CASE REPORT

Increased cholestatic enzymes in two patients with long-term history of ulcerative colitis: consider primary biliary cholangitis not always primary sclerosing cholangitis

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SUMMARY

Several hepatobiliary disorders have been reported in ulcerative colitis (UC) patients with primary sclerosing cholangitis (PSC) being the most specific. Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, rarely occurs in UC. We present two PBC cases of 67 and 71 years who suffered from long-standing UC. Both patients were asymptomatic but they had increased cholestatic enzymes and high titres of antimitochondrial antibodies (AMA)—the laboratory hallmark of PBC. After careful exclusion of other causes of cholestasis by MRI/magnetic resonance cholangiopancreatography (MRCP), virological and microbiological investigations, a diagnosis of PBC associated with UC was established. The patients started ursodeoxycholic acid (13 mg/kg/day) with complete response. During follow-up, both patients remained asymptomatic with normal blood biochemistry. Although PSC is the most common hepatobiliary manifestation among patients with UC, physicians must keep also PBC in mind in those with unexplained cholestasis and repeatedly normal MRCP. In these cases, a reliable AMA testing can help for an accurate diagnosis.

BACKGROUND

Inflammatory bowel diseases (IBD) namely ulcerative colitis (UC) and Crohn's disease (CD) are associated with several hepatobiliary disorders.[1 2] Indeed, liver involvement is not unusual in patients with IBD as almost one-third of patients have abnormal biochemical tests which therefore become a diagnostic challenge.[1–3] In most cases, the cause of these elevations will fall into one of three main categories. They can be a result of extraintestinal manifestations of the disease process, related to medication toxicity, or the result of an underlying primary liver disease unrelated to IBD.[1 4] Concerning the hepatobiliary complications of IBD fatty liver is considered the most common while primary sclerosing cholangitis (PSC) the most specific as approximately 70%–80% of patients with PSC have concomitant IBD and about 1.4%–7.5% of patients with IBD will develop PSC.[1–4] Less frequently, IBD-associated hepatobiliary disorders include autoimmune hepatitis (AIH)/PSC variant syndrome, IgG4-associated cholangiopathy, hepatic amyloidosis, granulomatous hepatitis, portal vein thrombosis, liver abscess and primary biliary cholangitis (PBC).[1–4]

PBC is an autoimmune cholestatic liver disease, characterised by the presence of antimitochondrial antibodies (AMAs), female predominance usually during the fifth and sixth decades of their life and histologically by a progressive inflammatory destruction of the small intrahepatic bile ducts.[5–8] The net result is the development of cholestasis, portal inflammation and fibrosis that may lead to cirrhosis and end-stage liver disease.[5–8] At diagnosis, the clinical manifestations varies from asymptomatic to symptomatic, or finally to advanced liver disease. However, it has been shown that a prompt diagnosis at early stages is of major importance as appropriate treatment may have favourable effect on the natural history of the disease and improve survival.[7 9] One of PBC characteristics is its associations with various autoimmune or immune-mediated diseases and syndromes like Hashimoto's thyroiditis, Sjögren syndrome, rheumatoid arthritis and coeliac disease but rarely with IBD.[1–5 7 10–16] Indeed, although PSC association with IBD and in particular with UC is a very well-known phenomenon, the frequency of PBC development in patients with a long-term history of UC is near zero.[1–5] Therefore, we present herein two patients with UC with biochemical indices of asymptomatic intrahepatic cholestasis proved to be due to PBC highlighting the need of strict adherence to the international guidelines of the diagnostic algorithm for the investigation of cholestasis irrespective of the underlying disease in an attempt to achieve a prompt, accurate and timely diagnosis as well as to avoid further unnecessary investigations like liver biopsy.[7 9 17–20]

CASE PRESENTATION

Case 1: A 67-year-old female patient with a long-standing history of UC for 17 years which was in complete remission at least the last 20 months was referred for consultation to the Outpatient Clinic of our department because of asymptomatic elevation of cholestatic enzymes of 5-year duration with repeatedly normal imaging studies of the liver and biliary tree including magnetic resonance cholangiopancreatography (MRCP). She suffered from arterial hypertension and hypercholesterolaemia

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and she was under ramipril and simvastatin the last 15 years. She was also under treatment with mesalazine 1 g twice per day for the underlying UC for a long period (15 years) but she denied ever consumption of herbal agents and/or dietary supplements, intravenous or nasal illicit drugs, or alcohol abuse. Her family history was unrevealing. The current clinical diagnosis from other departments was either small duct PSC as she denied liver biopsy, or drug-induced liver injury (DILI) although all medications were used many years before the elevation of γ-glutamyl transpeptidase (γ-GT) and alkaline phosphatase (ALP). Nevertheless, simvastatin had been discontinued by her doctor 6 months ago without any response concerning the biochemical indices of cholestasis. At presentation, she denied ever the presence of fatigue, pruritus, jaundice, itch, discomfort and/or pain in the right part of the abdomen or any other symptom while physical examination was unrevealing apart from a body mass index of 31.

Case 2: A 71-year-old male patient also with a long history of UC for 12 years in complete remission for the last 2 years was referred to the Outpatient Clinic of our department due to asymptomatic elevation of cholestatic enzymes of 4-year duration. Serial MRCP studies were also unrevealing. He had a history of type-2 diabetes mellitus under insulin and metformin the last 16 years and ankylosing spondylitis diagnosed 7 years ago for which he was currently under tumour necrosis factor α (TNFα) blockade treatment (40 mg adalimumab subcutaneously/14 days) for the last 2 years. He was also under treatment with mesalazine 1 g twice per day for the underlying UC for 10 years but he denied ever consumption of herbal agents and/or dietary supplements, intravenous or nasal illicit drugs, or alcohol abuse. His family history was unrevealing. His current clinical diagnosis from other departments was similar to that of case 1 patient although all medications were used either many years before or after the elevation of cholestatic enzymes. Nevertheless, adalimumab had been discontinued by his doctor 6 months ago without any response. As in case 1, the patient was completely asymptomatic while physical examination revealed the typical findings of ankylosing spondylitis (involvement with ankylosis of the lumbar spine along with involvement of the cervical spine accompanied by limited motion) and the presence of a lichen planus on his left tibia.

INVESTIGATIONS

Laboratory work-up (abnormal values) was as follows: (1) Case 1—ALT 56 IU/L (upper limit of normal, ULN:40), γ-GT 152 IU/L (ULN:38), ALP 156 IU/L (ULN:104) cholesterol 265 mg/dL, low-density lipoprotein cholesterol 195 mg/dL, high-density lipoprotein cholesterol 37 mg/dL, triglycerides 165 mg/dL and eosinophil count 520/μL. (2) Case 2—ALT 59 IU/L, γ-GT 202 IU/L and ALP 256 IU/L.

The remaining haematological, microbiological, virological and biochemical parameters including urine cultures and serological investigation for viral hepatitis A, B and C, tuberculosis, brucellosis, leishmaniasis and other parasites, serum immunoglobulin G (IgG) along with IgG4 subclass, IgA, IgM, rheumatoid factors, erythrocyte sedimentation rate, C reactive protein and ferritin levels were within normal limits in both patients. Chest X-ray and ECG were also unrevealing. Multiple stool samples from case 1 with mild eosinophilia were also negative for ova and parasites like *Enterobius vermicularis*, *Entamoeba histolytica*, *Cryptosporidium* and *Giardia* species. New abdominal ultrasonography, MRI of the abdomen and retroperitoneal space and magnetic resonance cholangiograpy were again negative in both patients.

DIFFERENTIAL DIAGNOSIS

As the imaging studies tested repeatedly normal, investigation for the liver autoimmune serology according to the international and our standard protocols for the diagnosis of autoimmune liver diseases including AIH and its variants as well as autoimmune cholestatic liver diseases like PBC and PSC was decided before the suggestion of a liver biopsy.[6–8 21–30] Accordingly, we performed an indirect immunofluorescence (IIF) assay on fresh frozen in-house cryostat sections of rat liver, kidney and stomach substrate which is the 'gold standard' for the screening of

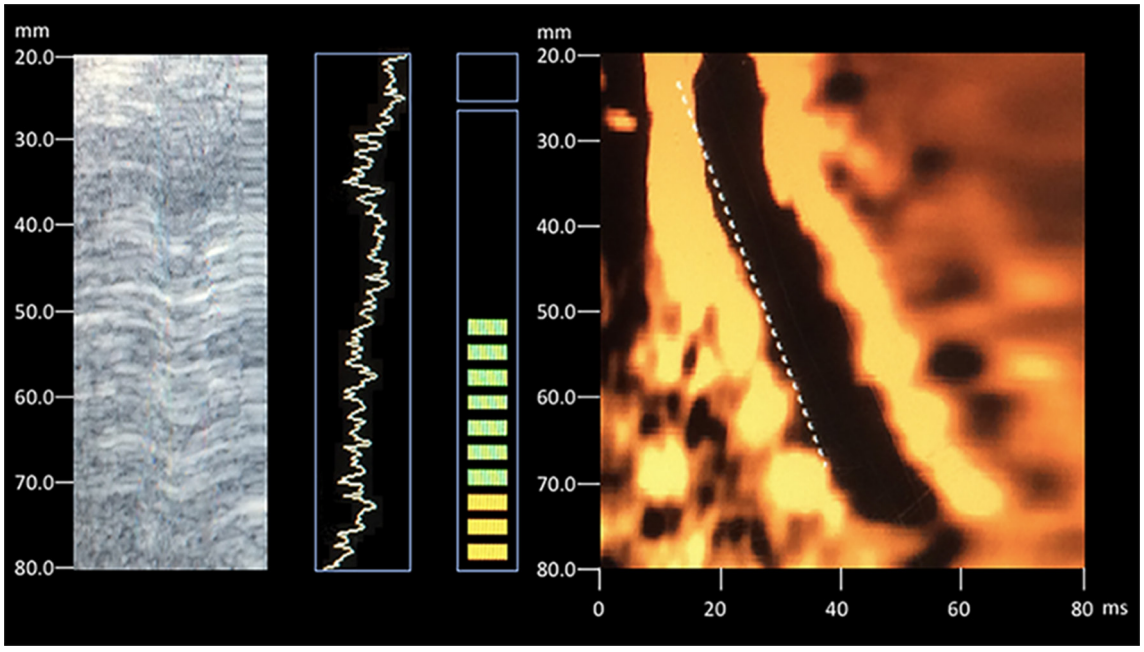

Figure 1 Transient elastography using the FibroScan device (Echosens, France) showed a fibrosis score of 8.1 kPa (IQR 1.7 kPa, range: 2.5-75 kPa) indicating a F2 fibrosis stage according to Metavir score staging.

antinuclear antibody (ANA), AMA and smooth muscle antibodies followed by molecularly based assays against specifically defined autoantigens (ELISAs and immunoblot tests).[5–8 21–23 25–27 29] The results showed the presence of high AMA by the three methods used in both patients making the diagnosis of PBC definite. In brief, the results were as follows: Case 1—AMA positivity by IIF (titre 1/320; positive titre ≥1/40); ELISA IgG AMA: 65 Units (cut-off: 20 Units) and IgA AMA: 1149 optical density (OD; cut-off: 135 OD). Case 2—AMA positivity by IIF (titre 1/320); ELISA IgG AMA: 128 Units and IgA AMA: 833 OD. Immunoblot on rat mitochondrial subfraction showed a strong positive 74 kDa band corresponding to the major AMA autoantigen (E2 subunit of pyruvate dehydrogenase complex) in both patients. In addition, using a specific ELISA, case 1 tested also high positive for antibodies against nuclear pore complex antigens like 210 kDa glycoprotein (anti-gp210, 92 Units; cut-off: 20 Units) which have long been considered as highly specific for PBC diagnosis (PBC-specific ANA).[5–8 28] As in both patients the diagnosis was obvious of that of PBC (biochemical intrahepatic cholestasis, AMA positivity by three methods and PBC-specific ANA), a liver biopsy was not offered. However, liver stiffness measurement was performed by transient elastography using the FibroScan device (Echosens, France) equipped with the standard M probe. The results showed a fibrosis score of 7.5 (case 1) and 8.1 kPa (case 2; figure 1) which denotes a F2 fibrosis stage according to Metavir score staging.[31]

TREATMENT

Both patients started 13 mg/kg/day ursodeoxycholic acid according to the European Association for the Study of the Liver (EASL) clinical practice guidelines for the diagnosis and management of PBC.[7]

OUTCOME AND FOLLOW-UP

Complete normalisation of γ-GT and ALP values since the second month of treatment was observed which was so far stable and sustained during follow-up as both patients remained asymptomatic with normal blood biochemistry for 18 (case 1) and 17 months (case 2).

DISCUSSION

The following major points have been raised from the present case series: (1) Although PSC is the most common and specific hepatobiliary manifestation among patients with UC with cholestasis, physicians must keep also PBC in mind in those with unexplained intrahepatic cholestasis. (2) In these cases, a reliable AMA testing according to the internationally accepted guidelines can help for an accurate and prompt diagnosis in order to avoid undiagnosis and/or misdiagnosis as attested by our two cases characterised by a significant delay of diagnosis.[6–8 23 25 29]

Indeed, both UC and CD have a variety of hepatobiliary manifestations.[1–4] In a recent systematic review of hepatobiliary disorders associated with IBD in 146 related articles, it was found that cholelithiasis was more frequent in CD (11%–34% of patients) than in general population and non-IBD patients (5.5%–15%).[1] In addition, PSC was more frequent in UC than in CD (0.76%–5.4% and 1.2%–3.4%, respectively). The mean prevalence of fatty liver was 23%, whereas liver abscess was encountered mainly in CD and portal vein thrombosis in 39%–45% of patients with IBD undergoing proctocolectomy.[1]

Concerning PBC, its association with IBD is rare as approximately only 25–30 sporadic cases have been reported so far, both with CD and UC, although with a predominance of UC.[32–41] In general, however, the PBC prevalence seems to be higher in IBD than in the general population (almost 30 times higher) whereas the disease tends to affect more frequently men when associated with IBD, with a female/male sex ratio 2:1, compared with 8–10:1 which is usually recorded in the non-IBD PBC population.[32 37] The mean age also tends to be younger although this was not the case in our patients while as in the present case series UC is usually diagnosed before PBC development.[1–4 40]

Most of the drugs used in IBD have been associated with DILI. The latter should be cautiously ruled out before a definite diagnosis of a liver disease associated with IBD. In particular, patients receiving immunosuppressive therapy, including biologics like TNFα-blockade agents, may suffer from hepatitis B reactivation and under some circumstances can induce autoimmune reactions including AIH.[42] However, this probability seems unlike as in both of our patients all medications were used either many years before or after the elevation of cholestatic enzymes whereas hepatitis B serological viral markers tested negative. Furthermore, statins and TNFα-blockade regimen had been discontinued the last 6 months without any response concerning the biochemical indices of intrahepatic cholestasis.

Considering PBC diagnosis, it is now widely accepted that the diagnosis can be safely done if at least two of the following three criteria were fulfilled namely, AMA seropositivity, elevated cholestatic enzymes and liver histology with PBC lesions. Actually, the previous and the current clinical practice guidelines for PBC published by EASL recommend considering liver biopsy only after negative serological screening and extended imaging, in patients with ongoing unexplained intrahepatic cholestasis.[7 43] In other words, EASL recommends against liver biopsy for the diagnosis of PBC, unless PBC-specific antibodies are absent or coexistent AIH or other disease is suspected.[7] Both of our patients had long-standing elevated cholestatic enzymes, negative extended imaging investigations and high titres AMA by using three methods establishing PBC diagnosis. In addition, the presence of mild eosinophilia in case 1 is a well-known

Learning points

- Ulcerative colitis (UC) and Crohn's disease are associated with several hepatobiliary disorders in almost one-third of patients.
- Fatty liver is considered the most common and primary sclerosing cholangitis (PSC) the most specific.
- Primary biliary cholangitis (PBC) is the most prevalent autoimmune liver disease, characterised by associations with various immune-mediated diseases and syndromes but rarely with inflammatory bowel diseases.
- Although PSC is the most common and specific hepatobiliary manifestation among patients with UC with cholestasis, physicians must keep also PBC in mind in those with unexplained intrahepatic cholestasis and repeatedly normal magnetic resonance cholangiopancreatography.
- In these cases, a reliable antimitochondrial antibodies testing according to the internationally accepted guidelines is of outmost importance to establish an accurate and prompt PBC diagnosis in order to avoid undiagnosis, misdiagnosis and further unnecessary investigations like liver biopsy and, therefore, to reduce the cost but also to promise our compliant patients an almost normal life expectancy concerning the PBC component if remission under treatment is achieved.

phenomenon in some patients with PBC at early disease which usually returns within normal range after ursodeoxycholic acid administration.[44]

The relationship of PBC with UC remains obscure as there are few reported cases regarding the combined presentation of these diseases. Although the pathogenesis of either disease has not yet been completely clarified, environmental and genetic factors are considered important in the susceptibility to both diseases suggesting that the two diseases may share common immunopathogenetic pathways.

In conclusion, the association of PBC with UC is rare but does exist. Therefore, not only PSC but also PBC should be considered in the differential diagnosis of hepatobiliary disease in patients with UC with unexplained cholestasis. In this context, an investigation for AMA seems to be of outmost importance to establish a firm PBC diagnosis.

Contributors GND and NKG had the original idea, designed the study and wrote the first draft of the manuscript. EP, VL and NKG collected and summarised the published literature and the data of the patients. GND and EP were the principal treating physicians, while VL made the laboratory investigation. GND and NKG made the final critical revision of the manuscript for important intellectual content. All authors have seen and approved the final version of the manuscript.

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