Abstract

Introduction: Hepatobiliary manifestations occur quite frequently in patients suffering from chronic inflammatory bowel disease (IBD) and are the root of morbidity and mortality. Primary sclerosing cholangitis is the most frequent and specific one. It carries the most significant clinical implications and remains a highly challenging disease to manage. Causes are likely related to inflammatory bowel disease through common pathogenetic mechanisms. Some other complications such as gallstone disease, steatosis and hepatic abscesses are directly or indirectly related to IBD. The spectrum of these manifestations varies according to the type of IBD.

Keywords: Liver disease; Primary sclerosing cholangitis; Inflammatory bowel disease; Ulcerative colitis. Crohn’s disease

Résumé

Introduction : Diverses manifestations hépatobiliaires peuvent s’associer aux maladies inflammatoires chroniques de l’intestin (MICI) et être source d’une importante morbi-mortalité. La cholangite sclérosante primitive est la manifestation la plus fréquente et la plus spécifique. Elle comporte les implications cliniques les plus importantes et reste une maladie hautement difficile à gérer. Son origine semble être liée à des mécanismes étiopathogéniques communs avec la maladie intestinale. D’autres complications telles que la lithiase biliaire, la stéatose et les abcès hépatiques sont directement ou indirectement liées à la MICI. Le spectre de ces manifestations varie selon le type de la MICI.

Mots clés : Pathologie hépatobiliaire ; Cholangite sclérosante primitive ; Maladie inflammatoire chronique de l’intestin ; Rectocolite ulcéro-hémorragique ; Maladie de crohn.

ملخص

قد تكون أعراض الكبد و الامراض الجراحيه مع مرض الأمعاء المزمن وتكون مصدرًا كبيرًا للمرض والوفاة. والعرض من هذه المصطلحات هو التحليل النقدي لهؤلاء الأعراض و المتعلقة عادةً مع مرض الأمعاء الأمامي. الهدف: البحوث الرسمية في الأدبيات الطبية على موقع "المجلات الطبية". النتائج: مرض الأمعاء المزمن هو مظهر من المظهر الأكثر تكرارًا وأكثر تحديًا. ويعتبر هذا التهاب نتاج داخلي وخارجي للمرض، داخل الكبد أو خارج الكبد، ويتميز بأنها تظهر مشكلة بشكل مباشر أو غير مباشر لمرض التهاب الأمعاء. الخاتمة: هناك حاجة إلى بحوث أكثر عمق لتحسين فهم المتبقيات في ظروف مرض الأمعاء والمظاهر النظامية لتحسين الرعاية الشاملة لـ مصابي المرض. الكلمات المفتاحية: مرض الأمعاء والأمراض الجراحيه مرض الأمعاء المزمن ; التهاب الأمعاء ; التهاب الكبد ; مرض الأمعاء المزمن ; التهاب الكبد المزمن ; ومرض كرون.

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INTRODUCTION

Inflammatory bowel diseases (IBD) are frequently associated with a wide array of extra intestinal manifestations. The first association between colonic ulceration and liver disease was described in 1874 by Thomas CH [1] which was confirmed by Lister JD in 1899 [2]. Over the next 100 years it has become well established that there is a close relationship between IBD and various hepatobiliary disorders (table I). Causes are likely related to IBD through common pathogenetic mechanisms. However, liver changes may in some cases arise from adverse reactions to some of the drugs commonly used in the treatment of IBD patients. The aim of this article was to review most important hepatobiliary disorders of inflammatory bowel disease without the hepatotoxic effects of the medications used in its management nor the risk of viral hepatitis reactivation.

Table I: Hepatobiliary disorders associated with IBD

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Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic progressive disorder of unknown aetiology characterized by inflammation, fibrosis and stricture formation in medium and large sized ducts in the biliary tree [3]. Common symptoms include itch and lethargy although many patients are asymptomatic, even with advanced disease [3]. Diagnostic criteria are summarized in table II.

The prevalence of PSC is low estimated at 20.9 cases per 100,000 of the population in men and 6.3 per 100,000 in women in the United States [4]. The disease is commonly associated with IBD, mostly with ulcerative colitis (UC). It is generally accepted that approximately 5% of patients with UC [5], and 3.4% of crohn’s disease (CD) patients [6] will have associated PSC. CD associated with PSC is generally seen in patients who have extensive colonic or ileocolonic disease, or in pediatric populations [5]. However, the prevalence of IBD in patients with PSC varies greatly depending on the study and geographic area from 23% in Japan [7] to 72% in UK [8].

The pathogenesis of PSC is unknown. Bacteria, toxins, viral infections, immunologic and genetic factors have been proposed. Possible explanations for the PSC association with IBD include the development of autoantibodies to an unknown antigen in an immunogenetically susceptible host which cross reacts with biliary and colonic epithelium and is capable of inducing complement activation [9]. Alternatively, the initiation of the immune response may be the ingress of bacteria or other toxic metabolites through the diseased bowel wall [5].

Usually IBD presents before PSC, although PSC can develop before onset of IBD and the beginning of both conditions can be separated in some cases by many years [10]. Mean age of diagnosis of PSC is the fifth decade of life with a strong male predominance. This male preponderance is absent in patients without associated IBD [11].

Risk factors for the development of PSC include, in addition to IBD and male sex, a family history of the disease [12] and a nonsmoking behavior [13].

PSC – associated UC is often mild, asymptomatic and runs a quiescent course [14]. It is associated with rectal sparing [15], more severe right sided disease, backwash ileitis and has a high risk of pouchitis after colectomy and ileo-anal pouch formation, occurring in up to 60% of PSC patients compared to 15% in patients with UC alone [16].

Several clinical studies have shown that PSC is a significant risk factor for the development of colorectal carcinoma and dysplasia in UC patients [17-19]. A meta-analysis proved a fourfold increase in colon cancer in UC patients with PSC when compared to UC alone (RR 4.26 95% CI 2.8-6.48) [20]. The risk of proximal cancer is particularly increased [19, 21]. Hence, annual screening colonoscopy is recommended in IBD patients with PSC [22]. Proctocolectomy does not appear to modify on the course of the PSC [23]. However, the natural history of UC following liver transplantation is variable [24-26]. The median reported survival in patients with PSC is approximately 12 years from the time of diagnosis with survival worse for those who are symptomatic.
at presentation [27]. PSC follows generally a progressive course, and the prognosis is poor. Cholangiocarcinoma is the most lethal complication of PSC. Its lifetime risk is higher in PSC patients with IBD than those with PSC alone, with an estimated annual incidence of 0.5 -1% [5]. At present, there is no proven effective medical therapy for PSC. Ursodeoxycholic acid (UDCA) is the only drug which has been demonstrated to have a positive effect. Preliminary studies of patients receiving high dose UDCA treatment showed a significant improvement in hepatic biochemical tests and slowed progression in cholangiographic appearances and liver fibrosis [28-29]. Also, some studies have shown that administration of UDCA may reduce the risk of colorectal cancer and dysplasia in patients with PSC and UC [30-31]. Orthotopic liver transplantation is the treatment of choice for patients with end-stage liver disease. Recurrence of PSC in the transplanted liver has been noted and is observed in up to 20% of patients [32].

Table II : Criteria for diagnosing PSC

- Cholestatic biochemical profile
- Generalized beading, structuring or irregularity of the biliary system based on cholangiography
- Interlobular and septal bile duct fibrosis and obliteration on liver biopsy in the absence of other causes of chronic liver disease
- Exclude other cause of liver disease such as biliary calculi, biliary tract surgery, congenital biliary conditions, AIDS associated cholangiopathy, ischaemic structuring, biliary neoplasms, chemical hepatitis, primary biliary cirrhosis or alcoholic liver disease

Small duct primary sclerosing cholangitis

Small duct PSC is a subset of PSC which is diagnosed on the basis of liver biopsy in the presence of a normal cholangiogram. It may progress to “classical” PSC in only 22.9% of cases [33]. Pericholangitis has been reported to be a common lesion associated with IBD with an estimated prevalence as high as 30% in selected patients undergoing liver biopsy [34]. Its course often parallels the bowel disease activity and severity. No specific therapy exists for this condition.

Ig G 4 cholangitis

Ig G 4 cholangitis is the biliary manifestation of IgG4 related disease, an inflammatory multiorgan disorder of unknown cause. It is a particular form of cholangitis that may mimic PSC. It is defined by increased serum Ig G 4, infiltration of biliary tract by Ig G 4 plasma cells with preferential involvement of the extrahepatic biliary tract, frequent association with another fibrotic pathology and especially type I autoimmune pancreatitis and good response to corticosteroids therapy [35]. Imaging shows mass forming lesions and / or strictures in the biliary tract [36]. Measuring serum Ig G4 levels to exclude Ig G 4-associated sclerosing cholangitis is recommended at the time of diagnosis of PSC. [37]

Cholangiocarcinoma

Cholangiocarcinoma is a devastating malignancy that presents late, is notoriously difficult to diagnose, and is associated with high mortality. The reported incidence of cholangiocarcinoma in patients with IBD is between 0.4% and 1.4%, which is 10-100 times greater than what is reported for the general population. It occurs predominantly in patients with UC, but has also been reported in patients with CD [38]. Vice versa the incidence of UC in patients with cholangiocarcinoma varies from 6% to 14% [39]. It is more common in men and occurs in the fourth and fifth decades, about 20 years earlier than in the general population [38]. Most cholangiocarcinomas develop in patients with pre-existing PSC [40]. The ability of tumor markers such as CA 19-9, carcinoembryonic antigen, CA 50, CA 242, and CA 125 to differentiate PSC and PSC with cholangiocarcinoma is not clear [41]. The greatest risk appears to be for those UC patients with pancolitis and for those with an average duration of 15 years of disease [42]. There is no apparent relationship between the development of cholangiocarcinoma and the activity of bowel disease as it may develop during prolonged remission and even following proctocolectomy [38]. Palliative surgery is the most effective
treatment but has little impact on prolonging the survival [43]. Similarly, the results of orthotopic liver transplantation have been disappointing due to early recurrences [44].

**Cholelithiasis**

The prevalence of gallstone disease in UC patients is similar to that observed in the general population [45]. Several investigators have reported that the frequency of cholelithiasis is increased in patients with CD of the ileum, or those having undergone ileal resection. The incidence of gallstone disease in these patients ranges from 13% to 34%, and this association is higher in older subjects [46]. The risk factors for gallstones in patients with CD include ileocolonic involvement, disease duration longer than 15 years, more than three previous recurrences, resection of more than 30 cm of ileum, need for more than 3 hospitalizations, multiple total parenteral nutrition events, and long hospital stay [45].

The mechanism of cholesterol gallstone formation in CD may be related to an abnormal bile lipid composition after ileal resection or disease. It is likely a result of altered enterohepatic bilirubin circulation [41]. When gallstones become symptomatic, laparoscopic or open cholecystectomy is the treatment of choice.

**Autoimmune hepatitis**

Patients with IBD are at increased risk of other of immune mediated liver disease including autoimmune hepatitis (AIH). AIH is present in 1% of patients with IBD [47-48]. Conversely, the incidence of IBD in patients with AIH varies from 4% to 30% [49]. The natural history and prognosis of chronic hepatitis are independent of the activity or severity of IBD [38]. However, one study [50] has reported significant improvement in AIH after colectomy. The association between AIH and PSC as an “overlap syndrome” may occur primarily in UC patients. AIH patients with colitis respond satisfactorily to immune suppression with corticoids and azathioprine. However, the presence of AIH-PSC overlap is associated with a poor treatment response [51].

**Steatosis**

Liver steatosis is the most common pathological liver finding in patients with IBD [52]. In a prospective study of 511 patients with IBD the prevalence of hepatic steatosis (defined by the intensity gradient between the liver and the kidney), after excluding other causes of steatosis, was 39.5% in patients with CD and 35.5% in patients with UC[53]. The pathogenesis of steatosis in IBD is not clearly understood. Unconfessed alcohol abuse, use of corticosteroids to control intestinal disease, malnutrition itself, and the passage of bacteria or endotoxins from the bowel have been implied [54]. No significant complications related to steatosis have been reported in patients with IBD.

**Portal vein thrombosis**

IBD patients are at risk of development of venous thrombosis, as a consequence of inflammatory hypercoagulable state [55]. The portal vein is a common site of thrombosis. It occurs most frequently in the post-operative setting and has been reported after proctocolectomy in UC patients [56]. A retrospective GETAID study found 40% of fortuitous portomesenteric thrombosis in inactive IBD patients [57]. Pylophlebitis is a special feature that is usually seen in patients with infectious complications of IBD [58]. Anticoagulation remains the mainstay of therapy.

**Hepatic amyloidosis**

Amyloidosis is a rare but serious complication of IBD, especially CD. It occurred in 0.9% of patients with CD and 0.07% of patients with UC with male preponderance [59]. Liver involvement rarely occurs without concurrent involvement of other organ systems. In a large retrospective analysis including 3050 patients with IBD, hepatic amyloidosis was diagnosed in only 6 patients [59]. Three of these presented with hepatomegaly and the remaining three were diagnosed at autopsy. There is no relationship between the site of bowel involvement and occurrence of amyloidosis [38]. Given the rarity of the condition and the need for liver biopsy for reliable diagnosis, the true incidence of hepatic amyloidosis and its prognosis in IBD is unknown. As with other causes of secondary amyloidosis, reversibility is probably achievable with treatment of the underlying condition.
Granulomatous hepatitis

Granulomatous hepatitis is an uncommon complication of IBD occurring in less than 1% of patients, mainly CD [38]. Patients are usually asymptomatic. Elevation in serum alkaline phosphatase is the main laboratory abnormality. Histology is required for diagnosis. The most common cause of granulomatous hepatitis in the setting of IBD is secondary to a medication, usually sulfasalazine, but the condition may also result from other causes such as malignancy, infections and idiopathic, such as sarcoidosis [52]. Outcome is generally favorable and progression to cirrhosis is exceptional. Symptomatic treatment is indicated and one case of regression after colectomy has been reported [60].

Liver abscess

Hepatic abscess is a rare complication of IBD. It is more prevalent in patients with CD occurring in 0.3% of cases [38], irrespective to the disease duration or localization [60]. The abscesses are frequently multiple, preferentially located in the right lobe [61]. An overall mortality of 21% for liver abscess in CD has been reported, and immunosuppressive treatment and delayed diagnosis of liver abscess may increase mortality in IBD [52]. Intra-abdominal abscesses, fistulous disease, and metronidazole or steroid therapy have been reported to be important predisposing factors in the pathogenesis of the disease [62]. Most common clinical manifestations include fever, chills, anorexia and abdominal pain with right upper quadrant tenderness. Leukocytosis and elevated levels of alkaline phosphatase are among the main laboratory abnormality. Morphological explorations including ultrasound and computed tomography are needed to establish the diagnosis. The infection is generally caused by a single germ [60]. Treatment includes broad spectrum antibiotics combined with percutaneous or surgical drainage.

CONCLUSION

Many hepatobiliary diseases are common in IBD. They usually manifest in abnormal hepatic biochemical tests. PSC carries the most significant clinical implications and remains a highly challenging disease to manage. The importance of an awareness of the implications and causes of abnormal hepatic biochemical tests in IBD patients cannot be overemphasized. Hepatic biochemical tests should be the routine for these patients. When abnormalities are detected, the general approach should be to test for the more common manifestations, and when excluded, proceed to test for the less common ones until a reliable diagnosis can be made.

REFERENCES

HEPATOBILIARY MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE


