the pancreatic region; no adequate images of the intrahepatic bile ducts were obtained. CT and laparoscopic intra-abdominal US showed a tumorous pancreatic mass and multiple enlarged regional lymph nodes. Pancreatoduodenectomy was performed. Histological examination demonstrated a chronic fibrosing inflammatory process involving the pancreas and common bile duct and non-specific, reactive lymph node abnormalities. Postoperatively, serum bilirubin levels normalized completely. Six weeks after the operation, however, he was readmitted because of recurrent jaundice (bilirubin 304 µmol/l). ERCP now showed numerous intrahepatic bile duct strictures (Fig 5). US and angiography of the hepatic artery, performed to rule out ischemic damage to the biliary tree, were normal. No specific treatment was instituted. Serum bilirubin levels normalized spontaneously while APh and γGT remained moderately elevated. Again, two years later symptoms of weight loss and pruritus recurred, accompanied by marked icteric cholestasis (bilirubin 120 µmol/l) and notable hypergammaglobulinaemia (serum IgG 31.7 g/l, normal <15.5).

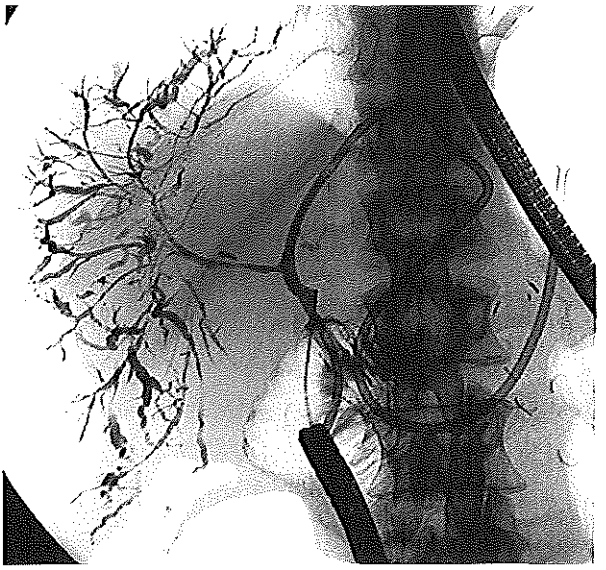

Figure 5. Endoscopic retrograde cholangiography 6 weeks after pancreatoduodenectomy was performed in patient no 7, showing severe multiple bile duct strictures and dilatations.

Discussion

In this report ten patients with an intriguing inflammatory disorder of the pancreato-biliary tract are described. A number of comparable cases has been reported during the last 25 years (Table II). Usually these patients were considered to have PSC with coincidental idiopathic chronic pancreatitis. Many descriptive names have been used, including 'lymphoplasmacytic sclerosing pancreatitis with cholangitis' (34), 'pancreatic pseudotumor with idiopathic fibrosclerosis' (29), 'inflammatory pseudotumor from sclerosing cholangitis' (25) and 'primary sclerosing cholangitis mimicking chronic pancreatitis' (30). Since we became aware of this particular syndrome we recognized several additional cases, particularly among patients previously regarded as having an atypical form of PSC or an ill-defined cholestatic-pancreatic disease. We speculate that this disorder may not be as rare as is suggested by the sporadic cases reported previously. Our experience suggests that the presenting features, in particular weight loss and painless obstructive jaundice leading to a high clinical suspicion of pancreatic cancer, is more or less uniform. In contrast, the individual natural history of the disease seems to vary substantially, ranging from a clinically unremarkable, non-progressive course to a course dominated by recurrent episodes of obstructive jaundice, either secondary to benign

compression of the common bile duct or to multifocal intrahepatic bile duct stricturing.

Obviously, the key question is whether our patients did not suffer from 'ordinary' PSC with a mere coincidence of idiopathic chronic pancreatitis. There are several arguments in favor of this hypothesis. Both PSC and 'sclerosing pancreatocholangitis' mainly affect male patients and both conditions are characterized by cholestasis. Also, in both diseases morphological bile duct abnormalities are very much comparable. On the other hand, there are a number of significant differences. Pancreatic enlargement suggesting malignancy, with exocrine and endocrine pancreatic insufficiency, is rarely observed in PSC (6, 7). IBD was neither found in our patients nor in any of the previously reported cases (13, 22-36, 38-42) while the prevalence among patients with PSC is at least 60% (43-47). Further, the mean age of 55 years at presentation in the present series and of 53 years in the literature cases (Table II) would be relatively high for PSC (43-47). In contrast to reported prevalences of serum pANCA of over 50% in PSC (48-50), none of our patients tested positive. Finally, marked improvements in morphological bile duct abnormalities and serum liver biochemistry following corticosteroid treatment were observed in a number of our patients. Such response is definitively not likely - and has not been reported - in PSC (51, 52). Although we acknowledge that these differences with 'ordinary' PSC provide us with no more than circumstantial evidence, most data seem to indicate that our patients did not have PSC with some form of coincidental pancreatic involvement but rather suffered from another disease. Since the fibrosing inflammatory process both affects the biliary tract and pancreas (13, 34) 'sclerosing pancreato-cholangitis' (53) may be an acceptable name for the condition.

Painless obstructive jaundice secondary to pancreatic enlargement constitutes a well-known diagnostic problem and a reliable distinction between cancer and chronic pancreatitis remains difficult, if not impossible, without histological examination. The initial clinical presentation of sclerosing pancreato-cholangitis can be highly suggestive of pancreatic cancer. In this context it should be noted that none of our patients had chronic pain suggesting the possibility of chronic pancreatitis. In general, in approximately 5% of patients presenting clinically with pancreatic malignancy pancreatoduodenectomy is performed for what postoperatively appears to be a misdiagnosis (54). As illustrated by our experience and by other reports (11, 13, 16, 30, 34, 36, 38) patients with sclerosing pancreato-cholangitis may be subjected to pancreato-duodenectomy for a benign disorder. One way to prevent this, at least in theory, would be to deliberately aim at adequate

cholangiography of the entire biliary tree in order to detect potential (intrahepatic) strictures. However, this would not prevent mis-diagnoses in case of rapid post-operative development of biliary strictures, a course also described previously by Stathopoulos et al. (36). Furthermore, inflammatory pancreatic enlargement, mimicking carcinoma, may also occur in the absence of intrahepatic biliary abnormalities (9, 11-13, 16).

The symptomatic treatment of sclerosing pancreato-cholangitis is straightforward. Bile duct obstruction due to pancreatic swelling can be treated by placement of biliary endoprostheses and exo- and endocrine insufficiency with pancreatic enzyme suppletion and antidiabetic drugs. Experience with treatment of the underlying inflammatory disease process is very limited. Ideally, the aim of therapy should be to restore normal pancreatic function and bile flow. Currently, the few data available suggest that the therapeutic response to corticosteroids can be excellent. We as well as others (23, 29, 35, 37, 42) found marked improvements in serum liver function tests in patients treated with corticosteroids. More importantly, biliary strictures disappeared or diminished in several patients and improved pancreatic function was observed as well. It should be noted, however, that we and others (22, 32, 39, 40) have also witnessed a favorable, non-progressive clinical course without immunosuppressive treatment. Further study of the etiology and natural course of the disease seems mandatory and hopefully will clarify whether and when medical therapy is indicated and what should be the primary aim of treatment.

The putative beneficial response to corticosteroids suggests that sclerosing pancreato-cholangitis has an immune-mediated etiology. The reported association with Sjögren's disease (22, 26, 28, 29, 40), also found in one of our patients, and the remarkable resemblance of sialographic and cholangiographic findings (55, 56) make it tempting to assume that these disorders share a common pathogenesis. It has also been suggested that this disorder is part of the spectrum of 'idiopathic multifocal fibrosis' (29, 35, 36, 41). This is supported by the fact that of 26 previously reported patients six also had Sjögren's disease, two had a fibrotic thyroid tumor, two had a retroorbital mass and two had retroperitoneal fibrosis (Table II).

In conclusion, we report on ten patients with a distinct inflammatory syndrome involving the pancreato-biliary tract. Patients typically are males and present with jaundice, weight loss and endocrine and/or exocrine pancreatic insufficiency. Imaging studies usually are compatible with a diagnosis of pancreatic cancer. The clinical evolution of the syndrome is highly variable. Clinicians should be aware of this condition that may

mimick both PSC and pancreatic cancer. Preliminary experience indicates that there may be a favorable response to immunosuppressive treatment.

Table I: Patient characteristics at presentation.

pat	sex	age (yrs)	weight loss (kg)	IBD	bilirubin (µmol/l)	APh (U/l)	liver histology	fecal elastase-1 (mg/g)	diabetes	concomitant disorders
1	M	63	6	absent	14	536	fib:mo, ifh, pi	n.a.	yes	
2	M	19	>5	absent	150	569	fib:mo, ifh, pi	n.a.	no	
3	M	48	30	absent	126	212	fib:mo, pi	<0.015	yes	M.Sjögren
4	M	80	>2	clinically: no	233	473	n.a.	<0.015	yes	hypothyroidism
5	M	61	20	absent	13	614	fib:mo, pi	<0.015	yes	
6	M	52	7	clinically: no	108	327	ifh, pi	<0.015	no	
7	M	57	12	absent	114	288	ifh, pi	<0.015 (Whipple)	no	
8	M	61	12	absent	47	1194	fib:mo, ifh, pi	n.a.	no	
9	M	46	20	clinically: no	174	269	n.a.	0.255	no	
10	M	63	10	clinically: no	88	2190	fib:se, pi	0.022	no	

Pat: patient; n.a.: not available; IBD: inflammatory bowel disease; APh: alkaline phosphatase;
fib: fibrosis; ifh: interface hepatitis; pi: portal infiltrate; mo: moderate; se: severe.
Fecal elastase concentration <0.100 mg/g indicates severe exocrine pancreatic insufficiency.

Table II: Cases reported in the literature.

Author	year	n	sex	age (yr)	jaundice	exocrine pancreatic insufficiency	diabetes	concomitant disorders
Waldram	1975	2	M/F	36 / 31	yes	yes	yes	M.Sjögren / M.Sjögren
Sjögren	1979	1	M	43	slight	yes	yes	submandibular gland fibrosis
Scully	1982	1	M	55	yes			
Jafri	1983	1	M	41	yes			
Montefusco	1984	1	F	48	yes			M.Sjögren
Thompson	1985	1	M	51	yes	yes	yes	
Versapuech	1986	1	M	63	no	yes	yes	M.Sjögren
Clark	1988	2	M	62/63	yes			fibrotic thyroid tumor and retroorbital soft tissue mass / Dupuytren
Zoltán Lászik	1988	1	M	37	no	yes		
Barreda	1989	1	F	30	yes			M.Sjögren
Bastid	1990	1	M	78	yes	yes		
Sood	1990	1	F	44	yes	yes	yes	
Kawaguchi	1991	2	M	69 / 74	yes			
Laitt	1992	1	F	51	yes			Riedel's thyroiditis and retroperitoneal fibrosis
Stathopoulos	1995	2	2 M	49 / 27	yes			
Chutaputti	1995	1	M	69	yes			retroperitoneal fibrosis
Beck	1996	1	F	59	yes			
Ectors	1997	1	M	77	yes			
Pohl	1997	1	M	68	no	yes	yes	
Nieminen	1997	1	M	32	yes		yes	M.Sjögren, pulmonary interstitial nodular infiltrations
Levey	1998	1	M	58	yes			large hyperplastic axillary lymph node, retroorbital mass
Kazumori	1998	1	M	58	yes		yes	

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Chapter 5

BILE DUCT LESIONS IN PORTAL VEIN THROMBOSIS

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Nederlands Tijdschrift voor Geneeskunde (Dutch), 1999; 143: 2057-2062.

Abstract

Four patients with portal vein thrombosis, three men of 51, 45 and 31 years and one woman of 22 years, presented with symptoms or signs of biliary obstruction. Laboratory investigations revealed cholestasis. Cholangiography demonstrated smooth indentations of the common bile duct consistent with external compression by collateral veins. The clinical course varied from spontaneous resolution of both symptoms and serum biochemical abnormalities to persistent cholestasis. In two cases, surgical treatment (splenorenal shunt and hepaticojejunostomy) failed due to the presence of numerous collateral veins. Biliary strictures secondary to the formation of a portal cavernoma, so-called portal biliopathy, is a fairly unknown complication of portal vein thrombosis. Although the majority of patients are asymptomatic, porto-systemic shunt surgery or endoscopic biliary intervention may be indicated in symptomatic cases.

Introduction

A network of collateral veins may develop in the hepatoduodenal ligament following thrombosis of the portal vein (1-3). Ultrasonographic imaging of this conglomerate of veins, which is called a portal cavernoma or cavernomatous transformation of the portal vein, may produce a characteristic picture (Fig 1).

The most frequent complication of portal vein thrombosis is bleeding from oesophageal or gastric varices (1, 4) or, less common, from ectopic varices in the duodenum or rectum (5). A rare and relatively unknown complication of portal vein thrombosis, involving the biliary tract, will be discussed by means of the case histories described below.

Case histories

Patient A, a 51-year-old male, presented with oesophageal variceal bleeding 20 years ago. Treatment consisted of a splenectomy. Portosystemic shunt surgery failed due to massive per-operative blood loss from collateral veins. On the basis of histological, ultrasonographical and angiographical examinations the diagnosis 'thrombosis of the portal and superior mesenteric veins' was made. A cause could not be identified.

Ten years ago, he presented for the first time with abdominal pain, jaundice, dark urine and discoloured stools. Laboratory investigations revealed cholestasis (Table I). Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated multiple strictures of the common bile duct. A diagnosis of primary sclerosing cholangitis was considered likely.

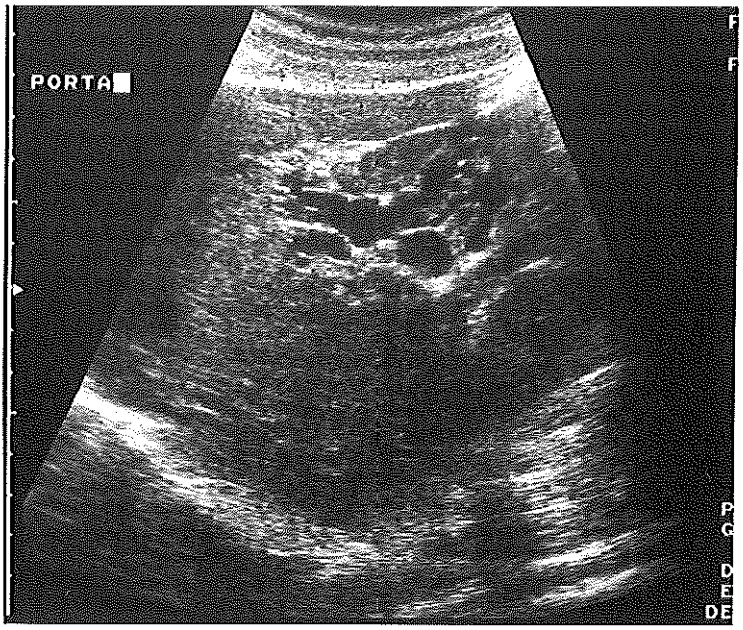

Figure 1. Ultrasonography of a portal cavernoma.

Within two weeks symptoms disappeared and serum liver tests normalized. Two years later, the same signs and symptoms recurred. At ERCP small intrahepatic stones were found in addition to the previously known abnormalities. A nasobiliary drain (Fig 2) was introduced for lavage of the biliary tree. Treatment had to be stopped because of the development of fever 24 hours later. The symptoms disappeared after antibiotic therapy and the patient was discharged in good general condition. After a duodenal variceal haemorrhage 1 year later and recurrent oesophageal variceal bleeding 2 years later, endoscopic sclerotherapy was initiated resulting in variceal eradication. One year ago he presented again with jaundice. ERCP revealed small concrements and smooth, undulating strictures of the common bile duct. Some small stones drained off after papillotomy. Just like six years ago the patient developed fever after biliary lavage but it disappeared as a result of antibiotic treatment. During the following year he was asymptomatic but serum liver tests indicating cholestasis persisted. Subsequently, an endoprosthesis was placed in the common bile duct for a period of 8 weeks. Six months later, he was asymptomatic and the serum liver tests had normalized.

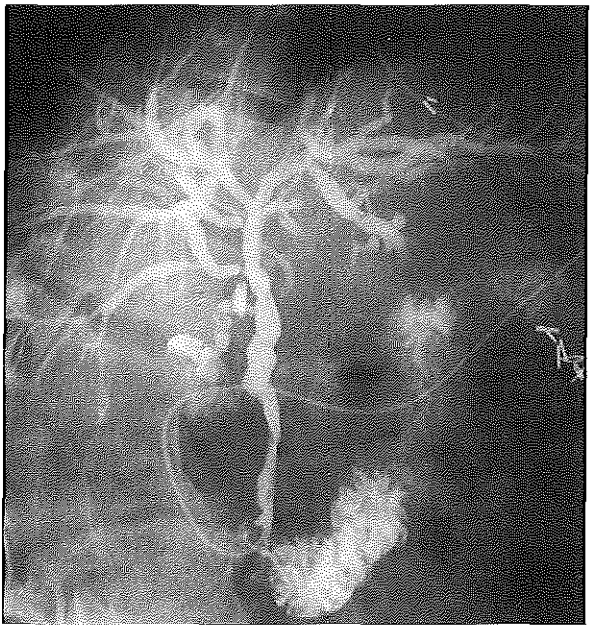

Figure 2. ERCP through nasobiliary drain.

Patient B, a 45-year-old male with a history of cholecystectomy for cholelithiasis and pancreatojejunostomy for chronic pancreatitis, was found by ultrasonography to have portal vein thrombosis with cavernomatous transformation. Because of recurrent pancreatitis two years later, an ERCP was performed; smooth, undulating strictures of the common bile duct, consistent with venous impressions, were demonstrated (Fig 3). A year ago he complained of upper abdominal pain; laboratory examination showed cholestasis (Table I). ERCP demonstrated smooth narrowing of the distal common bile duct, consistent with external compression, and slight bile duct dilatation with small calibre changes in the proximal part. A stent was placed endoscopically. Because of cholangitis due to stent clogging the endoprothesis had to be replaced 4 times during a period of 6 months. An attempt to create a surgical biliodigestive anastomosis failed because of the presence of multiple venous collaterals. Subsequently, two sessions of endoscopic balloon-dilatation of the distal common bile duct were performed but the serum liver tests did not improve. It is not clear whether this was caused primarily by compression of the distal common bile duct due to enlargement of the pancreatic head or biliary abnormalities secondary to the portal cavernoma. Perhaps a combination of the two factors is responsible. Recently, a metal 'self-expandable' endoprosthesis was placed in the distal common bile duct.

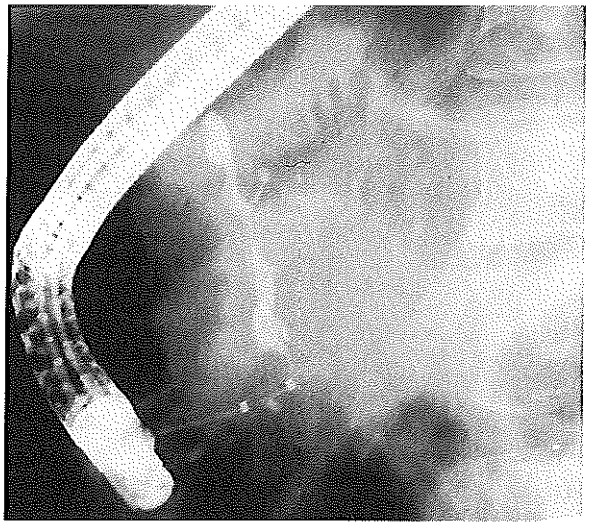

Figure 3. ERCP showing smooth, undulating strictures of the common bile duct.

Patient C, a 22-year-old female, presented with biliary colic-like pain and vomiting. Her medical history had been remarkable; the following diagnoses had been established: 'polyartritis nodosa', 'recurrent pericarditis', 'superior vena cava syndrome due to mediastinal lymphadenopathy', 'agenesis of the intrahepatic part of the inferior vena cava' and 'multiple oesophageal and gastric variceal haemorrhages due to thrombosis of the portal, splenic and superior mesenteric veins. In contrast to previous investigations, laboratory examination showed hyperbilirubinaemia (Table I). At ultrasonography multiple venous collaterals surrounding the common bile duct were seen. ERCP showed a smooth, flexible narrowing in the distal common bile duct, consistent with compression by collaterals. The signs and symptoms disappeared spontaneously and did not recur within the next four years.

Patient D, a 31-year-old male, had always been healthy until he was admitted with abdominal pain, fever and an infiltrate in the right quadrant 9 years ago. Laboratory examination showed, in addition to an elevated erythrocyte sedimentation rate of 75 mm/hour and leucocytosis of 24.9×10^9 /l, liver abnormalities indicative of cholestasis (table 1). Blood cultures were positive for streptococci. Ultrasonography showed portal vein thrombosis with a portal cavernoma. ERCP demonstrated biliary abnormalities comparable to those seen in patients A and B (Fig 2, 3). Despite extensive investigations no explanation for this clinical picture was found. The patient recovered spontaneously and the serum liver

tests normalized within a period of 6 months. Two years later he presented with symptoms of acute appendicitis. At laparotomy a retrocaecal inflamed appendix with adhesions to surrounding structures was found. Microscopical examination of the excised appendix showed appendicitis with perforation and peritonitis. The patient remained asymptomatic for the next 9 years. Retrospectively, it seems plausible that the first period of abdominal symptoms and septicaemia was probably also the result of appendicitis. The septicaemia may have caused thrombosis of the portal vein and, subsequently, the bile duct lesions.

Table 1. Serum liver tests in the 4 patients with portal biliopathy at the time of diagnosis.

	upper limit of normal	patient			
		A	B	C	D
total bilirubin	17 µmol/l	149	90	28	10
alkaline phosphatase	117 U/l	413	2765	64	908
γ-glutamyltranspeptidase	49 U/l	322	627	29	512
aspartate aminotranspherase	37 U/l	127	211	15	26
alanine aminotranspherase	41 U/l	253	197	10	75

Discussion

Portal hypertension secondary to biliary liver diseases, such as primary biliary cirrhosis and primary sclerosing cholangitis, is a well-known, frequently occurring finding. In contrast, biliary abnormalities resulting from (formation of venous collaterals in) portal hypertension are rare and relatively unknown. The patients had portal vein thrombosis in all published cases.

Bile duct lesions in portal vein thrombosis, also called 'portal biliopathy' (6), is rarely seen in the western world since the prevalence of portal vein thrombosis is low (1). In contrast, in Asian countries such as India, portal vein thrombosis is much more common and is one of the most important causes of portal hypertension (7). The reason for this considerable difference in prevalence is unknown. In more than 90% of cases in an Indian study, a cause could not be found (8). Cholangiographical studies show that biliary abnormalities are often present (80-100%) in these patients (8-10). The vast majority of these

patients remain asymptomatic. Mild to moderate elevations of serum bilirubin, alkaline phosphatase and transaminase levels are often found (9, 10). However, severe complications, such as cholestatic jaundice, cholangitis, abdominal pain (6, 11, 12) and secondary biliary cirrhosis (11), can occur and may even be the first manifestation of portal vein thrombosis (10, 11). As demonstrated by the course of disease in some of our cases, cholestasis may be transient. This could result from the passage of biliary sludge or concrements that were caused by the biliary strictures. Other possible explanations could be that biliary compression decreases over time due to the development of new venous collaterals elsewhere or due to initial other problems, such as septicaemia as in patient D.

Two, not mutually exclusive, explanations for the pathogenesis of this disorder have been suggested in literature. In portal vein thrombosis portoportal collaterals may develop around the occluded part of the vein; this phenomenon can be considered a natural adaptation and by-pass mechanism aimed at the maintenance of portal perfusion of the liver and reduction of the venous pressure in the venous splanchnic compartment. Collaterals that surround the bile ducts may lead to bile duct compression (8, 13). The second hypothesis is that thrombosis also occurs in the efferent veins and afferent arteries of the biliary tree during thrombotic occlusion of the portal vein. This might lead to ischaemic damage to the biliary ducts with subsequent development of fibrosis and strictures (10, 11).

Imaging studies may show involvement of the entire biliary tree, but the abnormalities are usually limited to the common and left hepatic bile ducts (8, 10). Smooth, undulating narrowing is seen in the most characteristic cases. Strictures, segmental dilatation, irregularities of the bile duct wall, pruning of intrahepatic bile ducts (8, 10) and concrements (6, 8, 11) sometimes in combination with calcification of the portal cavernoma (12) can also be found. The abnormalities may mimic the ones that can be found in primary sclerosing cholangitis or cholangiocarcinoma (10, 14). Therefore, the terms 'pseudo-sclerosing cholangitis' or pseudo-cholangiocarcinoma' (9) may be used to describe the abnormalities. The biliary lesions in portal biliopathy can be distinguished in particular from the abnormalities in primary sclerosing cholangitis by the smoother, undulating narrowing of the biliary lumen (8, 10). Sometimes it is possible to visualize the collaterals in the wall of the bile duct by means of ultrasonography (Fig 4).

Experience with the therapeutic possibilities for this disorder is limited. The construction of a surgical shunt, presumably the most rational approach, may result in complete disappearance of the biliary abnormalities (11, 15-17). Technically, however, this is not

always feasible. If other veins, in addition to the portal vein, are also occluded, shunt surgery may be impossible. Finally, biliary abnormalities can persist after the construction of a shunt. This could be an argument for the hypothesis that some patients have fixed (possibly ischaemic) strictures. In these cases, balloon-dilatation (10) or hepaticojejunostomy (6) may be indicated in second instance. Endoscopic placement of a stent (12-14, 18) or balloon-dilatation (11) may be successful, with or without additional extraction of biliary stones (15). One should be aware of the problems and dangers of a surgical approach. Surgical exploration of the hepatoduodenal ligament and identification of the bile ducts can be associated with significant blood loss due to extensive vascularisation (12), sometimes with a fatal outcome (6). If biliary tract surgery is considered, this should preferably be performed after portal decompression (6).

Portal biliopathy should be included in the differential diagnosis for patients with portal vein thrombosis and cholestasis. A non-intervention policy seems justified for asymptomatic patients. For symptomatic patients, surgical or endoscopical treatment may be chosen, depending on the extent of the thrombosis and the type of the biliary lesions.

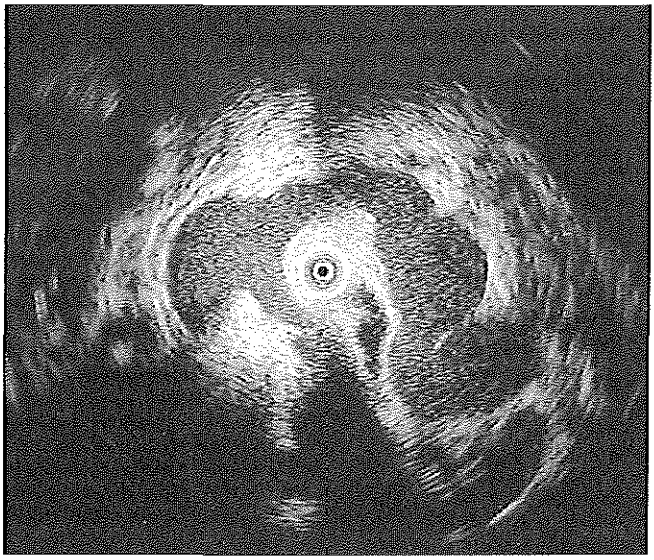

Figure 4. Intraluminal ultrasonography within the common bile duct showing venous collaterals adjacent to the bile duct wall.

Table 2. Most important causes of biliary strictures (19).

Primary sclerosing cholangitis
Ischaemia of bile ducts
Previous biliary surgery
'Graft-versus-host' disease
Rejection of liver transplant
Infusion of cytotoxic medication in the hepatic artery
Cholangiocarcinoma
Choledocholithiasis
AIDS-related cholangiopathy
Sclerosing pancreato-cholangitis (20)
Portal vein thrombosis

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Part II

Prognostication of Immunocholangitis

Chapter 6

THE PROGNOSTIC SIGNIFICANCE OF ANTIMITOCHONDRIAL ANTIBODY PROFILE TESTING IN PRIMARY BILIARY CIRRHOSIS

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Submitted

Abstract

In PBC the rate of disease progression varies considerably between individuals. On the basis of serological subtyping 4 AMA profiles (A, B, C and D) can be defined. The intriguing finding of previous studies that profile C/D is associated with a progressive course and profile A/B with a benign, non-progressive course is still a question of debate. We investigated whether AMA profiles predicted the clinical course for a cohort of Dutch PBC patients. Serum samples from 38 AMA-positive progressive patients (34 female; 2 samples per patient; median interval 2.5 yrs), 31 AMA-positive patients without evidence of progression for at least 6 years (26 female), 5 AMA-negative PBC patients, 5 non-PBC decompensated cirrhotics and 5 healthy volunteers were assessed. Progressive PBC was defined as the occurrence of liver transplantation (n=15), liver-related death (n=3), variceal bleeding (n=3), ascites (n=4) and histological cirrhosis (n=13). AMA profiles were determined without knowledge of the clinical data. In the progressive AMA-positive group, 13% (n=5) had profile A/B, 84% (n=32) had profile C/D; 1 case was only AMA-positive in immunofluorescence. A change from profile A/B to profile C/D or vice versa was not observed. In the non-progressive group, 13% (n=4) had profile A/B, 77% (n=24) profile C/D; 10% (n=3) had no profile. An AMA profile was not determined for the 15 AMA-negative control samples.

In conclusion, AMA profile testing yields reliable, reproducible results. However, our results do not support the suggestion that AMA profiles should be used as independent indicators of the ultimate clinical outcome of PBC. The divergent results of this and previous studies may be explained by the selection of different PBC patient populations.

Introduction

Demonstration of serum antimitochondrial antibodies (AMA) forms the corner stone of the diagnosis of primary biliary cirrhosis (PBC) (1-4). In addition to the diagnostic significance of AMA, prognostic value has been attributed to four PBC-specific AMA-subtypes which are based on the presence of anti-M2, -M4, -M8 and -M9 antibodies, respectively (5-8). Among PBC patients with anti-M4 and/or anti-M8 antibodies (AMA profile C/D) the course of the disease was progressive, leading to cirrhosis and hepatic decompensation, whereas the course among patients without anti-M4 and anti-M8 antibodies (AMA profile A/B) was found to be non-progressive for at least 10 years (9-12).

Up to now, AMA-subtype determination was not considered a potential tool for assessment of the prognosis. This may at least partly be related to the reported inability of other groups to reproduce the original laboratory results (13-15). The aim of this study was to confirm the previously reported prognostic value of AMA-subtypes for a heterogeneous population of Dutch PBC patients using the original laboratory facilities.

Patients and methods

From each of 38 AMA-positive PBC patients with progressive disease two serum samples were collected. The diagnosis of PBC was based on a combination of positive antimitochondrial antibodies (AMA) at a titre of ≥1:40 as shown by indirect immunofluorescence (IF), cholestatic serum liver tests, and compatible/diagnostic histological features. Progression was defined as: liver transplantation (for stage IV disease), liver-related death, variceal bleeding, ascites or histological stage IV disease. The main clinical features of these patients are in listed in table I. We tested two samples per patient in order to determine whether the profile remains the same over time. The interval between the two samples varied from one day to 10 years (median 2.5 years). Samples from transplanted patients were obtained before the procedure. In theory, and according to previous studies, the AMA profiles of sera from this group were expected to be C or D in (nearly) all cases.

In addition, serum samples from 31 AMA-positive non-cirrhotic PBC patients, who had remained clinically stable for at least 6 years, were analysed. The AMA profile of a proportion of these sera was expected to be A or B. Furthermore, serum samples from five PBC patients who tested AMA-negative with IF, five non-PBC patients with decompensated cirrhosis (alpha1-antitrypsin deficiency n=1, primary sclerosing cholangitis n=2 and alcoholic liver disease n=2) and five healthy volunteers were assessed. The main characteristics of these patients and volunteers are listed in table II. Thus a total of 122 serum samples were collected at the University Hospital Rotterdam and transported frozen to the Eberhard-Karls-University Hospital Tübingen, Germany, for analysis.

The AMA-subtypes were determined according to previously described techniques (12), without any knowledge about the corresponding patient. Samples were only identified by a number. The samples were tested for the presence of antinuclear antibodies (ANA) and smooth muscle antibodies (SMA). The serum samples were assigned an AMA profile as follows: profile A was defined as only anti-M9 positive in ELISA and Western blot, profile B as anti-M2 positive in complement fixation test (CFT) and/or ELISA, irrespective of the

presence or absence of anti-M9, profile C as anti-M2 in association with anti-M4 and/or anti-M8 in ELISA, irrespective of the presence or absence of anti-M9 and profile D as anti-M2 in association with anti-M4 and/or anti-M8 in ELISA and CFT, irrespective of the presence or absence of anti-M9. Subsequently the AMA profile results were analysed in relation to the presence or absence of PBC and the clinical course.

Results

Of the 69 AMA-positive PBC patients, 81% had profile C/D, 13% had profile A/B, 3% were only AMA-positive in IF and 3% were AMA-negative in both IF and ELISA/CFT (Fig 1).

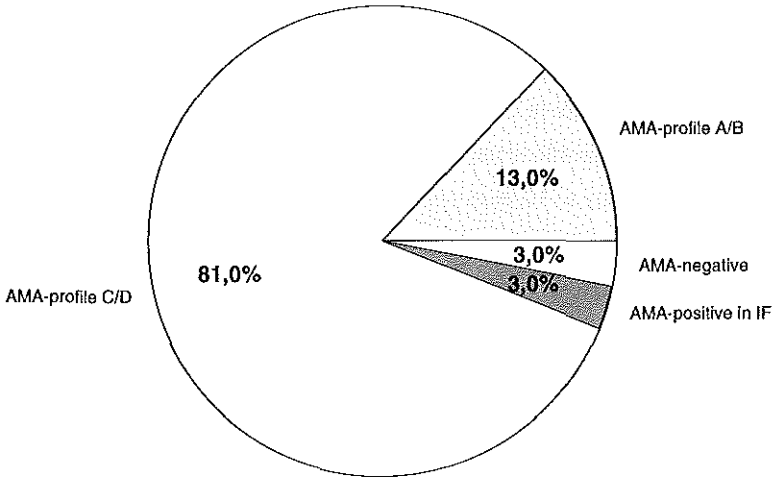

Figure 1. Distribution of AMA profiles among 69 AMA-positive (IF) PBC patients.

Antibody profiles for 38 PBC patients with a progressive course

Thirty-two (84%) of these patients were found to have AMA-profile C/D and 5 (13%) profile A/B (Table III). One patient tested only AMA-positive in IF, whereas ELISA as well as CFT were negative for all AMA-subtypes in both samples. For patients with profile A/B or without an AMA profile, progression was characterized by liver-related death, liver transplantation for end-stage cirrhotic disease and histologically documented cirrhosis in two cases each. AMA profile A was found for one patient with stage IV disease while the other

four had profile B. The AMA profile remained stable over time, since a change from profile A/B to profile C/D or vice versa was not observed. Eighty percent (4 of 5 patients) and 60% of the profile A/B patients tested positive for ANA and SMA, respectively. Eighty-four percent and 81% of the profile C/D patients tested positive for ANA and SMA, respectively.

Antibody profiles for 31 clinically stable AMA-positive PBC patients

Twenty-four (77%) of these patients were found to have profile C/D (Table III), 13% had profile A/B. Two patients were AMA-negative in IF, ELISA and CFT, and one patient was only AMA-positive in IF. Fifty percent and 75% of the patients with profile A/B tested positive for ANA and SMA, respectively. Thirty-three percent and 88% of the patients with profile C/D tested positive for ANA and SMA, respectively.

Antibody profiles for 15 negative controls

All AMA-negative PBC patients (n=5), non-PBC decompensated cirrhosis patients (n=5) and healthy volunteers (n=5) were AMA-negative in both IF and ELISA/CFT.

Discussion

In this study it appeared that 13% of patients with clinically progressive PBC have antimitochondrial antibodies of profile A/B, the profile that was previously found to predict a non-progressive course (12). Therefore we could not confirm that a progressive course is more or less restricted to patients exhibiting AMA-profile C/D. Furthermore, in this study the vast majority (81%) of AMA-positive PBC patients had profile C/D, thereby the potential impact of the AMA profile on the selection of patients for follow-up and evaluation of experimental treatment modalities may be relative.

A number of factors may explain the discrepancy in the findings between the present and previous studies. Selection bias seems to be the most likely explanation. The University Hospital Rotterdam is a tertiary referral centre for patients with liver disease in the Netherlands and therefore attracts proportionally more PBC patients with advanced liver disease, while the German PBC population (12) was partly chosen from screening programmes for autoantibodies. The fact that a relatively high proportion of stage I and II patients (89%) was included in the study by Klein et al. (12) with a consequently more favourable five-year survival rate compared to other PBC cohort studies (16-19) further supports the suggestion that the study populations were not comparable. Secondly, other

factors besides PBC itself may influence the rate of disease progression. The majority of patients with a progressive course and AMA profile A/B also tested positive for ANA and/or SMA, so other (overlapping) autoimmune features may have contributed to the final clinical outcome. However, it should be noted that all patients with a progressive course had proven PBC according to established diagnostic criteria and the majority of stable patients also tested positive for ANA and/or SMA. Finally, clinical outcome is not equivalent to clinical course. The retrospective design of the present study does not allow us to draw conclusions about whether AMA profiles differentiate between a rapid and a slow, but progressive, course. Observations during more prolonged follow-up, in particular of the large German population (12), may further elucidate this intriguing question. A further limitation of the design of the present study is the fact that sensitivity, specificity and predictive value of the AMA profile test could not be calculated since it is not known whether PBC patients who have been clinically non-progressive for at least six years will remain stable in the future.

Previous reports (13-15) have raised considerable doubt on the validity of anti-M4 and anti-M9 antibody determinations in PBC. Our data demonstrate that the reproducibility and specificity of AMA profile determinations can be excellent. None of the AMA-negative controls was assigned to an AMA profile group and AMA profiles remained unchanged over time.

The rate of disease progression varies considerable among individual PBC patients. Mathematical prognostic models, such as the Mayo model (20), use time-dependent variables to predict the clinical course and consequently indicate the timing of liver transplantation. In the early stages of PBC, however, these models cannot predict for each patient whether the course will be relatively benign or progressive. Previous studies on AMA and disease progression provided no evidence that AMA titres or the absence of AMA is related to disease progression (21, 22)

In conclusion, this study could not confirm that AMA profiles can be used as a reliable indicator of clinical outcome in PBC. The intriguing hypothesis that the prognostic potential of AMA depends on patient selection criteria requires further study.

Acknowledgements

We are grateful to P.A. Berg and R. Klein for performing the serological analyses and critically reviewing the manuscript.

Table I. Clinical features of progressive PBC patients.

Progressive PBC (n)	38
Sex (M/F)	4 / 34
Age (yrs) at sample 1; median (range)	56 (31 - 69)
Age (yrs) at sample 2; median (range)	58 (32 - 72)
Progression defined as:	
- liver transplantation (n)	15
- liver-related death (n)	3
- ascites (n)	4
- variceal haemorrhage (n)	3
- stage IV biopsy (n)	13

Table II. Characteristics of non-progressive PBC patients, non-PBC decompensated cirrhosis patients, AMA-negative PBC patients and healthy volunteers.

Non-progressive PBC (n)	31
sex (M/F)	5 / 26
Age (yrs); median (range)	56 (29 - 72)
Non-PBC decompensated cirrhosis (n)	5
sex (M/F)	1 / 4
Age (yrs); median (range)	41 (39 - 53)
AMA-negative PBC (n)	5
sex (M/F)	1 / 4
Age (yrs); median (range)	58 (43 - 69)
Healthy volunteers (n)	5
sex (M/F)	0 / 5
Age (yrs); median (range)	26 (22 - 48)

Table III. The AMA profiles found for the five categories.

sera obtained from	profile A/B n (%)	profile C/D n (%)	no AMA profile n (%)
progressive PBC	5 (13%)	32 (84%)	1 (3%)*
non-progressive PBC	4 (13%)	24 (77%)	3 (10%)**
AMA-negative PBC	0 (0%)	0 (0%)	5 (100%)
non-PBC cirrhosis	0 (0%)	0 (0%)	5 (100%)
healthy volunteer	0 (0%)	0 (0%)	5 (100%)

*AMA was only positive in immunofluorescence.

**One patient was only AMA-positive in immunofluorescence; two tested AMA-negative.

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Chapter 7

THE RISK AND PROGNOSTIC SIGNIFICANCE OF MAJOR CLINICAL EVENTS, IN PARTICULAR BILIARY COMPLICATIONS, IN PRIMARY SCLEROSING CHOLANGITIS

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Submitted

Abstract

The incidence and prognostic significance of major clinical complications in PSC, including the development of dominant bile duct strictures, cholangiocarcinoma and colorectal carcinoma, cholangitis and de-novo inflammatory bowel disease (IBD), are poorly documented. These aspects were assessed in a cohort of 163 patients (67% males; median age 33 (12-72) years) followed for a median period of 6.6 (0.04-21) years. At the time of diagnosis 59% had associated IBD. Median transplantation-free survival was 13.5 years; there was a clear difference between asymptomatic (15.3 years) and symptomatic patients (7.7 years) (p=0.0002 log-rank test). The 10/20-year risks for dominant bile duct strictures and cholangiocarcinoma were 29/35% and 7/17%, respectively. The 10-year risk for de-novo IBD was 26%. For the total cohort of patients and those with IBD at presentation, the 10-year risks for colorectal cancer were 9% and 14%, respectively. The 10/20-year risk for both colorectal carcinoma and cholangiocarcinoma was 15/25%. Univariate analyses showed that higher age, cirrhosis, symptomatic presentation, higher serum bilirubin and lower serum albumin levels predicted shorter transplantation-free survival. Multivariate analysis revealed that age (RR 1.04; 95% CI 1.02-1.06) and symptomatic presentation (RR 2.5; 95%-CI 1.4-4.5) were independent prognostic variables of decreased transplantation-free survival. Time-dependant analyses showed that the development of dominant bile duct strictures (RR 2.6; 95%-CI 1.2-5.6) or cholangitis (RR 7.3; 95%-CI 2.9-18.3) was a predictor of a high risk of dying. These results underline the progressive character of the disease and the markedly decreased life expectancy of affected patients. A more favorable prognosis can be expected in the absence of symptoms of liver disease, e.g. when PSC is diagnosed in the context of IBD associated with liver test abnormalities. Patients with PSC have a high lifetime risk for developing bile duct and colerectal cancer.

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by fibrosing inflammatory stricturing and destruction of extrahepatic and/or intrahepatic bile ducts (1). The disease may progress to biliary cirrhosis, with complications arising from hepatic decompensation and portal hypertension. In addition, during the course of the disease more specific complications may occur, including the development of 'dominant' bile duct strictures (2, 3), bacterial cholangitis (1) and bile duct

cancer. The latter is by far the most feared complication with a reported survival rate which is independent of liver transplantation and does not exceed 20 percent (4-6). Since the majority of patients also suffer from long-standing inflammatory bowel disease (IBD), the development of colerectal cancer constitutes another life-threatening problem.

Several studies have reported on the natural history and prognostic determinants of (transplantation-free) survival (7-11). The risk and prognostic significance of dominant bile duct strictures and bacterial cholangitis, however, have not been defined. In addition, relatively little is known about the lifetime risk for bile duct cancer (12, 13) and colorectal cancer (14).

Therefore, the aim of the present study was to better define the natural history of PSC, focussing on the long-term risks and prognostic significance of disease-specific complications.

Patients and methods

One hundred and sixty three PSC patients were included in the study. This cohort consisted of all patients seen at the University Hospital Rotterdam in the period 1980-1998 and all patients who participated in a prospective cohort study in the Netherlands in the period 1990-1998. The diagnosis of PSC was based on typical findings on endoscopic retrograde, percutaneous transhepatic or peroperative cholangiography (15) or the presence of characteristic histologic liver abnormalities (peri-cholangiolar 'onion-skin' fibrosis (16)) in combination with serum liver tests indicating cholestasis and the presence of IBD. Small-duct PSC was diagnosed when cholangiography was performed but did not reveal diagnostic biliary abnormalities in the presence of the triad IBD, cholestatic serum liver profile and characteristic liver histologic abnormalities. Patients with bile duct abnormalities possibly attributable to such causes as previous bile duct surgery, ischemia, portal vein thrombosis or sclerosing pancreato-cholangitis (17) were excluded. Patients presenting with one of the following symptoms or signs which were the reason for initiating subsequent diagnostic studies were classified as symptomatic: pruritus, fatigue, jaundice, cholangitis, ascites, variceal bleeding, hepatic encephalopathy and cholangiocarcinoma.

A dominant bile duct stricture was defined as a cholangiographically documented, marked stricture in either the common bile duct or one of the main hepatic ducts, diagnosed in the context of recent or aggravation of jaundice. A biliary stricture was not

regarded as 'dominant' when cholangiocarcinoma was subsequently diagnosed within a period of twelve months. Follow-up cholangiography was not routine. Diagnosis of colorectal carcinoma and cholangiocarcinoma was based on histological studies.

Statistical analysis

For the purpose of this study follow-up was considered to start at the time PSC was diagnosed. Data were collected until December 1998. Primary end-points were death and liver transplantation. Secondary end-points were cholangiocarcinoma, colorectal cancer, dominant bile duct stricture, bacterial cholangitis and de novo IBD. Transplantation-free survival and the incidence of secondary end-points were computed by the Kaplan-Meier method and compared between groups by means of the log-rank test.

The following factors, which were considered to have potential prognostic significance, were evaluated by univariate analysis: age, sex, symptomatic presentation, cirrhosis, IBD, serum bilirubin, albumin, aspartate aminotranspherase (AST), alanine aminotranspherase (ALT), immunoglobulin G, creatinin, alkaline phosphatase (APh), gamma-glutamyltranspeptidase (γGT), prothrombin time (PT) and anti-thrombin-III levels. Factors in univariate analyses with a p-value <0.20 were assessed by multivariate analysis. Multivariate Cox analyses with the backward elimination procedure were used to examine baseline prognostic factors and time-dependant prognostic factors, i.e. dominant biliary strictures and cholangitis. A p-value <0.05 was considered statistically significant.

Results

In the study period 163 patients with PSC were diagnosed and followed for a median period of 6.6 (0.04-21) years. Clinical, biochemical and histological baseline characteristics are listed in table I. For the 2.5% of the patients who were lost to follow-up data were censored at the time of last contact. One hundred and thirteen patients (69%) were seen at least once at the University Hospital Rotterdam. For 90% of the patients diagnosis of PSC was based on typical cholangiographic abnormalities ("large duct PSC") while 4% were classified as "small-duct PSC". In 6% of the cases cholangiography was not performed or was unsuccessful, and the diagnosis was based on characteristic histologic lesions in combination with serum liver test abnormalities and the presence of IBD. One hundred and nine of 163 patients (66.9%) were male. The median age at diagnosis was 30.5 years (12-72) for males and 40 (14-59) years for females (p=0.054). At

the time of diagnosis, five patients had undergone colectomy for IBD. Jaundice was the presenting symptom in 27% of the cases; overall, for 37% of the patients signs and symptoms, as listed in table II, were the reason for initiating diagnostic studies.

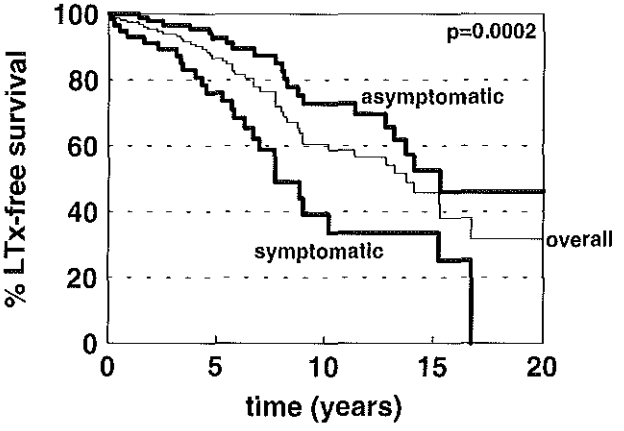

Figure 1. Kaplan-Meier curves showing the probability of surviving free of liver transplantation for all patients (thin line) and for those who were asymptomatic or symptomatic at presentation. Probability of transplantation-free survival was significantly higher for asymptomatic than for symptomatic patients (p=0.0002).

Course of PSC

Median transplantation-free survival for the entire cohort was 13.5 years (Fig 1). Nineteen patients died, 17 from causes clearly related to either PSC or IBD (table III). Liver transplantation was performed in 28 patients. Prognosis for patients with asymptomatic disease at diagnosis was markedly better than for those with symptomatic disease: median transplantation-free survival 15.3 versus 7.7 years, respectively (p=0.0002). The presence or absence of cirrhosis was found to be another significant prognostic factor according to univariate analysis (Fig 2).

One patient presented with cholangiocarcinoma and 8 developed this malignancy during follow-up. In one of these cases cholangiocarcinoma was an incidental finding at transplantation. The risk for cholangiocarcinoma at 10 and 20 years was 7% and 17%,

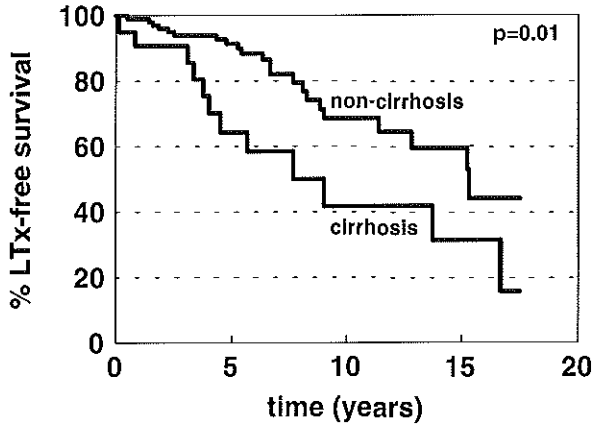

Figure 2. Kaplan-Meier curves showing the probability of surviving free of liver transplantation for patients with and without cirrhosis at presentation. Probability of transplantation-free survival was significantly higher for those without cirrhosis than cirrhotic cases (p=0.01).

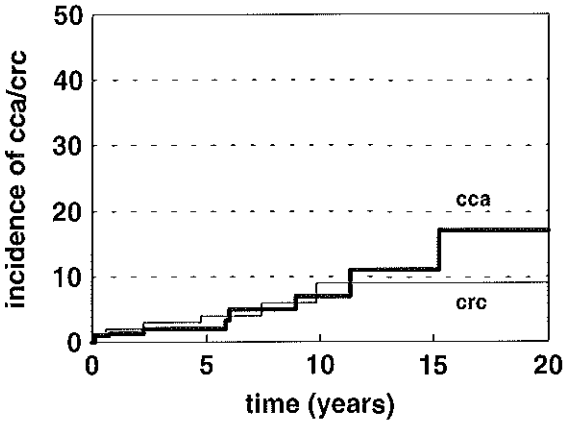

Figure 3. Kaplan-Meier curves showing the actuarial incidences of cholangiocarcinoma (cca) and colorectal cancer (crc) in the cohort of 163 patients.

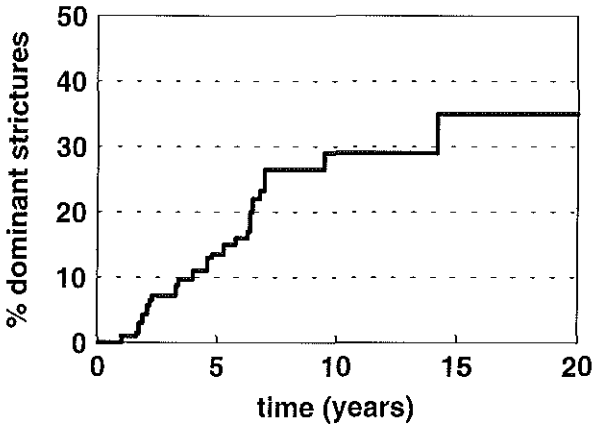

Figure 4. Actuarial cumulative incidence of dominant bile duct strictures from time of diagnosis PSC.

respectively (Fig 3). The 10-year risk for colorectal cancer was 9% (Fig 3) for the total cohort and 14% for patients with concurrent IBD (n=95) at diagnosis. Colorectal cancer was only found in patients already known to suffer from IBD at the time PSC was diagnosed. The 10 and 20-year cumulative incidences of colorectal and bile duct cancer were 15% and 25%, respectively.

During follow-up 7 out of the 45 patients, who were initially found to be free of IBD as indicated by colonoscopy, developed IBD; the 10-year incidence of de novo IBD was 26%.

The risk of developing dominant biliary strictures was 29% after 10 years and 35% after 20 years (Fig 4). The majority of 29 patients who developed dominant strictures were treated endoscopically with temporary placement of biliary endoprostheses (n=23) or endoscopic balloon dilatation (n=2). Endoscopic therapy failed technically in one case. In the remaining three patients therapy consisted of hepaticojejunostomy, percutaneous biliary treatment or ursodeoxycholic acid.

The 10 and 20-year risks for bacterial cholangitis were 19% and 29%, respectively.

Multivariate and time-dependant analysis of transplantation-free survival

Age, symptoms at presentation, cirrhosis and serum levels of bilirubin and albumin were baseline factors with a predictive value according to univariate analyses. Multivariate analysis revealed that both age and symptomatic presentation had an independent

prognostic value (table IV). Time-dependant multivariate analyses demonstrated that the development of dominant biliary strictures and cholangitis were independent significant prognostic factors. Combined analysis of the factors predictive according to multivariate and time-dependent assessments showed that age, symptomatic presentation and the development of dominant biliary strictures (borderline) and cholangitis were all of prognostic significance for future liver transplantation or death (table IV).

Discussion

The results of this long-term cohort study of PSC show that the course of the disease is characterized by relatively frequent characteristic complications, including the development of dominant bile duct strictures, cholangitis and cholangiocarcinoma. These biliary complications were found to have negative prognostic significance. We confirmed previous findings that symptomatic disease, the presence of cirrhosis, elevated serum bilirubin and lowered serum albumin levels and high age at presentation were all predictors of a high risk of dying or needing liver transplantation (7-11).

The problem of dominant biliary strictures in PSC has been well described (3, 18, 19) but data on the risk for this complication has not been reported previously. We found that over a 20-year period, about one-third of all patients can be expected to develop symptomatic, major biliary strictures. The present study suggests that, despite therapeutic interventions, these strictures seem to be associated with a subsequent unfavorable course. In this context it should be noted that among the 28 patients undergoing liver transplantation dominant strictures as such were not a primary reason for transplantation. In only two cases was the presence of dominant strictures considered to be one of the significant reasons for placing a patient on the waiting list.

The occurrence of cholangitis during follow-up had a clear negative prognostic impact. This finding may partly be explained by the fact that recurrent cholangitis was one of the reasons for transplantation in five of the 28 transplant recipients. However, recurrent cholangitis was never the sole or primary indication for liver transplantation.

Median transplantation-free survival for our cohort of patients of 13.5 years was slightly better than previously reported values of approximately 12 years (7, 8, 10). The higher proportion of patients (63%) diagnosed following the detection of serum liver test abnormalities without the presence of clear clinical signs or symptoms in the present series compared to the Mayo (21%) (7), King's College (16%) (8) and Swedish (44%) (10) series

may explain this small difference. The median serum bilirubin level of 31 μmol/l in the Mayo clinic cohort (7), which was twice as high as that for our patient group, supports this explanation.

Data on the risks for bile duct and colorectal cancer in PSC is scarce. Farges et al. reported a 10-year risk for cholangiocarcinoma of approximately 30% for a group of 51 PSC patients (12), whereas Kornfeld et al. found a 10-year risk of 11% (13). In the latter study the large majority of tumors were detected within two years of the diagnosis of PSC. In contrast, we found a more gradual pattern of incident new cases over a period of 20 years, with 10 and 20-year risks of 7% and 17%, respectively.

The 10-year risk for colorectal cancer for the entire cohort was 9%, which was substantially higher than the 4% previously reported by the Mayo Clinic group (14). Differences in patient populations, in particular in the proportion of patients with previous colectomy, may account for these diverging results. Comparison of our findings with the results of other studies (20-22) that have assessed the risk for colorectal cancer in PSC is difficult because these studies used a combined end-point of both colorectal dysplasia and cancer.

In conclusion, the results of this study underline that PSC frequently runs a progressive course. Affected patients, in particular older patients presenting with already advanced disease, have a markedly decreased life expectancy. Prognosis is considerably more favorable for patients presenting without symptoms of liver disease, a situation which is common since diagnostic studies frequently are undertaken following the detection of biochemical liver test abnormalities in the presence of IBD. The occurrence of typical PSC-specific complications, such as dominant biliary strictures and cholangitis, is associated with decreased transplantation-free survival. Patients with PSC carry a high lifetime risk for cholangiocarcinoma or colorectal cancer.

Table I. Clinical, laboratory and histologic baseline characteristics of the cohort of 163 PSC patients.

Age (mean, range) in years	35.1 (12-72)
Male / female (n)	109 / 54
No cirrhosis / cirrhosis[§] (n)	108 / 23
IBD (%)	
no*	41.4
ulcerative colitis	37.0
Crohn's disease	11.7
undeterminate colitis	9.9
Previous colectomy (n)	5
Bilirubin (µmol/l), normal <17	15.5 (4-307)
Albumin (g/l), normal >35	41.1 (21-52)
APh (U/l), normal <75	294 (35-2325)
AST (U/l), normal <30	55 (4-918)

[§] histology available for 131 patients.

* endoscopically verified in 67.2% of cases.

IBD: inflammmatory bowel disease.

Laboratory values of serum tests expressed as median and range.

Table II. Type of presentation leading to diagnosis of PSC (n=160).

Symptomatic presentation (n (%))	59 (36.9%)
jaundice	43 (26.9%)
cholangitis	2 (1.3%)
jaundice+cholangitis	1 (0.6%)
ascites / variceal bleeding	1 (0.6%)
cholangiocarcinoma	1 (0.6%)
pruritus or fatigue	11 (6.9%)
Asymptomatic presentation (n (%))	101 (63.1%)
liver test abnormalities and IBD	63 (39.4%)
liver test abnormalities, no IBD	34 (21.3%)
coincidental	4 (2.5%)

Information not available for 3 patients.

Table III. Causes of death of 19 PSC patients.

Cause	***number of patients***
Cholangiocarcinoma	7
Hepatic failure	6
Variceal bleeding	2
Colorectal cancer	1
Peritonitis/appendicitis	1
Sepsis (following colectomy for UC)	1
Unknown	1

Table IV. Analysis of prognostic factors of transplantation-free survival.

	β (SE)	RR	95%-CI	p-value
Univariate				
age	0.04 (0.01)	1.04	1.02-1.06	0.000
symptomatic presentation	1.00 (0.30)	2.73	1.51-4.93	0.001
cirrhosis	0.72 (0.37)	2.05	0.99-4.23	0.05
bilirubin	0.006 (0.002)	1.01	1.002-1.01	0.002
albumin	-0.067 (0.025)	0.94	0.89-0.98	0.007
Multivariate				
age	0.04 (0.01)	1.04	1.02-1.06	0.001
symptomatic presentation	0.90 (0.30)	2.45	1.35-4.46	0.003
Time-dependant				
dominant stricture	0.97 (0.39)	2.64	1.24-5.62	0.01
cholangitis	1.98 (0.47)	7.27	2.89-18.3	0.000
Combined time-dep+multivar.				
dominant stricture	0.73 (0.39)	2.07	0.96-4.48	0.06
cholangitis	1.71 (0.52)	5.54	1.99-15.4	0.001
age	0.03 (0.01)	1.03	1.01-1.05	0.01
symptomatic presentation	0.95 (0.31)	2.59	1.41-4.77	0.002

β: regression coefficient, SE: standard error, RR: relative risk, CI: confidence interval.

Appendix

The other members of the Dutch multicenter PSC study group are: D.J. Bac, Ikazia Hospital, Rotterdam; M.C.J.M. Becx, Overvecht Hospital, Utrecht; J. van Hattum, K.J. van Erpecum, University Medical Center Utrecht; J.D. van Bergeijk, B.M.J. Witteman, Hospital 'De Gelderse Vallei', Wageningen; L.G.J.B. Engels, Maasland Hospital, Sittard; A.C. Hoek, Van Weel-Bethesda Hospital, Dirksland; P. Spoelstra, D.P.F. van Houte, Medical Center Leeuwarden; R.W. de Koning, Canisius-Wilhelmina Hospital, Nijmegen; M.C.M. Rijk, Hospital 'De Baronie', Breda; S.W. Schalm, University Hospital Rotterdam; J. Scherpenisse, Reinier de Graaf Hospital, Delft; M. Schrijver, Bronovo Hospital, Den Haag; J.W. de Bruijne, Carolus Hospital, Den Bosch; W.N.H.M. Stuifbergen, St. Elisabeth Hospital, Tilburg; T.G. Tan, St. Streekziekenhuis Midden-Twente, Hengelo; A.J.P. van Tilburg, St. Franciscus Hospital, Rotterdam; R.A. de Vries, Rijnstate Hospital, Arnhem; F.J.W. ten Kate, Academic Medical Center, Amsterdam.

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Part III

Treatment of Immunocholangitis

Chapter 8

BUDESONIDE OR PREDNISONE IN COMBINATION WITH URSODEOXYCHOLIC ACID IN PRIMARY SCLEROSING CHOLANGITIS: A RANDOMIZED DOUBLE-BLIND PILOT STUDY

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American Journal of Gastroenterology,2000;95:2015-22.

Abstract

PSC has characteristics of an (auto)immune-mediated disease; however, few studies have evaluated corticosteroid therapy for this disorder. We performed an 8-week double-blind randomized pilot study to assess the effects of additional treatment with 9 mg budesonide (n=6) versus 3 mg budesonide (n=6) versus 10 mg prednisone (n=6) in patients who had been treated with UDCA (mean dose 12 mg/kg/day) for at least five months without achieving biochemical remission. Pruritus and fatigue were evaluated using visual analogue scales. Serum liver biochemistry was measured every four weeks. At entry and at the end of the trial, adrenocorticotrophic hormone (ACTH) and dehydroepiandrosterone (DHEA) were measured to assess effects on the pituitary-adrenal axis. Duodenal bile was collected for assessment of biliary corticosteroid activity. Pruritus decreased significantly more in the prednisone group compared to both the 3 mg and the 9 mg budesonide groups ($p<0.05$). Alkaline phosphatase (mean: -23.4%; p=0.03) and immunoglobulin G (mean: -16.2%; p=0.04) decreased in the prednisone group, while bilirubin, γ-glutamyl transferase, aspartate aminotransferase and alanine aminotransferase did not change significantly. No significant clinical and liver biochemical changes were observed in the 3 mg and 9 mg budesonide groups. Significantly larger drops in serum ACTH were found in the 10 mg prednisone group (-40.7%; p=0.04) and 9 mg budesonide group (-36.6%; p=0.02) compared to the 3 mg budesonide group (+19.0%). No significant differences in percentage change in baseline values for DHEA between the three treatment arms were found. Mononuclear cell proliferation assays did not demonstrate corticosteroid activity in bile. Auto-immune hepatitis was observed in one case (9 mg budesonide) when corticosteroids were tapered off. The results of this pilot study suggest only minor beneficial short-term effects of prednisone but not budesonide on symptoms and serum liver tests in UDCA-treated PSC patients.

Introduction

The aetiology of primary sclerosing cholangitis (PSC) is unclear. An (auto)immune background is suggested (1, 2) by the strong association between PSC and inflammatory bowel disease (IBD) (3, 4), the presence of the autoantibody pANCA (5-8) and an increased prevalence of HLA B8 DR3 DR52a genotypes (9-11). Furthermore, an overlap syndrome between autoimmune hepatitis (AIH) and PSC has been described (12-14).

Few studies have evaluated the effects of corticosteroid treatment in PSC. Prednisone therapy has only been assessed in open-label studies (15, 16). The use of corticosteroids in

cholestatic liver disease has been discouraged because of potential side-effects, in particular osteoporosis (17). Systemic side-effects of corticosteroids may be avoided by replacing prednisone by budesonide, which is a potent corticosteroid with a high first-pass effect (18), resulting in low systemic availability and potentially fewer side-effects (19).

Improvements in serum liver function tests and histology have been observed following ursodeoxycholic acid (UDCA) monotherapy in PSC (20-22). Although effects on disease progression were absent after 2 years of treatment (23), the drug is still being used extensively in PSC. In view of these facts, a double-blind randomized pilot study was initiated to evaluate the efficacy and safety of budesonide and prednisone in addition to UDCA maintenance therapy for PSC patients.

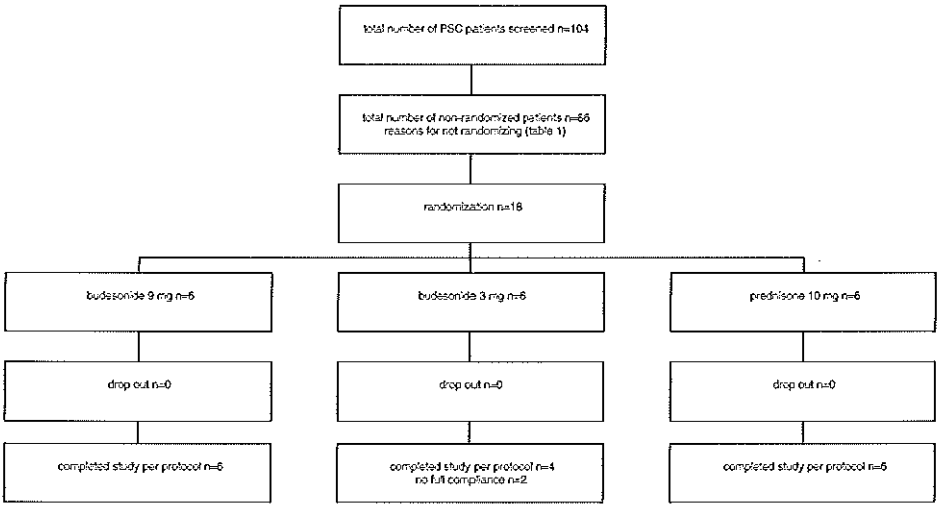

Figure 1. Study profile.

Patients and methods

A total of 104 PSC patients was screened for eligibility; a flow diagram according to the CONSORT statement (24) is given in Figure 1. Reasons for not participating are listed in Table I. Eighteen patients were recruited. The diagnosis of PSC was based on characteristic findings on endoscopic retrograde cholangiography (ERC) (25) in 17 cases. Typical histological lesions (pericholangiolar "onion-skin" fibrosis) (26) in combination with both a serum alkaline phosphatase (APh) level elevated to more than twice the upper limit of

normal (ULN) and the presence of IBD led to the diagnosis of PSC in one patient. Prior to the study, all patients had been treated with UDCA (mean dose 12 mg/kg body-weight/day) for at least five months, without achieving biochemical remission, defined as normalization of APh, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Exclusion criteria were: age >65 years, use of immunosuppressive drugs such as corticosteroids, azathioprine, cyclosporin or methotrexate, pregnancy, evidence of PSC-associated AIH, previous cholecystectomy, presence of a biliary stent and cirrhosis with a Child-Pugh score >6 (27).

Patients were randomized by assigning consecutive treatment numbers which corresponded to trial medication. Patients were randomized to take 10 mg/day prednisone (two 5 mg tablets of prednisone and three placebo capsules Budenofalk®), 3 mg/day budesonide (one 3 mg Budenofalk® capsule, two placebo capsules and two placebo tablets of 5 mg prednisone) or 9 mg/day budesonide (three 3 mg Budenofalk® capsules and two placebo tablets of 5 mg prednisone) for eight weeks. Verum and placebo medication was of identical appearance. Treatment with UDCA was continued. Three blocks of six patients were generated. In each block, the three treatment options were equally and randomly distributed. One block of six treatment numbers was allocated to each participating centre: University Hospitals Rotterdam, Utrecht and Leuven. The randomization list was generated by Allphamed, Goettingen, Germany; the medication was packed accordingly. Follow-up data were collected every 4 weeks. Blood analysis including bilirubin, APh, γ-glutamyl transferase (γ-GT), AST, ALT, immunoglobulin G (IgG), immunoglobulin M (IgM), albumin and prothrombin time was performed by standard automated procedures. Separation of APh isoenzymes was performed by agarose gel electrophoresis (Titan Gel®, Helena Laboratories, Gateshead, United Kingdom). Quantitation of APh isoenzyme fractions was performed by computerized scanning techniques (Sharp, JX330P). At baseline and after eight weeks, blood was drawn to assess adrenocorticotrophic hormone (ACTH) and dehydroepiandrosterone (DHEA) after 30 minutes of bedrest, at 09.00 a.m., to determine effects on the pituitary-adrenal axis. The severity of pruritus and fatigue was quantified with visual analogue scales (VAS), starting one week before administration of the study medication. Patients were asked to indicate daily the severity of pruritus and fatigue on a 10 cm scale during the complete study period. After the 8-week study period all patients received treatment with 5 mg prednisone per day; subsequently, prednisone was tapered off in three weeks.

Poor compliance was defined as taking less than 90% of the study medication. The study was approved by the Medical Ethics Committees of each of the three participating hospitals and all patients gave written informed consent. All assessments, except the quantitation of APh isoenzymes, were performed before the randomization code was broken.

Collection of bile and determination of biliary corticosteroid activity

Bile was collected using duodenal intubation under fluoroscopic control at entry and on the last day of treatment. Gall-bladder contraction was induced by intravenous injection of 2 μg of ceruletide (Takus®, Pharmacia & Upjohn GmbH, Erlangen, Germany). A maximum dose of 6 μg ceruletide was given in steps of 2 μg. Duodenal bile was collected in ice chilled tubes and stored at -20°C until further analysis.

Mononuclear cells (MNCs) were isolated by Ficoll density centrifugation of heparinized blood from one healthy individual. 10^5 MNCs were incubated in RPMI culture medium supplemented with 10% AB-serum in the presence of pre-treatment and post-treatment bile in a final dilution of 1:1000 (optimal dilution determined in previous experiments). A mixture of diphtheria/tetanus toxoid was used for antigenic stimulation of MNC proliferation. To obtain reference values, prednisolone was added to the cultures in final dilutions of 10^{-4}, 10^{-6} and 10^{-8} mol/l in the presence of bile collected at entry. Cultures without diphtheria/tetanus toxoid were used for determination of background MNC proliferation. MNCs were incubated at 37°C in 5% CO_2-atmosphere for five days; ^{3}H-thymidine was added 24 hours before harvesting. ^{3}H-thymidine incorporation was measured with a liquid scintillation counter and MNC proliferation was expressed as counts per minute (cpm). Phytohaemagglutinin was used to check the proliferative potential of the MNCs. Every culture was performed in triplicate.

Statistical analysis

Since no data on the effects of budesonide and prednisone on liver biochemistry in PSC patients receiving UDCA were available and because this was a pilot study, a statistical power analysis was not performed. A group of six patients per treatment arm was considered sufficient for this pilot study to get an impression of the efficacies. Data were analysed according to the intention-to-treat principle. Mean daily VAS scores per week for pruritus and fatigue were calculated by dividing the total score for one week by seven. Because the normal ranges for serum liver tests differed in the three participating centres,

results are expressed as multiples of the upper limit of normal (ULN). The Kruskal-Wallis test was used to assess overall differences between the three treatment arms. Paired t-tests were applied after verifying that differences between pre-treatment and post-treatment values exhibited an approximately normal distribution; otherwise, Wilcoxon's signed-rank test was used. A p-value ≤ 0.05 was considered statistically significant.

Results

At entry, the three groups were largely comparable in terms of clinical and biochemical characteristics (Table II). The mean age was 43 years (range 26-65); 14 patients were male and 11 (61%) had a history of IBD. No significant differences in biochemical and clinical values at entry between the three groups existed. Compliance was good; two patients used 88% of the study medication, all others used 100% as indicated by pill count.

Pruritus and fatigue

The number of patients reporting pruritus at entry and after eight weeks was four and three in the 10 mg prednisone group, two and none in the 3 mg budesonide group and one and two in the 9 mg budesonide group, respectively. The median difference between baseline and 8 weeks score was +0.15 points for the 3 mg budesonide group, -0.1 for the 9 mg budesonide group and -1.1 for the 10 mg prednisone group. The median decrease from baseline in the 10 mg prednisone group was significantly greater compared to the other groups (both $p<0.05$) (Fig 2).

Eleven patients complained of fatigue at entry: three in the 10 mg prednisone group, three in the 3 mg budesonide group and five in the 9 mg budesonide group. After eight weeks, eight patients complained of fatigue: two in the 10 mg prednisone group, three in the 3 mg budesonide group and three in the 9 mg budesonide group. The median change from baseline of the fatigue score was similar in all groups (all 0.6) (Fig 3).

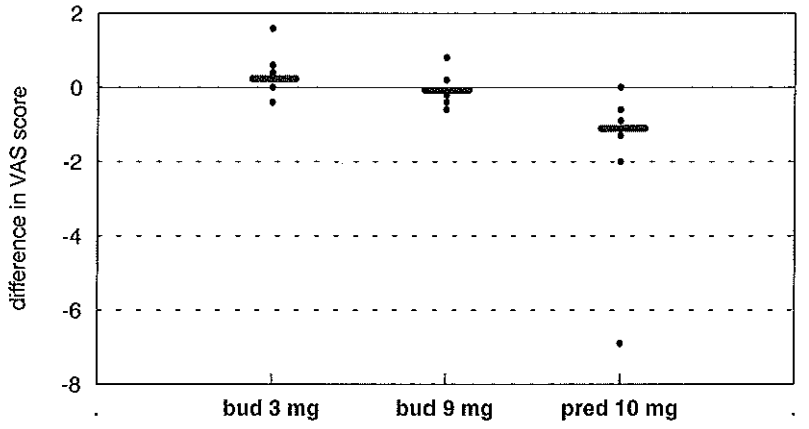

Figure 2. The difference between pre-treatment and 8-week VAS pruritus score in 3 mg budesonide (bud 3 mg), 9 mg budesonide (bud 9 mg) and 10 mg prednisone (pred 10 mg) groups. Horizontal bars indicate medians.

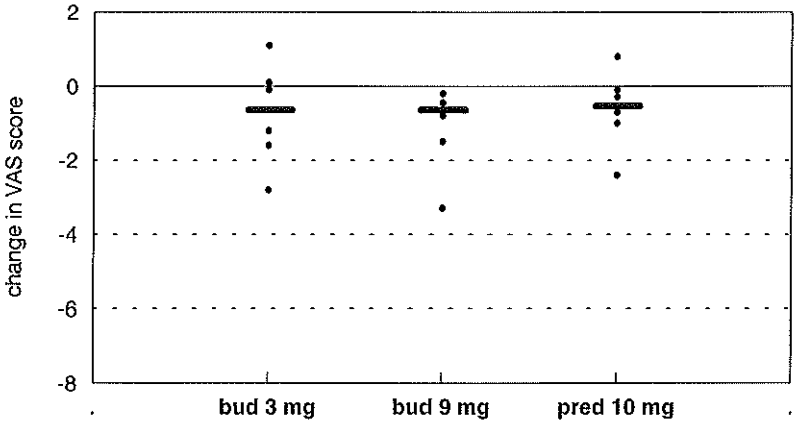

Figure 3. The difference between pre-treatment and 8-week VAS fatigue score in 3 mg budesonide (bud 3 mg), 9 mg budesonide (bud 9 mg) and 10 mg prednisone (pred 10 mg) groups. Horizontal bars indicate medians.

Serum liver tests

In the 10 mg prednisone group, the mean changes from baseline in APh (-23.4%, p=0.03; 95%-confidence interval: -42.7% to -4.2%) (Fig 4) and IgG (-16.2%, p=0.04; 95%-ci: -24.8% to -7.5%) were significantly less than zero after eight weeks of treatment. The liver and bone APh isoenzyme fractions decreased by a mean of 27.6% (95%-ci: -54.5% to -

0.8%; p=0.04) and 10.0% (95%-ci: -38.1% to +18.0%; p=0.9), respectively. No significant changes in serum liver tests were observed in the 3 mg budesonide and 9 mg budesonide groups. The mean changes in APh and IgG in the 10 mg prednisone group, however, did not differ significantly from the changes in the 3 mg and 9 mg budesonide groups. Serum bilirubin (Fig 5), AST, ALT, γGT and IgM did not change significantly in the 10 mg prednisone group. Albumin and prothrombin time remained stable in all three groups.

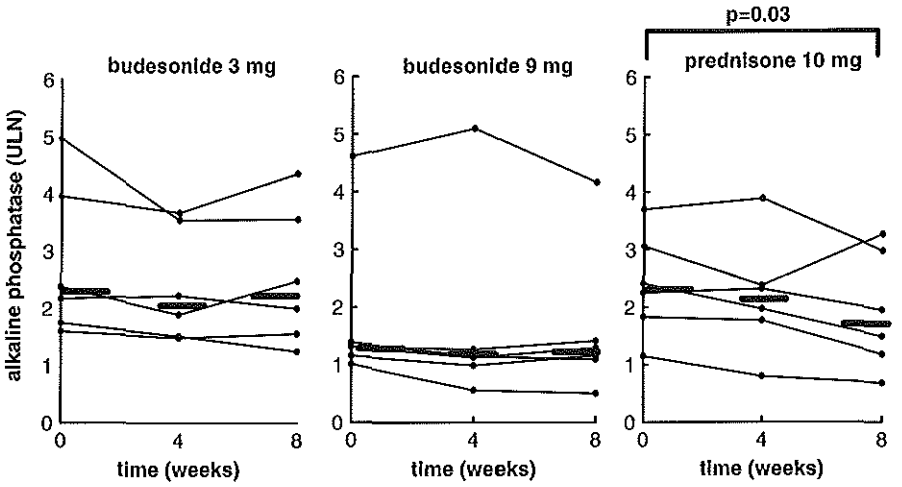

Figure 4. Course of serum alkaline phosphatase in the 10 mg prednisone, 9 mg budesonide and 3 mg budesonide groups. Data are expressed as multiples of the upper limit of normal (ULN). Horizontal bars indicate medians.

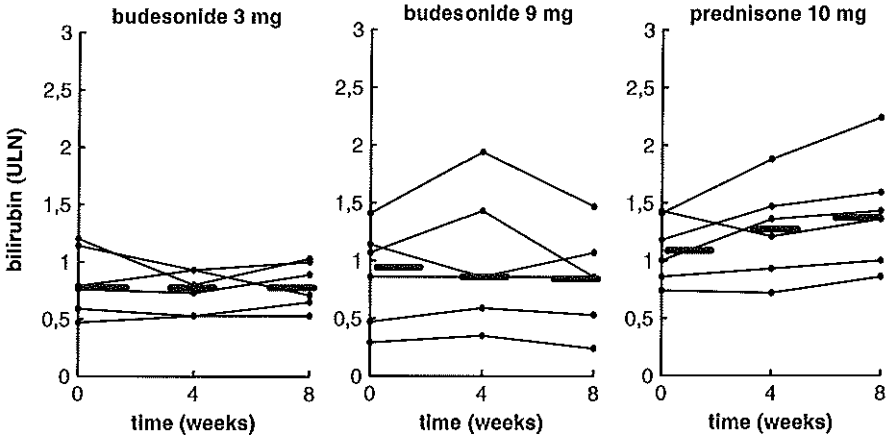

Figure 5. Course of serum bilirubin in the 10 mg prednisone, 9 mg budesonide and 3 mg budesonide groups. Data are expressed as multiples of the upper limit of normal (ULN). Horizontal bars indicate medians.

Pituitary-adrenal axis

Significantly greater decreases in serum ACTH were found in the 10 mg prednisone group (-40.7%; p=0.04) and 9 mg budesonide group (-36.6%; p=0.02) compared to the 3 mg budesonide group (+19.0%)(Table III). No significant differences in percentage change in baseline values for DHEA between the three treatment arms were found.

Adverse events

A 42-year-old male patient was diagnosed with PSC in 1991. At regular follow-up examinations transaminases were mildly elevated and IgG was normal. He was allocated to the 9 mg budesonide group; he had also taken rifampicin for pruritus in the preceding 6 months. When prednisone was tapered off marked hepatitis developed: serum bilirubin 105 µmol/l (normal <17 µmol/l); ALT 595 U/l (normal <30); IgG 23.2 g/l (normal <16). Antinuclear antibodies (titre 1:2560), anti-DNA (>50 IE/ml), anti SS-A and anti SS-B antibodies tested positive. Serological markers for hepatitis A, B and C were negative. A liver biopsy revealed dense portal mononuclear infiltrates with interface hepatitis, numerous Councilman bodies and collapse of liver parenchyma. Combination treatment with prednisone (30 mg/day) and azathioprine (50 mg/day) was instituted, resulting in rapid

normalization of serum bilirubin, ALT and IgG. An overlap syndrome of PSC and AIH was diagnosed.

One patient, who received 10 mg prednisone per day reported slightly impaired vision and itching of the eyes. In the 9 mg budesonide group, one patient reported increased facial acne and another patient complained of nausea. These side-effects were found to be transient. No other adverse events were noted.

Biliary corticosteroid activity

Duodenal bile collection was successful in 15 cases; it failed in two patients of the 9 mg budesonide group and one patient of the 3 mg budesonide group. Mean cpm of diphtheria/tetanus toxoid-stimulated MNCs incubated with bile collected at entry with and without *in vitro* addition of 10^{-8} mol/l prednisolone was 11504.0 (sd 6235.1) and 15614.6 (sd 6188.1), respectively (p=0.01). Thus, it was possible to measure an inhibitory effect comparable to that of prednisolone at a concentration of 10^{-8} mol/l, corresponding to a concentration of 10^{-5} mol/l in undiluted bile. Mean cpm of diphtheria/tetanus toxoid-stimulated MNCs incubated with bile collected at entry and at the end of the study was 15614.6 (sd 6188.1) and 15073.9 (sd 8586.3), respectively (p=0.36). In none of the groups could an inhibitory effect of post-treatment bile compared with pre-treatment bile on MNC proliferation be demonstrated.

Discussion

This study indicates that in PSC patients receiving treatment with ursodeoxycholic acid additional therapy with 10 mg prednisone per day or 3 or 9 mg budesonide per day does not result in major short-term improvements in clinical and laboratory parameters of the disease, although treatment with 10 mg prednisone per day was associated with a significant decrease in pruritus as assessed by visual analogue scores.

Currently, no effective medical treatment has been found for PSC. This study was based on the hypothesis that both immunologically mediated inflammatory activity (1) as well as bile acid-related liver damage contribute to the gradually progressive liver disease that characterizes PSC. Consequently, a therapeutic approach based on combined treatment with ursodeoxycholic acid and low-dose immunosuppressives was considered of interest.

We chose deliberately for a relatively short pilot trial considering the virtual lack of data indicating a beneficial effect of corticosteroids in PSC and the potential significant side-

effects of these agents. Therefore, the results of this 8-week study do not allow conclusions as to the possible long-term effects of such treatment regimen but they do seem to indicate an absence of major short-term benefits. The results of this 8-week study do not allow conclusions as to the possible long-term effects of such a treatment regimen but they do seem to indicate an absence of major short-term benefits. In this context, it should be noted that the patients included in this study had relatively mild liver disease, as indicated by the biochemical test results at entry, which may a priori have limited the chance to observe significant changes in liver biochemical parameters upon treatment with immunosuppressives. On the other hand, in two other chronic autoimmune liver disorders, primary biliary cirrhosis (28) and autoimmune hepatitis (29), a biochemical response to corticosteroid therapy was already apparent after only four weeks of treatment.

Interpretation of the effect of corticosteroids on pruritus is markedly hampered by the considerable variation in both the number of symptomatic patients and the severity of pruritus among the treatment groups. Moreover, this study was not placebo-controlled. Therefore, the observed beneficial effect of prednisone should be interpreted with caution and would require confirmation in further studies. Interestingly, a positive effect of corticosteroids on pruritus has also been reported for another cholestatic liver disease, primary biliary cirrhosis (28, 30). This effect could be related to the reported ability of corticosteroids to induce cytochrome P450-3A activity (31), which is analogous to the action of the well-known antipruritic drug rifampicin.

Budesonide is a potent corticosteroid with high receptor affinity. It is rapidly metabolized in the liver into almost inactive metabolites (32). In theory, a high concentration of active drug could be delivered to the biliary tract, whereas systemic concentrations remain low. On the other hand, budesonide might be inactivated before exerting its immunosuppressive effect. The first hypothesis is not supported by the results of our experiments with duodenal bile, showing absence of increased immunosuppressive action in bile of patients treated with budesonide.

This study demonstrates that suppression of the pituitary-adrenal axis by 10 mg prednisone per day and 9 mg budesonide per day was comparable while 3 mg budesonide per day had no such effect. Although the systemic availability of budesonide is reported to be low (32, 33) we, in accordance with others (19, 34), found that in patients treated with 9 mg budesonide as well as 10 mg prednisone the pituitary-adrenal axis was significantly suppressed.

In general, patients tolerated the low-dose corticosteroid regimen well. One exceptional serious adverse event was observed in a patient treated with 9 mg budesonide per day who developed severe, corticosteroid-responsive hepatitis when corticosteroids were tapered off. We are not aware of any similar cases. Although the aetiopathogenesis of this event remains speculative, available data suggest that in this patient manipulation of the immune system triggered the development of an autoimmune-mediated liver disease.

Relatively few studies have evaluated the effects of immunosuppressive drugs in PSC and the findings are inconsistent. No evidence was found for beneficial effects of D-penicillamine (35), cyclosporin (36), methotrexate (37, 38) or combination therapy with colchicine and prednisone (16). Conversely, serum liver tests appeared to respond favourably to treatment with tacrolimus (39) whereas some benefit of treatment with prednisone monotherapy has been reported for a series of ten patients (15).

In conclusion, in this pilot study only minor short-term beneficial effects of treatment with prednisone but not budesonide were noted in PSC. The apparent benefit-risk ratio of immunomodulating agents, as assessed in this and previous studies, does not therefore support long-term evaluation of these agents in PSC.

Table I. Reasons for not randomizing a patient.

patient refused	13
use of immunosuppressive medication	13
biochemical remission	33
no UDCA treatment	8
previous cholecystectomy	4
biliary stent	2
Child-Pugh score >6	3
presence of malignancy/other severe disease	6
PSC associated AIH	1
age >65 years	3

AIH: autoimmune hepatitis.

Table II. Features at entry.

	Prednisone 10 mg n = 6	Budesonide 9 mg n = 6	Budesonide 3 mg n = 6
Age (years)	44.5 (10.9)	46.4 (9.7)	38.9 (12.3)
Sex (male/female)	M 6 / F 0	M 4 / F 2	M 4 / F 2
UDCA dose (mg/kg)	11.8 (2.2)	10.4 (2.2)	14.6 (6.8)
IBD (n)	3 UC / 1 CD	2 UC / 1 CD	4 UC / 0 CD
Treatment with			
5-ASA (n)	4	3	3
Rifampicin (n)	0	1	0
Bilirubin (ULN)	1.1 (0.3)	0.9 (0.4)	0.8 (0.3)
APh (ULN)	2.4 (0.9)	1.8 (1.4)	2.8 (1.4)
γ-GT (ULN)	6.5 (5.0)	6.4 (7.9)	7.8 (6.6)
AST (ULN)	1.2 (0.4)	1.2 (1.0)	1.3 (0.4)
ALT (ULN)	2.0 (0.9)	1.7 (2.2)	1.9 (0.6)
Albumin (ULN)	1.0 (0.3)	1.0 (0.3)	1.0 (0.2)
IgG (ULN)	1.2 (0.7)	0.9 (0.3)	1.0 (0.3)

Means with standard deviation in parentheses. IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: Crohn's disease; 5-ASA: 5-amino salicylic acid

Table III. Effects of prednisone and budesonide on the pituitary-adrenal axis.

	Entry	End	Δ	p*
ACTH (pg/l)				
Prednisone 10 mg	48.0 (14.6)	27.5 (21.9)	-40.7 (23.0)	0.130
Budesonide 9 mg	35.8 (7.3)	21.7 (9.1)	-36.6 (13.4)	0.064
Budesonide 3 mg	38.1 (13.4)	44.0 (14.5)	+19.0 (13.6)	0.219
DHEA (μmol/l)				
Prednisone 10 mg	5.4 (2.8)	2.6 (1.0)	-39.2 (15.9)	0.081
Budesonide 9 mg	5.8 (3.3)	3.7 (3.1)	-40.9 (10.4)	0.052
Budesonide 3 mg	3.7 (1.5)	3.5 (1.4)	-7.1 (8.4)	0.359

Means with standard deviation in parentheses. Δ: percentage change from baseline with standard error of the mean in parentheses.

* within group comparison.

Acknowledgement

We gratefully acknowledge the ongoing support of MCJM Becx, Ziekenhuis Overvecht, Utrecht; J Scherpenisse, Reinier de Graaf Gasthuis, Delft; JJ Uil, Ziekenhuis de Gelderse Vallei, Wageningen; MCM Rijk, Ziekenhuis de Baronie, Breda; PC van de Meeberg, Slingeland Ziekenhuis, Doetinchem; DJ Bac, Ikazia Ziekenhuis, Rotterdam; and G. Ghillebert, H. Hartziekenhuis, Roeselare; H.J.L. Dieteren, Tramedico B.V., Weesp; H.-D. Tauschel, Dr. Falk Pharma GmbH, Freiburg, Germany.

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Chapter 9

SCLEROSING PANCREATO-CHOLANGITIS RESPONSIVE TO STEROID THERAPY

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Lancet 1999; 354: 43-44.

Multiple fibrosing inflammatory strictures of the biliary tree can be caused by primary sclerosing cholangitis (PSC) or may be secondary to a number of other diseases. In both primary and secondary sclerosing cholangitis success of medical treatment has been limited. Reversibility of biliary abnormalities upon treatment with immunosuppressives has not been documented. We report on multifocal bile duct stenoses responding to glucocorticosteroids in four patients with a rare inflammatory disorder involving the pancreato-biliary tract.

Four male patients (aged 19, 51, 61, 63 years) with an unremarkable medical history presented with weight loss (6-12 kg) and jaundice. The most pertinent laboratory results were: elevated ESR (55-89 mm/h); hyperbilirubinaemia (n=3; bilirubin 47-150 µmol/l); elevated alkaline phosphatase (307-539 U/l; N<120), decreased faecal elastase-1 levels (tested in three patients) indicating severe exocrine pancreatic insufficiency and previously unknown hyperglycaemia (n=1). Ultrasound and CT studies showed diffuse (n=2) or focal (n=2) pancreatic enlargement. Endoscopic retrograde cholangiopancreatography (n=3) and percutaneous transhepatic cholangiography (n=1) demonstrated multiple strictures of the intrahepatic bile ducts (n=4), distal stenoses of the common bile duct (n=2) and narrowing and irregularity of the main pancreatic duct (n=3). Liver biopsy specimens revealed periductal inflammation and fibrosis (n=4). During diagnostic laparotomy, performed in two cases, diffuse swelling of the entire pancreas without features of malignancy was noted. A pancreatic biopsy from one patient showed fibrosis and extensive inflammatory infiltrates; malignancy was not found. There were no clinical symptoms of inflammatory bowel disease and colonoscopy, carried out in three cases, was normal.

For all 4 patients, the diagnosis was pancreatitis associated with 'PSC-like' bile duct abnormalities on a presumably autoimmune basis and therapy with prednisone (0.5-1.0 mg/kg/day, tapered to a maintenance dose of 5-10 mg/day) was instituted. One patient also took 50 mg azathioprine daily and two patients received biliary endoprostheses temporarily. In all cases, complete clinical remission was observed, as confirmed by normalization of biochemical liver function tests, improvement in liver histology (n=2) and ultrasound studies indicating disappearance of pancreatic swelling. The patient with diabetes mellitus became normoglycaemic. Repeat cholangiography showed complete disappearance of bile duct stenoses after three months in one patient (figure 1A+B) and marked improvements in biliary abnormalities after two years in the other three patients.

The peculiar type of pancreatic disease in our patients is quite different from pancreatic abnormalities that have been reported previously in PSC[1]. Furthermore, the absence of inflammatory bowel disease and the favourable response to corticosteroids plead against this diagnosis. Four similar patients with a favourable response to corticosteroid treatment have been described[2-5] but effects on radiological bile duct abnormalities were not assessed. Our patients seem to fit within an entity that has been reported under the name of 'lymphoplasmacytic sclerosing pancreatitis with cholangitis', 'pancreatic pseudotumor with idiopathic fibrosclerosis', 'inflammatory pseudotumor from sclerosing cholangitis', and others.

Awareness of this intriguing syndrome may prevent confusion with pancreatic malignancy and unnecessary surgery. Until the aetiopathogenesis and natural history have been defined more precisely, no clear recommendations with respect to medical therapy can be made. However, our observations as well as those of others at least suggest that corticosteroids should be considered for patients who apparently seem to suffer from 'sclerosing pancreato-cholangitis'.

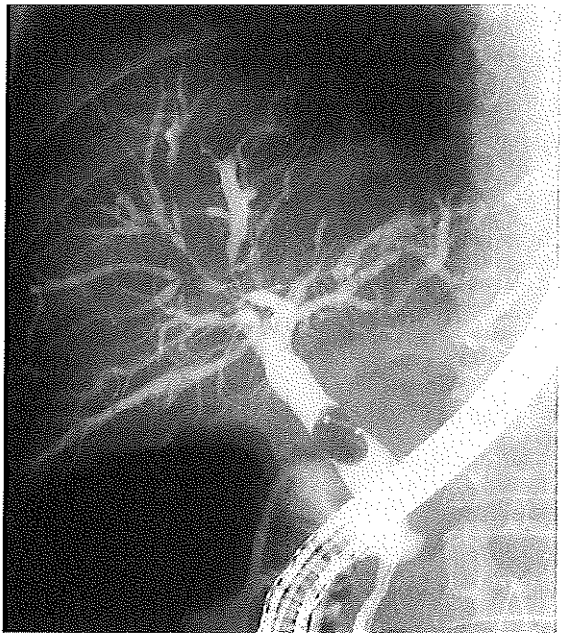

Figure 1A. Pre-treatment endoscopic retrograde cholangiography (ERC) showing stenosis of the intrapancreatic part of the common bile duct (CBD) and multiple centrally located

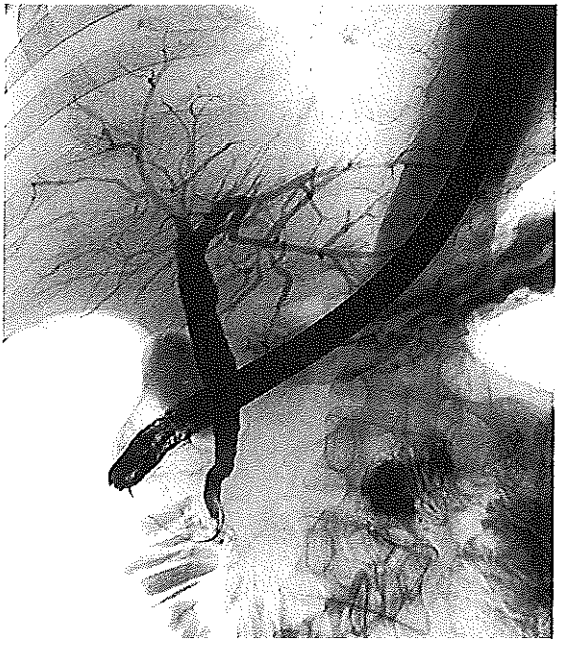

Figure 1B. ERC after three months of prednisone and azathioprine therapy showing disappearance of the CBD stenosis as well as the intrahepatic bile duct strictures.

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Chapter 10

NO BENEFICIAL EFFECTS OF TRANSDERMAL NICOTINE IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: RESULTS OF A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CROSS-OVER STUDY

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European Journal of Gastroenterology and Hepatololgy, in press.

Abstract

Smoking is associated with a decreased risk of primary sclerosing cholangitis. We aimed to explore the therapeutic efficacy of and tolerance for transdermal nicotine treatment in this disease. Twelve patients (11 males; 37±6 years; 6 with ulcerative colitis) who did not achieve complete biochemical remission on ursodeoxycholic acid (14 mg/kg/day) were treated in a randomized cross-over trial with transdermal nicotine (15 mg/day) or a placebo, each for eight weeks (4-week washout period between treatments). One patient developed de novo ulcerative colitis and two did not complete the entire protocol because of intercurrent bacterial cholangitis. Baseline values (mean + range) were: bilirubin 1.3 (0.5-2.6), APh 2.5 (1.4-4.7), γGT 7.7 (0.7-38), AST 1.9 (0.5-3.2), ALT 2.4 (0.4-7.3) and bile salts and 10.9 (2.1-39) times the upper limit of normal. No significant effect on pruritus or fatigue was noted during either period, but a small increase in bodyweight was observed during placebo treatment. No significant differences were observed between the two treatment modalities after 8 weeks in bilirubin (nicotine vs placebo: +13% vs -6% change from baseline), APh (-3% vs -17%), γGT (-11% vs -13%), AST (+2% vs -10%), ALT (-1% vs -11%) or bile salts (+36% vs -3%). Transdermal nicotine does not seem to have a clear short-term beneficial effect in primary sclerosing cholangitis treated with ursodeoxycholic acid.

Introduction

Primary sclerosing cholangitis (PSC) is a progressive cholestatic liver disease characterized by multifocal strictures of intrahepatic and extrahepatic bile ducts, which frequently leads to biliary cirrhosis and liver failure (1). Approximately 70% of patients with PSC have associated inflammatory bowel disease, usually ulcerative colitis (2). Conversely, 2 to 7% of those with ulcerative colitis have concomitant PSC (3, 4). The aetiology of PSC is unknown but is thought to be (auto)immune-mediated. Nevertheless, in a number of randomized controlled trials a clear benefit of treatment with various immunosuppressive agents, such as D-penicillamine (5), methotrexate (6) or corticosteroids (7), could not be demonstrated. Although treatment with ursodeoxycholic acid (UDCA) improves serum liver tests (8, 9) and is prescribed on a large scale for PSC patients, this therapeutic modality may have no beneficial effect on the course of the disease (10).

Smoking of cigarettes is associated with a decreased risk of ulcerative colitis (11). Treatment with transdermal nicotine patches may improve symptoms and histology in active ulcerative colitis (12, 13), supposedly by influencing the synthesis of various cytokines (14). Three case-control studies have demonstrated that cigarette smoking is also associated with a decreased risk

of PSC (15-17). These findings suggest that transdermal nicotine might have a beneficial effect in PSC. We therefore performed a placebo-controlled cross-over study to explore safety and efficacy of transdermal nicotine treatment in PSC.

Patients and methods

Exclusion criteria for the study were: smoking within three months prior to entry, use of immunosuppressive drugs such as corticosteroids, azathioprine, cyclosporin or methotrexate in the previous six months, active ulcerative colitis (18), Crohn's disease, pregnancy, presence of a biliary endoprosthesis, evidence of PSC-associated autoimmune hepatitis and cirrhosis with a Child-Pugh score >6 points (19). The diagnosis of PSC was based on characteristic findings on endoscopic retrograde cholangiography (20). Prior to the study, all patients had been treated with UDCA (mean dose 14 mg/kg bodyweight/day) for at least six months, without normalization of alkaline phosphatase (APh), aspartate aminotransferase (AST) or alanine aminotransferase (ALT).

Patients were randomized to receive the transdermal nicotine patch or an identical placebo patch (Nicorette®, Pharmacia & Upjohn AB, Stockholm, Sweden) for eight weeks. After a wash-out period of four weeks, cross-over to the opposite treatment for another eight weeks followed. The starting nicotine dose was 5 mg/day. The dose was increased by 5 mg every three days until a maintenance dose of 15 mg daily was achieved. The nicotine or placebo patches were applied from 7:00 a.m. until 23:00 p.m.. Treatment with UDCA was continued in the same dose as before.

Follow-up data were collected at 4-week intervals. Blood analysis performed on these occasions included: bilirubin, APh, γ-glutamyl transpeptidase (γ-GT), AST, ALT, lactate dehydrogenase (LD), total cholesterol, total bile salts, albumin, prothrombin time (PT), immunoglobulin G (IgG), erythrocyte sedimentation rate (ESR) and haematological indices (haemoglobin level, leucocyte and thrombocyte counts). Systolic and diastolic blood pressures, heart rate and bodyweight were also measured. Severity of pruritus and fatigue were quantified at baseline and during both treatment periods: patients were asked to indicate severity of pruritus and fatigue on 10 cm visual analogue scales (VAS) every night at bedtime during the study period.

The study was approved by the Medical Ethics Committees of the two participating hospitals and all patients gave written informed consent.

Statistical analysis

Since no data on the effects of transdermal nicotine on serum liver tests in PSC patients during UDCA maintenance therapy were available, a formal statistical power analysis was not performed. Twelve patients, treated according to a cross-over study design, were considered sufficient to get an impression of the potential efficacy of nicotine. Data were analysed according to the intent-to-treat principle; of one patient, who dropped out after 4 weeks of treatment in the second period, the last-observation-carried-forward method was used to obtain an 8-weeks outcome. A per-protocol analysis was also performed. Mean daily visual analogue scores for pruritus and fatigue for each week were calculated by dividing the total week score by seven. Serum liver tests were expressed as multiples of the upper limit of normal (xULN). Statistical analysis of these parameters was performed after logarithmic transformation to obtain approximately normal distribution. The absence of possible carry-over and period effects was assessed using methods appropriate for cross-over studies (21). Paired t-tests were used to compare the effects of both treatments. In a single instance, Wilcoxon's signed-rank test was used. A two-sided p-value ≤ 0.05 was considered statistically significant.

Results

Twelve patients with PSC (11 males) were included in the study. The median age was 37 (range 29-50) years. Six patients suffered from ulcerative colitis which was clinically in remission in all cases. Both intra- and extrahepatic bile ducts were affected in all cases. Other baseline patient characteristics are listed in Table I.

Adverse events and drop-outs

One patient with increasing ESR and thrombocyte counts and decreasing haemoglobin during the trial period appeared to have developed severe de novo ulcerative colitis, according to colonoscopic evaluation performed after the study. Two patients dropped out of the study after the first period because of cholangitis necessitating endoscopic stent placement: one in the wash-out period following placebo, the other in the second period after 4 weeks of nicotine treatment. The nicotine dosage had to be reduced to 7.5 mg per day in two cases because of nausea, vomiting and dizziness which occurred within one week of treatment.

Symptoms and physical examination

No statistically significant changes in pruritus or fatigue were observed during either period. Mean change in bodyweight was +1.0 (SD 1.0) kilogram and +0.1 (SD 1.4) kilogram during

placebo and nicotine treatment, respectively (p=0.04). No significant changes in heart rate or blood pressures were found during the placebo or nicotine treatment periods.

Serum liver tests

Mean changes in serum liver tests during nicotine treatment did not differ significantly from those during placebo treatment (Table II). Subgroup analysis for patients with and without ulcerative colitis yielded the same conclusion. Overall, serum markers for cholestasis (in particular APh; Fig 1) and hepatitis tended to decrease more during the placebo period than during the nicotine period, but significance was not reached. Haematological indices remained stable during both treatment periods. Separate analysis without the patients who did not complete the entire study protocol gave essentially the same results.

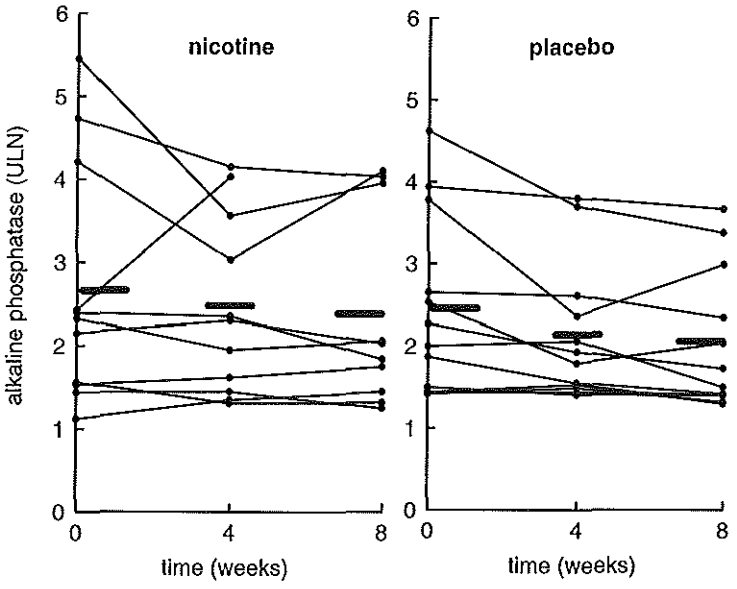

Figure 1. Course of serum alkaline phosphatase (APh) in PSC patients during eight weeks of nicotine and placebo treatment. Data are expressed as multiples of the upper limit of normal (ULN). Horizontal bars indicate means.

Discussion

In this study, we found no evidence of a beneficial effect of short-term transdermal nicotine administration on symptoms and serum liver tests for PSC patients on UDCA maintenance therapy. Previous uncontrolled observations of the oral administration of nicotine to PSC patients (22) are in agreement with the results of this study.

The reasons for this study were the previously reported association of PSC with nonsmoking (15-17) and the positive effects of transdermal nicotine treatment on ulcerative colitis (12, 13), which exhibits a similar association with nonsmoking (11). We chose to continue treatment of our patients with UDCA because a synergistic effect of hydrophilic bile salts and additional immunomodulating therapies might positively influence liver biochemistry and the course of PSC. We therefore cannot exclude the possibility that liver biochemistry improves in patients who do not receive UDCA.

Another possible explanation for the absence of significant effects on liver biochemistry may be that the amounts of nicotine administered in this study were relatively low. In ulcerative colitis, it has been suggested that a nicotine dose of 20-25 mg/day is more effective than a dose of 15 mg/day (13), as used in the present study. However we also took into account the fact that high nicotine dosages are associated with a high incidence of side-effects and marked drop-out rates (12, 13). Our patients tolerated a dose of 15 mg/day reasonably well. The somewhat unexpected finding of a slight but statistically significant increase in bodyweight in the placebo period compared to the nicotine period may be explained by the well-known ability of nicotine to suppress appetite (23, 24). This effect, however, cannot be considered positive for patients with a chronic cholestatic liver disease.

A third explanation may be that the apparent association between PSC and nonsmoking (15-17) is biased by concomitant ulcerative colitis (25). The development of ulcerative colitis in one of our trial patients, who had had two normal colonoscopic examinations in the past 10 years, underlines the difficulty of assessing the true prevalence of ulcerative colitis in PSC.

A further explanation for the absence of apparent beneficial effects of nicotine may be that the drug decreases the risk of developing PSC but does not change the course of stablished disease. All of our patients had extensive intrahepatic and extrahepatic bile duct abnormalities when they were included in the study.

Finally, both the relatively small number of patients studied and the duration of treatment may explain why we were unable to detect a positive effect of nicotine.

When we calculated the 95% confidence interval for the difference (nicotine minus placebo) of the percentage decrease from baseline of APh, we found this interval to range from -1% up to

34%. Although this range is obviously wide, it also shows that the advantage of nicotine is at most a 1% greater decrease as compared to placebo. Such a decrease is clinically irrelevant.

There were several reasons for choosing a treatment period of two months. The main reason was that, in the absence of data with respect to potential benefits, safety and tolerance, it was considered ethically difficult to recruit patients for a blinded trial of longer duration. The possibility was realized that beneficial treatment effects could only become apparent after more prolonged treatment. However, this was considered unlikely considering the reported experience with nicotine in ulcerative colitis. We also believe that a drug that has no positive short-term effects on biochemical liver tests and/or symptoms is unlikely to have significant therapeutic potential when administered for longer time. Moreover, to establish whether a treatment influences the natural course of slowly progressive disorders such as PSC requires large populations treated and followed for many, at least 3-5, years. Such studies are only justified and feasible when sufficient evidence for a potential long-term treatment effect has been established. Therefore, this study was primarily intended as a pilot investigation, to explore the potential efficacy and tolerance of a new treatment option.

A substantial number of medical therapies has been evaluated in controlled trials with PSC patients. The first reports on the effects of treatment with UDCA on serum liver tests were promising (8, 26, 27), but long-term effects on clinical disease progression have been disappointing so far (10). No clear-cut beneficial effects were found for monotherapy with D-penicillamine (5), methotrexate (6), or a combination of UDCA with budesonide, prednisone (7) or methotrexate (28). Although, the present study does not definitively exclude a beneficial effect of nicotine treatment for PSC patients, the results indicate that such effect is not likely.

Table I. Baseline characteristics of 12 patients with primary sclerosing cholangitis.

age (years)	37.1 ± 6.3
Sex (male / female)	11 / 1
intra- / extrahepatic PSC / combined	0 / 0 / 12
UDCA dose (mg / kg / day)	13.5 ± 4.1
ulcerative colitis (n)	6 (50%)
5-amino salicylic acid (n)	6 (50%)
bilirubin (xULN)	1.3 (0.5-2.6)
APh (xULN)	2.5 (1.4-4.7)
γGT (xULN)	7.7 (0.7-38.0)
AST (xULN)	1.9 (0.5-3.2)
ALT (xULN)	2.4 (0.4-7.3)
LD (xULN)	0.7 (0.5-1.2)
total cholesterol (xULN)	0.9 (0.6-1.4)
total bile salts (xULN)	10.9 (2.1-39.0)
albumin (xULN)	0.8 (0.7-0.9)
PT (xULN)	0.9 (0.7-1.1)
IgG (xULN)	1.2 (0.8-1.7)

Means with ranges in parentheses. xULN: multiples of the upper limit of normal.

Table II. Mean percentage changes from baseline (95% confidence intervals in parentheses) of serum liver tests during nicotine and placebo treatment.

	Nicotine		placebo		*p*-value*	
	0 vs 4 weeks	0 vs 8 weeks	0 vs 4 weeks	0 vs 8 weeks	0 vs 4 weeks	0 vs 8 weeks
Bilirubin	+11 (-18, +50)	+13 (-16, +52)	+2 (-11, +17)	-6 (-16, +5)	0.61	0.22
Aph	-4 (-19, +14)	-3 (-18, +14)	-12 (-21, -1)	-17 (-22, -11)	0.21	0.06
γ-GT	-5 (-19, +11)	-11 (-20, 0)	-10 (-21, +3)	-13 (-22, -3)	0.42	0.62
AST	+1 (-29, +43)	+2 (-24, +37)	-6 (-18, +7)	-10 (-24, +7)	0.65	0.33
ALT	0 (-31, +47)	-1 (-29, +39)	-9 (-28, +14)	-11 (-28, +12)	0.50	0.49
LD	-7 (-20, +7)	-11 (-33, +17)	+6 (-6, +18)	+4 (-5, +15)	0.17	0.25
Cholesterol	-2 (-10, +7)	-4 (-12 +6)	0 (-7, +7)	-2 (-9, +6)	0.83	0.77
Bile salts	+13 (-32, +87)	+36 (-12, +110)	+37 (-20, +136)	-3 (-38, +52)	0.53	0.30
Albumin	-1 (-6, +3)	-5 (-15, +7)	-2 (-6, +1)	-3 (-7, +2)	0.76	0.70
PT	-1 (-4, +3)	-1 (-5, +3)	-1 (-7, +6)	0 (-7, +8)	0.98	0.68
IgG	-1 (-6, +4)	+4 (-4, +13)	+2 (-1, +5)	+2 (-3,- +6)	0.38	0.63

* *p*-value for the comparison of the %-changes from baseline during nicotine and placebo treatment

Acknowledgement

We gratefully acknowledge the support of Dr M.C.J.M. Becx, Ziekenhuis Overvecht, Utrecht; Mrs. B.A.W. Dietz, Pharmacist, Pharmacia & Upjohn B.V., Woerden and Mrs L.M. Hanff, Pharmacist, Department of Pharmacy, University Hospital Rotterdam, the Netherlands.

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Summary

Primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC), collectively also called immunocholangitis, are not well-defined liver diseases. Both terms represent a wide range of disorders whereby some characteristics may be indicative of one of the diseases in the restricted sense.

Demonstration of antimitochondrial antibodies and non-suppurative destructive cholangitis in patients with cholestatic serum liver tests justifies the diagnosis of PBC. However diagnostic evaluation should not be stopped at this point and concomitant liver-related signs and symptoms should not be disregarded. When severe (icteric) hepatitis with hypergammaglobulinaemia occurs in a PBC patient, the possibility of a PBC-autoimmune hepatitis (AIH) overlap syndrome should be considered. Cholestatic jaundice, often accompanied by refractory pruritus and weight loss, in a non-cirrhotic PBC patient with normal liver synthesis capacity may be indicative of premature ductopenic PBC. These variants of ordinary PBC can be seen as the extremes of the PBC spectrum. In the PBC-AIH overlap syndrome, inflammation of (lobular) liver parenchyma determines the clinical, biochemical and histological patterns. In contrast, severe interlobular bile duct loss dictates the clinical, biochemical and histological patterns of the premature ductopenic variant of PBC.

When cholangiography shows multiple biliary strictures and dilatations, PSC should not be diagnosed automatically since the biliary system possesses a rather limited repertoire of responses to a large variety of local and systemic pathological processes. Identical cholangiographical pictures can be encountered in 'sclerosing pancreato-cholangitis' and PSC. Sclerosing pancreato-cholangitis is distinguished from PSC in the narrow sense by its occurrence in middle-aged men, the absence of concomitant inflammatory bowel disease and an initial presentation mimicking that of pancreatic cancer. Furthermore, in addition to systemic disorders such as AIDS, 'graft-versus-host' disease and systemic idiopathic fibrosis, local abnormalities such as portal vein thrombosis followed by cavernomatous transformation may also cause sclerosing cholangitis. As in PBC, AIH can also coincide with PSC. The PSC-AIH overlap syndrome seems to occur in approximately 10% of a PSC patient population, thereby suggesting a higher prevalence than was previously presumed.

This further differentiation of sclerosing cholangitis and primary biliary cirrhosis is not only scientifically interesting from the standpoint of classification, but also has clear value

for clinical decision-making with respect to prognosis and treatment of the individual patient. The abnormalities of sclerosing pancreato-cholangitis respond quite well to therapy with prednisone, whereas PSC does not seem to benefit from this approach. Other pharmaseutical options, such as nicotine and budesonide, also do not have a positive influence on PSC. In case of an overlap of PSC or PBC with AIH immunosuppressive therapy with prednisone and possibly also azathioprine should be instituted. The AIH-component in particular can be suppressed effectively in these disorders. In contrast to ordinary PBC the premature ductopenic variant does not seem to benefit from treatment with ursodeoxycholic acid and immunosuppressives. Consideration of early liver transplantation for treatment of refactory pruritus and prevention of ongoing weight loss seems indicated for this category of patients.

In addition to the establishment of a diagnosis that describes the disorder of the individual patient, a reliable estimation of the prognosis of that disease is an important aspect of the management of a patient with immunocholangitis. The mathematical prognostic models developed by the Mayo Clinics merely facilitate the timing of liver transplantation, since the entry variables of these models depend on the severity of the liver disease itself. Several factors which are independent of the stage of PBC, such as AMA-profiles and AMA-titres, unfortunately have turned out to be unable to differentiate between a progressive and a relatively benign course of disease. In PSC, a prognostic factor which is independent of the stage of disease is also unknown. However, the occurrence of PSC-specific complications, such as a dominant bile duct stricture, suppurative cholangitis or cholangiocarcinoma, during the course of disease appears to be associated with a shorter transplantation-free survival.

An increase in our knowledge of these diseases will hopefully enable us to determine the prognosis for the individual immunocholangitis patient in order to institute tailor-made treatment in the future.

Samenvatting

Primaire scleroserende cholangitis (PSC) en primaire biliaire cirrose (PBC), tezamen ook wel immuuncholangitis genoemd, zijn niet twee duidelijk afgebakende leverziekten. Beide vertegenwoordigen spectra van aandoeningen waarvan sommige kenmerken een indicatie kunnen zijn voor één van beide ziekten in engere zin.

Het aantonen van antimitochondriale antistoffen (AMA) en non-purulente destructieve cholangitis bij een patiënt met cholestatische leverfunctiestoornissen rechtvaardigt de diagnose PBC. Hiermee dient niet de diagnostische evaluatie te worden beëindigd en eventuele bijkomende lever gerelateerde verschijnselen te worden genegeerd. Wanneer ernstige (icterische) hepatitis met hypergammaglobulinemie bij een PBC patiënt wordt gevonden, moet stellig rekening gehouden worden met de mogelijkheid van een PBC-autoimmuunhepatitis (AIH) overlap syndroom. Cholestatische icterus, vaak gepaard gaande met therapie-resistente jeuk en gewichtverlies, bij een non-cirrotische PBC patiënt met een normale eiwit leversynthese capaciteit kan wijzen op prematuur ductopene PBC. Deze varianten van reguliere PBC zouden beschouwd kunnen worden als uitersten van het PBC spectrum. Bij het PBC-AIH overlap syndroom staat zowel klinisch, biochemisch als histologisch inflammatie van het (lobulaire) leverparenchym op de voorgrond. Bij de voortijdig ductopene PBC variant daarentegen bepaalt het ernstige interlobulaire galgangverlies het klinisch, biochemisch en histologisch beeld.

Wanneer bij cholangiografie multipele galgangstricturen en -dilataties worden gevonden dient niet automatisch de diagnose PSC te worden gesteld. De galboom heeft namelijk slechts een beperkt repertoire van reactie mogelijkheden op een breed scala van lokale en systemische aandoeningen ter beschikking. Identieke cholangiografische beelden van scleroserende cholangitis kunnen zowel bij PSC als bij 'scleroserende pancreato-cholangitis' worden gevonden. Deze laatst genoemde aandoening onderscheidt zich van PSC in engere zin doordat het voornamelijk voorkomt bij mannen van middelbare leeftijd, niet gepaard gaat met inflammatoire darmziekte en de initiële presentatie sterk lijkt op die van patiënten met een pancreascarcinoom. Naast systemische aandoeningen, zoals onder andere AIDS, 'graft-versus-host' ziekte en systemische idiopathische fibrose, kunnen lokale aandoeningen zoals trombose van de vena portae met cavernomateuze transformatie eveneens de oorzaak van scleroserende cholangitis zijn. Evenals bij PBC bestaat er bij PSC ook een overlap syndroom met AIH. Het PSC-AIH overlap syndroom lijkt in ongeveer 10% van de PSC patiënten populatie voor te komen en lijkt daarom minder zeldzaam dan voorheen werd gedacht.

Deze verdergaande differentiatie van scleroserende cholangitis en primaire biliaire cirrose is niet alleen wetenschappelijk gezien interessant vanuit het oogpunt van classificatie, maar heeft tevens duidelijke waarde voor beslissingen betreffende behandeling en inschatting van de prognose van een individuele patiënt. De afwijkingen

passend bij scleroserende pancreato-cholangitis lijken zeer goed te reageren op behandeling met prednison, terwijl PSC niet lijkt te responderen op deze behandeling. Andere medicamenteuze behandelings opties voor PSC, zoals nicotine en budesonide, lijken de ziekte evenmin in gunstige zin te kunnen beïnvloeden. Wanneer er sprake is van een overlap syndroom met AIH, zowel bij PSC als PBC, dient immunosuppressieve behandeling met prednison, eventueel aangevuld met azathioprine, in principe gegeven te worden. Met name de AIH component van deze ziektebeelden kan hiermee worden onderdrukt. In tegenstelling tot 'reguliere' PBC lijkt de premature ductopene variant van PBC geen baat te hebben van behandeling met ursodeoxycholzuur en immunosuppressiva. Snellere overweging van levertransplantatie in verband met invaliderende therapie-resistente jeuk en voorkoming van verdergaand gewichtsverlies, ondanks intacte lever eiwitsynthese en afwezigheid van cirrose, is bij deze categorie PBC patiënten aangewezen.

Een betrouwbare inschatting van de prognose van de ziekte is, naast het stellen van een diagnose die zoveel als mogelijk is afgestemd op het ziektebeeld van de individuele patiënt, een ander belangrijk aspect van de behandeling van een immuuncholangitis patiënt. De mathematische prognostische modellen die ontwikkeld zijn door de Mayo Clinics kunnen slechts helpen bij de timing van levertransplantatie aangezien de uitgangsvariabelen van deze modellen een uiting zijn van de ernst van de leverziekte. Verschillende factoren die onafhankelijk zijn van het stadium van PBC, zoals AMA-profielen en AMA-titers, blijken helaas geen onderscheid te kunnen maken tussen patiënten met een progressief of een relatief goedaardig ziektebeloop. Bij PSC is evenmin een prognostische factor, die onafhankelijk is van het ziektestadium, bekend. Het optreden van PSC-specifieke complicaties, zoals een dominante galgangstenose, cholangitis of cholangiocarcinoom, tijdens het beloop van de ziekte blijkt echter geassocieerd te zijn met een slechtere transplantatie-vrije overleving.

Hopelijk zal toename van onze kennis van deze ziekten ons in de toekomst in staat stellen een op de individuele immuuncholangitis patiënt toegespitste prognose te bepalen om een op maat gesneden therapie te kunnen instellen.

Dankwoord

Een proefschrift schrijven is een gezamenlijke onderneming. Daarom zou ik graag een aantal mensen willen bedanken voor hun hulp. Op de eerste plaats alle patiënten die aan de onderzoeken hebben meegewerkt. Zonder deelname van patiënten is een klinische studie niet mogelijk. Ex aequo op de eerste plaats Henk van Buuren, mede-bedenker van dit boekje. Beste Henk bedankt voor je enthousiaste en zorgvuldige begeleiding. De jaren bij jou op de kamer waren plezierig en bovenal erg gezellig. Ik mis onze vrijdagmiddag-avond borrel al. Professor Solko Schalm zou ik willen bedanken voor de vrijheid die hij mij gaf mijn onderzoek zo veel mogelijk naar eigen inzicht in te richten. Het is inderdaad veel spannender gedurende de onderzoeksperiode nieuwe studies te verzinnen dan een vooropgezet plan blindelings uit te voeren. Professor Gerard van Berge Henegouwen zou ik willen bedanken voor de gastvrijheid en het mogen gebruik maken van de faciliteiten van de afdeling Gastroenterologie van het UMCU. Ik voelde me er meteen welkom. Uw talent om mensen te stimuleren en tegelijkertijd op hun gemak te stellen is ongeëvenaard.

De firma's Zambon Nederland B.V. en Tramedico Nederland B.V. hebben door hun ondersteuning van de nederlandse PBC en PSC studiegroepen het uitvoeren van de studies mede mogelijk gemaakt. Met name Gerrit Paarlberg zou ik hierbij willen bedanken. De dames van het (trial)secretariaat van de Afdeling Maag-, Darm- en Leverziekten: Sylvia de Vlaming, Mieke Pruijsten, Wil van Weert en Marcelle Houtman stonden altijd klaar secretariële hulp te bieden. Jan Boot zorgde ervoor dat de computer aan de praat bleef. Met collega arts-onderzoekers Bart van Hoogstraten, Michael Groeneweg, Pieter Honkoop, Frank Bekkering, Tekla van Rossum, Annick van Nunen, Leonieke Wolters en Thjon Tang was het altijd lachen in de duiventil van Dijkzigt. Bij Wim Hop en Bettina Hansen, bio-statistici, kon altijd hulp worden ingeroepen. Beste Wim, na een uurtje stoeien met Stata op jouw kamer dacht ik het allemaal weer te begrijpen. Pieter Zondervan en Monica Seijbel van de afdeling Pathologie hebben veel geholpen bij histologische onderdelen van het onderzoek. De samenwerking met de Utrechtse maag-, darm- en leverartsen Karel van Erpecum en Jan van Hattum was erg prettig. De leden van de beoordelingscommissie dank ik hartelijk voor hun tijd en moeite het manuscript te beoordelen.

Lieve papa en mama, bedankt voor jullie stimulans en vertrouwen in mij. Lieve Mariëlla, jouw hulp was onmisbaar.

Curriculum vitae

De auteur van dit proefschrift werd geboren op 15 april 1972 te Dordrecht. In 1990 behaalde hij het V.W.O. diploma aan de Willem de Zwijger scholengemeenschap in Papendrecht. In dat zelfde jaar werd begonnen met de studie Geneeskunde aan de Erasmus Universiteit Rotterdam. In 1994 was hij gedurende een half jaar als student werkzaam op de afdeling Klinische Microbiologie en Antimicrobiële Therapie van de Erasmus Universiteit Rotterdam. In 1996 werd gedurende 5 maanden onder begeleiding van H.R. van Buuren post-doctoraal onderzoek verricht naar de resultaten van endoscopische sclerotherapie bij patiënten met varicesbloedingen op basis van vena portae thrombose op de afdeling Maag-, Darm- en Leverziekten (toen nog Inwendige Geneeskunde II) van het Academisch Ziekenhuis Rotterdam Dijkzigt. Hij behaalde het artsexamen op 20 december 1996. Van januari 1997 tot april 2000 was hij werkzaam als arts-onderzoeker op de afdeling Maag-, Darm- en Leverziekten van het Dijkzigt Ziekenhuis. Tijdens deze periode werd onder begeleiding van H.R. van Buuren, professor S.W. Schalm en professor G.P. van Berge Henegouwen onderzoek verricht op het gebied van immuuncholangitis, hetgeen de basis vormde voor dit proefschrift. Sinds mei 2000 is hij in opleiding tot maag-, darm- en leverarts.