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Clinical Characteristics and Outcomes of Inflammatory Bowel Disease Associated with Primary Sclerosing Cholangitis in Northeastern Brazil

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Abstract

Background: Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver and is highly associated with Inflammatory Bowel Disease (IBD).

Objective: Our aim was to evaluate the prevalence of PSC, phenotypic characteristics, outcomes in a cohort of IBD patients from a single-center in Northeastern of Brazil.

Methods: Data were analyzed retrospectively; risk factors of Ulcerative Colitis (UC)-PSC were compared with UC alone.

Results: Of 601 IBD patients, 20 had PSC (3.3%). PSC was higher in UC 4.7% (15/321) than Crohns Disease (CD) 1.8% (5/280) p=0.040. The mean of follow-up time was 78 months. Of 20 IBD-PSC, large biliary ducts were affected in 70% (7 intrahepatic, 1 extrahepatic, 6 both intra and extrahepatic), small duct PSC in 30%, pancolitis was present in 95%, backwash ileitis in 10%, and rectal sparing in no patient. Three IBD-PSC patients (15%) underwent liver transplantation, 1 developed gallbladder cancer, 2 (10%) colon cancer compared to 5 (3%) in IBD alone p=0.011.2), 2 IBD-PSC died with sepsis secondary to cholangitis. In the subgroup analysis, UC-PSC was associated with gender, male sex (60 % UC-PSC *vs* 36.1% UC; p=0.018), age (24.5±12.5 UC-PSC *vs* 37.4±16.1 UC; p=0.011) and pancolitis (93.3% in UC-PSC *vs* 29.7% in UC; p<0.001). Smoking, alcoholism and family history of IBD were not associated with UC-PSC.

Conclusion: Prevalence of PSC was 4.7% in UC and 1.8% in CD patients. Pancolitis were present in most of IBD patients with concomitant PSC. Male sex and younger age were associated with UC-PSC.

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Introduction

Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the intra and extrahepatic bile ducts, leading to the formation of multifocal stenosis interspersed with areas of biliary tree dilation [1]. The etiopathogenesis of PSC is not clear, however most patients progress to cirrhosis, ultimately requiring liver transplantation. Additionally, no medical therapy has been shown to significantly interrupt PSC progression [2].

PSC is highly associated with Inflammatory Bowel Disease (IBD). Around 50% to 80% of the patients with PSC are also diagnosed with IBD; but the inverse association is much lower, with a prevalence of PSC in patients with IBD around 2.4% to 7.5% in Ulcerative Colitis (UC) and 3.4% in Crohn's Disease (CD) [3].

IBD-PSC may represent a unique phenotype with outcomes diverse from those seen in PSC or IBD alone [4]. Patients with PSC-UC have been associated with lower inflammatory bowel activity, higher prevalence of pancolitis, preferential reaching of the right colon with rectal sparing and backwash ileitis [4]. A higher rate of colorectal carcinoma in IBD- PSC patients compared to IBD patients without concomitant PSC [5].

A recent review has shown that geographic variations may exist in the IBD-PSC phenotype, as well as PSC-IBD concurrence rates [6]. The epidemiologic data and characteristics of IBD with concomitant PSC have been well described in Northern Europe and United States. However, data are scarce from certain regions, such as Latin America and Brazil; of note, in this region the incidence of IBD has been increasing in the last decades [7]. Expanding epidemiological data regarding IBD-PSC with respect to the frequency of their concurrence and the impact on disease-related outcomes are needed in order to allow for earlier diagnoses, appropriate follow-ups and more efficient treatments.

It has been shown that geographic variations may exist in the IBD-PSC phenotype [6]. The epidemiologic data and characteristics of IBD with concomitant PSC have been well described in Northern Europe and United States. Although the incidence of IBD has been increasing in the last decades in Brazil [7], there is few reports in IBD-PSC, and any study from Northeastern of the country.

The aim of the study was to evaluate the prevalence of PSC, phenotypic characteristics and outcome in a cohort of IBD patients followed in a single-center in Northeastern Brazil.

Methods

Study design

This retrospective study involved a cohort of patients who were registered and followed up at a referral center specialized in IBD care at the Walter Cantídio Hospital of Federal University Hospital, in Fortaleza Ceara Northeastern of Brazil, between January 2005 to December 2019.

Study location

The Walter Cantídio Hospital is a Teaching Hospital located in Fortaleza, the capital of the State Ceará Northeastern Brazil. The IBD Center provides care to low- income patients through the Public Health System (Sistema Único de Saúde - SUS) and is a reference in a IBD care for the State which has an estimated population of 9.1 million inhabitants. The IBD Center started providing care for IBD patients since February 2005.

Patients

It was evaluated 601 IBD patients and identified 20 IBD-PSC patients. The mean of follow-up time was 78 months. The IBD diagnosis was based on clinical evaluation and the results of endoscopic, radiological and histological exams. IBD was categorized according to age at diagnosis, location and behavior following the Montreal Classification [8]. Sociodemographic aspects included gender, age at diagnosis of IBD and PSC, family history of IBD, smoking and alcohol use. All patients with IBD disease have liver function tests routinely each three months. The indications for liver transplantation, as well as their achievements, were also analyzed.

Procedure

PSC was diagnosed based on cholangiography demonstrating characteristic changes of the bile duct with segmental dilations and multifocal restrictions in a patient with cholestatic biochemical profile, excluding secondary causes of sclerosing cholangitis [9]. The distinction between intra- and extrahepatic disease was based on the confluence of bile ducts in the hepatic hilum [10]. Patients with normal cholangiography, but with clinical and biochemical characteristics compatible with PSC, were submitted to liver biopsy for histological evaluation. The small-duct PSC was established based in following criteria: normal cholangiography, histologic characteristics typical of or consistent with PSC, other causes of liver disease could be excluded. [11]. Moreover, overlap Autoimmune Hepatitis (AIH), was diagnosed based on simplified criteria for autoimmune hepatitis published by Hennes et al in 2008 [12].

Data collection

All clinical data were extracted from a digital research database. A detailed hand search of patient files was performed in IBD-PSC patients to look for data that are not regularly included in the questionnaires. The data Between January 2005 to December 2019.

Ethics approval

The study was designed and conducted in accordance with the Helsinki declaration as revised in 2008. The study protocol was approved by the competent Institutional Research Ethics Committee of the Hospital Universitário Walter Cantídeo UFC, Ceará Brazil and filed under number 3.168.019.

Data analysis

The SPSS Statistics for Windows (version 21.0, IBM Corp, Armonk, NY, USA) was used to perform all statistical analyses. Categorical variables were represented as absolute and relative frequencies (%). Pearson's chi-square test or Fisher's exact test was used to compare categorical variables, when appropriate. Normality of distribution for quantitative variables was evaluated using the Kolmogorov-Smirnov. Mean value (standard deviation) was used to describe normally distributed variables. A p-value of less than 0.05 was considered as statistically significant.

Results

Among 601 IBD patients, 321 had Ulcerative Colitis (UC) and 280 had Crohn's Disease (CD). Overall, 3.3% patients (20/601) had PSC. The prevalence of PSC was higher in UC at 4.7% (15/321) compared to 1.8% in CD (5/280). Of 20 IBD-PSC, 60% were male, mean age at diagnosis of IBD-PSC was 33.1 years

and mean of follow-up was78 months (Table 1).

PSC was diagnosed before (i.e. more than 6 months before), simultaneously (i.e. within 6 months), or after the diagnosis of IBD (i.e. more than 6 months after) in 10%, 20%, and 70% of patients, respectively. Average time between diagnoses was 5.6 years when IBD was diagnosed before PSC and 3.5 years when IBD was diagnosed after PSC (Table 1).

Overall, 70% (14/20) of IBD-PSC patients (3 CD-PSC and 11UC-PSC) had involvement of large ducts (7 intrahepatic 1 extrahepatic ducts), 6 (30%) both intra and extrahepatic ducts. Six patients (30%) (2 CD-PSC and 4 UC-PSC) had small ducts PSC, 2 of them had autoimmune hepatitis (AIH) overlap syndrome. The ratio of male to female sex was 1:5 in small-duct PSC group and 2.8: l.0 in large-duct PSC group.

Pancolitis was present in 95% (19/20) of IBD-PSC patients, while rectal sparing was not found in any of the 20 patients with PSC-IBD. Two patients (10%) had backwash ileitis (Table 1).

Table 1: Clinical and epidemiological characteristics of PSC-IBD patients (N=20).

Patient characteristics	N (%)
Gender, male	12 (60%)
Median age at PSC diagnosis (years)	33.1
Duration of follow-up (median, year)	6.5
Median age at IBD diagnosis (years)	27.6
IBD phenotype	
Ulcerative colitis	15 (75%)
Crohn's disease	5 (25%)
IBD-undetermined	-
Disease behavior, n(%)	
Rectal sparing	-
Backwash ileitis	2 (10%)
Initial diagnosis	
IBD first	14 (70%)
PSC first	2 (10%)
Simultaneous	4 (20%)
Median duration from diagnosis of IBD to PSC (years)	5.6
Median duration from diagnosis of IBD to PSC (years)	3.5
Type of PSC	
Intrahepatic ducts only	7 (35%)
Extrahepatic ducts only	1 (5%)
Both intra- & extrahepatic ducts	6 (30%)
Small duct PSC	6 (30%)
Colectomy	4 (26%)
Colorectal cancer	2 (10%)
Gallbladder cancer	1 (5%)
Cirrhosis	9 (45%)
Liver transplantation candidacy	4 (20%)
Undergoing Liver transplantation	3 (15%)

Abbreviations: PSC: Primary Sclerosing Cholangitis; UC: Ulcerative Colitis.

During the follow up, two patients developed colorectal carcinoma, requiring colectomy, and 1 developed gallbladder cancer. In IBD patients without PSC, 3% (5/581) developed colorectal cancer *vs* 10% (2/20) in IBD patients with PSC (p=0.011). One UC-IBD patient required colectomy due to clinical intractability. Nine patients developed liver cirrhosis, 4 of which were candidates for liver transplant. Of these, 3 patients were transplanted, while one died of sepsis prior to undergoing liver transplantation. Patients who underwent liver transplantation had severe pancolitis and were steroid-dependent even after liver transplantation. For these, it was indicated treatment of IBD with biological therapy and one of them underwent colectomy due to activity of the disease. Post-transplant immunosuppression varied throughout the follow-up, ranging from a calcineurin inhibitor (tacrolimus) to an antimetabolite (azathioprine or mycophenolate mofetil), with or without prednisone.

Of the 5 patients with PSC-CD, 3 (60%) were male, with a mean age at diagnosis of 29 years. Two patients (40%) had intrahepatic duct involvement, 1 (20%) both intra and extrahepatic ducts involvement and 2 (40%) had small ducts PSC. All five patients had pancolitis, 3 (60%) had small-bowel involvement. Three patients had penetrating disease. Two patients developed colorectal cancer. It was not possible to compare PSC-CD with DC without PSC due to small number of CD-PSC patients.

When we compare the characteristics of PSC-UC with isolated UC we observed that the mean age at diagnosis of patients with UC-PSC was lower (24.5 ± 12.5 *vs*. 39.4 ± 16.1 years; p= 0.011, the prevalence of pancolitis was higher in UC-PSC group (93.3% *vs*. 29.7%; p<0,001). Furthermore, use of biologics for the treatment of IBD was higher in the PSC-UC (26.7%) than in isolated UC (4.25%) (p<0,001*)*. Family history of IBD, alcohol consume and smoking was similar between groups (Table 2).

Table 2: Clinical and epidemiological characteristics of PSC-IBD patients (N=20).

Patient characteristics	UC WITH PSC (N=15)	UC WITHOUT PSC (N= 306)	*p*
Gender, male, n (%)	9 (60%)	112 (36.1%)	0.018
Median age ± SD symptom onset (years)	24.5 (±12.5)	39.4 (±16.1)	0.011
Median age ± SD at UC diagnosis years	27 (±11.8)	39,4 (±16)	0.009
Familiar history of IBD	3 (20%)	38 (29%)	0.752
Disease location, n (%)			
Ulcerative proctitis (E1)	-	117 (38.2%)	
Left ulcerative colitis (E2)	1 (6.7%)	98 (32%)	
Pancolitis (E3)	14 (93.3%)	91 (29.7)	< 0.001
Infliximab use	4 (26.7%)	13 (4.3%)	< 0.001
Smokers, n (%)	2 (13.3%)	86 (28%)	0.315
Alcohol abuse, n (%)	6 (40%)	103 (33.7%)	0.352

Abbreviations: PSC: Primary Sclerosing Cholangitis; UC: Ulcerative Colitis.
p values were calculated using the Pearson χ2 test or Fisher exact test.

Discussion

In the present study we evaluated the occurrence of PSC and outcome in a cohort of IBD patients in Northeastern Brazil, we also evaluated risk factors associated with UC-PSC.

The overall prevalence of IBD-PSC, including small duct PSC, was 3.3% in this study, in concordance with others reports from Western population in which the rate is 2.0% to 11% [13,14]. PSC was more frequent in UC (4.7 %) than in CD (1.8 %) cases, in agreement with most of the studies [15,16]. The CD-PSC prevalence was higher than reported by Fraga et al., in Switzerland, who diagnosed PSC in 0.58% (9/1547) of the cases [14].

Focusing on the characteristics of UC-PSC, we observed that there is a predominance of male gender, unlike isolated UC, in which the percentage of females was higher. The highest percentage of male UC-PSC patient is in agreement with results from several studies [4,14,17]. UC-PSC patients presented at a significantly earlier age (24.5 y), compared with non UC-PSC in line with reports from Korea [18]. On the other hand, others reported that the mean age for IBD diagnosis is higher among PSC-IBD patients compared with IBD controls [4]. The majority of the studies showed that that the UC-PSC patients had more frequently extensive disease and pancolitis, when compared with UC patients without concomitant PSC [4,5,14,15], in agreement 92% of our patients with UC-PSC presented pancolitis. We did not observe rectal sparing in any UC-PSC patients, and backwash ileitis was present in only one patient. Studies from Korea and Netherland found similar results [15,18]. Several studies had shown that patients with UC-PSC may present more often backwash ileitis and rectal sparing but the data are controversial [13].

About environmental exposure, history of current or prior smoking or alcohol consumption were similar between group of UC patient with and without concomitant PSC. This lack of association has also been reported in previous studies, such as that of Kumagai et al in 2018 [17]. Another study report cigarette smoking as significant independent protective factor for PSC development [14]. Familiar history of IBD was not associated with UC-PSC.

It was not possible to compare CD-PSC with alone CD due to the small number of CD- PSC cases in our cohort; however, all five PSC-CD patients presented with pancolitis and three of them showed concomitant small bowel disease, one had perianal fistula. In agreement, several studies have shown higher rates of colitis and ileocolitis in CD-PSC than in isolated CD [19,20].

Several studies have been shown that the risk of colorectal cancer is higher in patients with IBD-PSC compared to IBD alone, particularly in the subgroup of UC-PSC [21]. In our study, of twenty IBD-PSC cases, two (10%) developed colorectal cancer, requiring proctocolectomy, both of them in the CD-PSC group. This has been previously reported by Rasmussen et al., who evaluated nine patients with CD-PSC and found two patients with colon cancer, suggesting that PSC might also contribute to malignancy in the CD [20]. One UC-PSC patient developed gallbladder cancer. Of note, PSC increase risk of cholangiocarcinoma, gallbladder carcinoma, hepatocellular carcinoma, and colorectal cancer malignancy compared to the general population [21].

The large-duct was affected in 70% of IBD-PSC patient in this study , been 7 intrahepatic, 1 extrahepatic ducts, 6 both intra and extrahepatic ducts. The small-duct was involved in 30% of IBD-PSC patients. Higher prevalence of both intra and extrahepatic ducts (69%) has been reported [22]. The prevalence of small-duct PSC in IBD patient is controversial been reported approximately in one-fourth of that of large-duct in UC-PSC [23] and twice as prevalent as large-duct in CD-PSC [20].

In this cohort, nine IBD-PSC patients developed cirrhosis and four were candidates for LT. Of these, 3 underwent LT while one died of sepsis prior to LT. Two patients after four years of LT had an exacerbation of the UC and required escalation of therapy, while one required colectomy. In agreement, a study from Mayo Clinic showed that up to 40% of IBD-PSC patients after LT needed escalation of IBD-related therapy, in spite of immunosuppression. Near one-quarter of IBD-PSC patients required colectomy post-LT [24].

This study has some limitations. Firstly, the relatively small sample size; however, IBD-PSC is not common, this is someone expected as this was a single center study. Secondly, the retrospective design of this study. Thirdly, since this study was conducted in a tertiary care center, the patient population may have a higher proportion of severe IBD patients.

Conclusion

In conclusion, the prevalence of PSC among IBD patients in our study seems similar to that reported worldwide. The majority of IBD-PSC patients had pancolitis, however rectal sparing was not observed**.** IBD-PSC is associated with more frequent colorectal neoplasia development, cirrhosis and poor prognosis. Our data highlight the need for close follow-up of IBD patients with concomitant PSC.

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