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Clinical course of primary sclerosing cholangitis and concomitant ulcerative colitis — a preliminary report of retrospective study among patients from Southern Poland

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Abstract: Both ulcerative colitis (UC) and primary sclerosing cholangitis (PSC) are chronic and progressive diseases of uncertain etiology, that may affect one patient. Approximately 70% of PSC cases are also diagnosed with UC, whereas in the group of UC the prevalence of PSC is about 2–5%. The aim of the study was to compare clinical courses of PSC and UC in patients diagnosed with both diseases to those with the confirmed diagnosis of either PSC or UC. Three groups were distinguished and evaluated: patients with PSC and UC (n = 17) and two control groups: patients with PSC (n = 4) and with UC (n = 13). Clinical data, symptoms, laboratory tests, results of the magnetic resonance cholangiopancreatography and colonoscopy were analyzed to compare clinical courses of these diseases between the groups. Conclusion: there is no correlation between clinical course of simultaneous PSC and UC. However, it may differ depending on co-occurrence of the other disease.

Key words: primary sclerosing cholangitis, ulcerative colitis, inflammatory bowel disease, autoimmune liver disease.

Introduction

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of complex etiology, with progressive course, inflammation, fibrosis and stricturing of biliary tree, that leads to destruction of both extra- and intra-hepatic bile ducts, cholestasis and end-stage liver disease [1, 2]. Majority of patients are asymptomatic at the time of diagnosis, which in such cases is

established only by an isolated elevation of serum cholestasis parameters, especially alkaline phosphatase (ALP) and also alanine aminotransferase (ALT), aspartate transaminase (AST) and gamma — glutamylotranspeptidase (GGTP) [3, 4]. Clinical symptoms of PSC include: hepatosplenomegaly, pruritus, excoriations and jaundice. Most of PSC patients (97%) present at least one type of autoantibody in the serum and 81% of them are positive for more than 3 types of autoantibodies. These include mainly anti-neutrophil cytoplasmic, anti-nuclear, anti-smooth muscle, anti-endothelial cell and anti-cardiolipin antibodies [5, 6].

Magnetic resonance cholangiopancreatography (MRCP) is currently considered as a gold standard in PSC evaluation [7, 8]. Endoscopic retrograde cholangiopancreatography (ERCP) is used in patients, who cannot undergo MRCP or when direct intervention on bile ducts is required. Pathological biliary tract demonstrates multifocal strictures which may be separated by dilatations or present as a diffuse narrowed segments. Following types of the disease may be distinguished according to the extent of lesions within the biliary tract: affecting only intra-hepatic, only extra-hepatic, or both only intra- and extra-hepatic bile ducts [1].

The main goal of the management of PSC is to retard its progression and prevent further complications, such as bacterial cholangitis, vitamin deficiencies, dysplasia and end-stage liver disease. Pharmacological treatment comprises immunosuppressants, anti-inflammatory agents and ursodeoxycholic acid (UDCA). Since etiology remains largely unknown, the treatment has not been conclusively proven to alter the natural history of the disease [9]. Prognosis is still poor and median survival without liver transplantation after diagnosis is 10 to 12 years [10–13].

The majority of patients with PSC (70–90%) has underlying diagnosis of ulcerative colitis (UC). The prevalence of UC is higher when rectal and sigmoid biopsies are routinely obtained [14]. Conversely, patients with UC have about 5% prevalence of concomitant PSC [15].

UC is a diffuse superficial inflammation of mucous membrane of the large intestine. Clinical course is intermittent and characterized by recurrent exacerbations of active inflammatory process separated by remissions. It commonly affects the rectum and may extend to proximal parts of the colon and, less often, Bauhin's valve and the terminal segment of the ileum [16].

The most common manifestation of UC includes chronic diarrhea with stools containing blood and mucus, sometimes accompanied by cramps and, in more severe cases, continuous bleeding. Other symptoms are usually result of severe diarrhea and blood loss e.g. anemia, electrolyte abnormalities [17]. Diagnosis is based mainly on clinical symptoms, typical endoscopic findings and characteristic histological features [18]. The most prevalent extra intestinal manifestation in UC is hepatobiliary involvement, which is considerably more frequent in UC than in Crohn's disease [19]. The pathogenesis of hepatobiliary manifestations associated with UC may be related to liver-gut cross talk such as in PSC, PSC/autoimmune hepatitis overlap and IgG4-associated cholangitis [19]. Therapy of UC is based mainly on anti-inflammatory and immunosuppressive agents. Patients diagnosed with PSC and concomitant UC (PSC/UC) often present with altered course of both of them. The severity of PSC seems to have a 'protective' influence on UC activity. Although it is associated with greater extent of changes in the large intestine and a higher risk of colorectal

cancer, the course of UC is usually clinically more quiescent [20]. The course of PSC also depends on comorbid UC. The data suggest that concurrent inflammatory bowel disease (IBD) may be associated with poorer prognosis, lower median age of onset, higher risk of serious malignant complications and lower transplant-free survival [5, 21]. The aim of the study was to compare clinical courses of PSC and UC as co-existing diseases to the course in patients diagnosed with either PSC and UC, to find correlations between statuses of these diseases, on the basis of MRCP, colonoscopy and biochemical parameters analysis, among patients of the Department of Gastroenterology and Hepatology, Jagiellonian University, Kraków, Poland.

Material and methods

Seventeen patients diagnosed with both PSC and UC (mean age 35.1 ± 9.59 years) and two control groups: patients diagnosed with either PSC (4 subjects; mean age 34.3 ± 2.5 years) or UC (13 individuals; mean age 38.4 ± 20 years) were included into the study. Statistical analysis revealed no significant difference in age between all the groups. Table 1 summarizes main characteristics of patients (Table 1).

The diagnosis was based on classic diagnostic criteria using current gold standard methods: MRCP with both clinical and laboratory findings (PSC), colonoscopy and clinical symptoms (UC). Exclusion criteria included: other inflammatory or cholestatic diseases as well as secondary sclerosing cholangitis and other IBD. Clinical data were obtained from medical records of patients hospitalized in the Department of Gastroenterology and Hepatology, University Hospital, Kraków, between 2009 and 2014 years. The protocol of the study was approved by the Jagiellonian University Bioethical Committee. All patients provided their informed consent.

Total number of visits in each group was as follows: 56 in study group, 11 in group of patients diagnosed with PSC only and 34 in patients diagnosed with UC. We have analyzed clinical symptoms, morphological and biochemical parameters in blood: C-reactive protein (CRP), red blood cells (RBC), hematocrit (Hct), hemoglobin (Hb), white blood cells (WBC), platelets (PLT), albumin, ALT, AST, GGTP, ALP, bilirubin, prothrombin time (PT), INR, APTT and severity of the disease (established in endoscopic and imaging techniques). Follow-up was censored at the time of last clinical visit. Within all the groups there were patients treated with immunomodulators (azathioprine, 5-aminosalicilic acid (5-ASA), glicocorticosteroids, tacrolimus). PSC patients received additionally UDCA. Among UC patients there were individuals treated with anti-TNF agents.

Four of the patients were qualified for liver transplantation, one of them as a matter of urgency due to liver insufficiency.

The statistical analysis was performed using Statistica 10 software (StatSoft Inc., Tulsa, Oklahoma, United States) with license to the Jagiellonian University Medical College. The distribution of variables was checked with the Shapiro-Wilk test. A p-value less than 0.05 was considered statistically significant.

Table 1. Characteristics of patients in studied groups.

Variables	PSC (n = 4)	p-value	PSC & UC (n = 17)	p-value	UC (n = 13)
Age, mean (± SD)	34.3 (± 2.5)	0.862	35.1 (± 9.59)	0.083	38.4 (± 20)
Male sex, %	100%	–	76.5%	–	76.9%
Age at diagnosis of PSC, mean (± SD)	30.5 (± 0.71)	0.783	28.3 (± 10.8)	–	–
Age at diagnosis of UC, mean (± SD)	–	–	27.1 (± 11.8)	0.239	33.82 (± 17.37)
Mean no. of hospitalizations (±SD)	2.75 (± 0.5)	0.121	3.65 (± 1.41)	0.025	2.62 (± 2.57)
Bile duct involvement (number of individuals, %)					
— intrahepatic only	0 (0)	–	2 (11.75)	–	–
— extrahepatic only	1 (25)	–	2 (11.75)	–	–
— intra and extrahepatic	3 (75)	–	13 (76.5)	–	–
— gall bladder	1 (25)	–	4 (23.5)	–	–
Bowel involvement (number of individuals, %)					
— rectum	–	–	1 (5.9)	–	1 (7.7)
— sigmoid colon	–	–	2 (11.8)	–	2 (15.4)
— left colitis	–	–	2 (11.8)	–	5 (38.5)
— pancolitis	–	–	8 (47)	–	5 (38.5)
Other information (number of individuals, %)					
Liver transplantation qualification	No data	–	4 (23.5)	–	–
Colectomy during follow-up	–	–	1 (5.9)	–	No data
Cholangiocarcinoma during follow-up	No data	–	1 (5.9)	–	–
Colorectal cancer during follow-up	–	–	1 (5.9)	–	1 (7.7)
Therapeutic management (number of individuals, %)					
Immunomodulators	2 (50)	–	16 (94)	–	11 (84.6)
Biologic agents	0 (0)	–	0 (0)	–	2 (15.4)
UDCA	3 (75)	–	16 (94)	–	0 (0)

Results

Average age at the diagnosis of each disease was lower among PSC/UC patients than in control groups (PSC: 28.3 vs 30.5 years; UC: 27.1 vs 33.82 years) but the difference was statistically irrelevant ($p = 0.783$ and $p = 0.239$ respectively). In the PSC/UC group we found

that in 4 cases PSC diagnosis preceded the UC symptoms, whereas 8 patients were primarily diagnosed with UC. In 7 cases, exacerbation of PSC coexisted with the UC remission. 5 patients were hospitalized with PSC and UC exacerbations coexisting at the same time. The hepatobiliary tract involvement was evaluated according to localization of lesions (extra- or intra-hepatic ducts and gall bladder). Intra-hepatic bile ducts alone were more commonly affected in PSC/UC patients as compared to PSC group (n = 2; 14.3% vs n = 0; 0%). Total biliary tree involvement (presence of lesions within both intra- and extra-hepatic ducts) was more prevalent in PSC/UC patients than in control group (n = 13; 76.5% vs n = 3; 75%), so was presence of changes within gall bladder (n = 4; 23.5% vs n = 1; 25%).

Extent of lesions in colon was assessed during colonoscopy. The results are presented in Table 1. Prevalence of pancolitis (defined as disease extending proximal to splenic flexure [22]) was higher among patients with comorbid PSC (n = 8; 61.54% vs n = 5, 38.5%). Left-sided colitis (disease involving segments distal to splenic flexure) was found in 38.46% of patients with UC compared to 15.38% of patients with underlying PSC.

Laboratory tests were presented in Table 2. Anemia (Hb <13.5 g/dl in men or <12 g/dl in women) was more common in the UC group than among individuals with underlying PSC (58.8% vs 38.46%) and patients with PSC alone (n = 0, 0%). Serum level of CRP was similarly elevated in both PSC/UC and UC patients, however in PSC patients it did not reach the upper normal limit in majority of cases. The activity of ALP in serum was higher in PSC/UC patients as compared to PSC alone (p = 0.017); GGTP was also increased, however the difference was not statistically significant. The mean INR value was within the normal ranges in all the groups.

Table 2. Laboratory results in patients of studied groups.

Variables (mean ± SD)	PSC (n = 4)	p-value	PSC & UC (n = 17)	p-value	UC (n = 13)
Albumin, mg/dl	–	–	40.15 (± 7.37)	0.287	36.56 (± 8.85)
Bilirubin, umol/l	13.85 (± 2.82)	0.105	73.14 (± 80.20)	0.0009	6.2 (± 5.11)
ALP, IU/l	122 (± 60.44)	0.017	425.2 (± 462.68)	0.000002	65.92 (± 19.7)
GGTP, IU/l	164.25 (± 242.61)	0.149	233.9 (± 210.55)	0.000002	25.92 (± 16.97)
ASP, IU/l	42.3 (± 36.12)	0.417	58.7 (± 34.07)	0.000226	16.57 (± 4.47)
ALT, IU/l	48.67 (± 52)	0.369	82.22 (± 59.38)	0.000005	16.6 (± 6.43)
INR	1.03 (± 0.04)	0.824	1.1 (± 0.18)	0.914	1.06 (± 0.08)
PT, s	11.78 (± 0.3)	0.583	12.4 (± 1.63)	0.493	12.1(± 2.13)
APPT, s	32.4 (± 3.66)	0.55	33.8 (± 4.63)	0.192	32.25 (± 6.96)
RBC, $\times 10^6$/ul	4.84 (± 0.45)	0.26	4.33 (± 0.75)	0.263	4.03 (± 0.87)
Hb, g/dl	14.65 (± 1.35)	0.08	12.52 (± 2.33)	0.825	12.08 (± 2.72)
WBC, $\times 10^3$/ul	8.75 (± 1.55)	0.178	7.4 (± 3.34)	0.301	8.29 (± 3.12)
PLT, $\times 10^3$/ul	236 (± 52.22)	0.56	280.52 (± 164.65)	0.34	326.63 (± 143)
CRP, mg/l	4.31 (± 2.28)	0.30	27.59 (± 41.02)	0.546	23.89 (± 22.71)

Discussion

Almost every published data concerning PSC summarizes its course as highly variable. So is emphasized the fact that it is associated with intestinal bowel diseases. Our results seem to confirm these observations.

It was revealed that PSC is more common in men than women, which is consistent with published literature [4, 5]. The PSC diagnosis is usually established before the age of 40 and our study also provides a confirmation of that fact [5]. The influence of comorbid UC on the age of diagnosis remains to be explained. Some authors reported the higher age of disease onset in the group with concomitant UC compared to PSC alone, whereas others reported the opposite tendency [23]. In our study the age of PSC onset was lower in patients with underlying UC, however the difference was not statistically significant (28.3 vs. 30.5 years, $p = 0.9$). The study revealed that UC diagnosis predated the symptoms of PSC in 8 cases (compared to 4, when PSC was diagnosed before UC). This result is consistent with majority of reports [23]. ALP elevation — considered to be the main feature of PSC [4, 5] — was significantly elevated in 96% of patients suffering from PSC, however only in 30% of cases ALP elevation was greater than 3 times upper the normal range. Our data suggest also that bilirubin level is not diagnostic for PSC as it did not exceed upper normal limit in 56% of hospitalized patients (other authors reported on 60% [5]). The extent of lesions in the hepatobiliary tract observed in our patients in MRCP was the most often classified as both intra- and extra-hepatic involvement, which was previously reported in several studies [5]. According to Rojas-Feria M. *et al.* in 41% of cases PSC presents with lesions within the gall bladder and cystic duct [14]. In our study, the prevalence of gall bladder involvement was lower than it was reported by other authors and similar in the aspect of influence of underlying colon disease (25% vs 23.5% for PSC and PSC/UC respectively) [14].

Analysis of the UC activity in certain parts of the colon led us to several conclusions. We have observed a slightly elevated incidence of pancolitis among patients with confirmed PSC compared to patients with no comorbidities (61.5% vs 38.5%). Disease limited to the left part of the colon was found in 61.5% of patients with UC compared to 38.5% of patients with underlying PSC. This result is consistent with a study of Sano *et al.* (2011), which involved more profound histological examination [23]. The authors suggest, that massive inflammatory infiltration was less frequent in the group of patients with comorbid PSC.

The majority of reports also suggests that the extent of colon lesions in PSC/UC group may, in most cases, be described as pancolitis [24]. However there is a substantial amount of evidence of the opposite conclusion [24] and moreover one of the reports indicates the influence of each disease onset — whether UC preceded or followed the PSC diagnosis — more prevalent was pancolitis and right-sided colitis respectively [25]. Our study does not contribute to substantiate this outcome due to the limited group.

One of the patients enrolled into the study developed cholangiocarcinoma during the follow-up. About 10–15% of the patients with PSC develop this neoplasm at some time [26]. There were also two cases of colorectal cancer: one in patient with UC with newly diagnosed PSC and the other in individual with UC alone.

Difference in clinical course between these two diseases derives from their complicated genetic background, however it represents approximately 10% of all risk factors and their implication have not been defined yet [27, 28]. Genotyping HLA alleles in patients suffering from UC, PSC and combined PSC-UC provides an evidence that HLA profile differs in UC patients in respect of concomitant PSC, however the opposite trend is not observed-difference in HLA alleles frequency between PSC patients with and without concurrent UC is not statistically significant [27].

The presented data were collected retrospectively, therefore its value is limited by completeness and accuracy of clinical information included in patients' medical records. However, this was not the only limitation to our study. Since it was single-center database, the number of patients also limits certain analysis and so that it is difficult to drown some of the conclusions. Nonetheless, the prevalence of IBD among PSC patients indicates the need for special surveillance and screening for intestinal disease within this group, before the symptomatic IBD appears.

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Conflict of interest

None declared.

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