Gastroenterology and Hepatology from Bed to Bench.

MEDICAL EDUCATION

Education case: a case-based approach to overlap syndromes in autoimmune liver disease in patient with ulcerative colitis

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ABSTRACT

Simultaneous occurrence of immune-based gastrointestinal diseases and autoimmune hepatitis, although not common, is of clinical importance. Some clinical and laboratory findings such as severe pruritus and elevated alkaline phosphatase raise suspicion of a biliary disease which overlaps autoimmune hepatitis. A strong clinical suspicion of overlap syndrome in a patient with autoimmune hepatitis prompts more diagnostic evaluations like MRCP, liver biopsy, and secondary laboratory tests. Patients who fall into the category of overlap syndrome proceed with timely monitoring of known complications including colorectal carcinomas, cholangiocarcinomas, and gallbladder cancers. It is strongly recommended that all simultaneous immune-based involvements be searched prior to labeling a patient as having pure autoimmune hepatitis.

The current study attempted to express all challenges about a case with overlap syndrome referred to the gastroenterology ward of Taleghani Hospital and to review the latest articles and related guidelines about the diagnosis, treatment, complications, and surveillance of the mentioned patient with autoimmune hepatitis (AIH), primary sclerosing cholangitis (PSC), and inflammatory bowel disease (IBD).

Keywords: Autoimmune hepatitis, Primary sclerosing cholangitis, Inflammatory bowel disease, Ulcerative colitis, Overlap syndrome.

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Case study

MM is a 29-year-old obese woman who referred to the GI clinic for evaluation and management of elevated liver tests. She had an unremarkable medical history. The patient was taking pantoprazole to relieve occasional dyspepsia. She denied alcohol, tobacco, or illicit drug use. Apart from the presence of non-alcoholic fatty liver disease in her mother, she did not mention a family history of liver disease or significant gastrointestinal disease. Other than some minor fatigue, she had no complaint of other constitutional symptoms. On physical examination, she was found to be mildly jaundiced without stigmata of chronic liver disease. On abdominal exam, no hepatosplenomegaly or ascites were observed. Her laboratory findings are shown in Table 1. Abdominal ultrasound showed liver with a normal size and echo pattern and a normal-sized spleen with no focal masses or ascites.

1. What are the probable differential diagnoses and which tests are required to confirm the diagnosis?

The pattern of liver enzyme elevation is an important factor in the evaluation of hepatobiliary abnormalities. Liver diseases could be categorized into the three subgroups of cholestasis, hepatocellular injury, and isolated hyperbilirubinemia.

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Table 1. The Patient's Laboratory Findings.

Test	Result	Normal Range
White blood cell (WBC)	6700/ µL	4500-11000/µL
Hemoglobin (Hb)	14.2 mg/dl	11-15 mg/dl
Platelet (Plt)	328000	150-450 × 10^3
Prothrombin time (PT)	12 Sec	12-13 Sec
Partial thromboplastin time (PTT)	32 Sec	24-42 Sec
Lactate dehydrogenase (LDH)	472 U/L	150-500 U/L
Serum albumin	4.2 g/dl	3.8-5.5 g/dl
Blood urea nitrogen (BUN)	12 mg/dl	8-20 mg/dl
Serum creatinine	0.7 mg/dl	0.5-1.1 mg/dl
Aspartate transaminase (AST)	338 U/L	Up to 41 iU/L
Alanine transaminase (ALT)	480 iU/L	Up to 41 iU/L
Alkaline phosphatase (AlkP)	376 U/L	80-306 U/L
Total bilirubin	2.8 mg/dl	Up to1.2 mg/dl
Hepatitis A IgM	Negative	Negative
Hepatitis B surface antigen (HBsAg)	Negative	Negative
Hepatitis B core antibody (HBcAb)	Negative	Negative
Hepatitis C antibody	Negative	Negative
Antinuclear antibody (ANA)	1.3	<1.2
Anti-smooth muscle antibody (ASMA)	1/20	Up to 1/10
Serum immunoglobulin-G (IgG) level	1,800 mg/dl	640-1,430 mg/dl
Anti-mitochondrial antibody (AMA)	Negative	Negative
Serum ceruloplasmin level	50 mg/dl	15-60 mg/dl
Serum iron	112 mcg/dl	35-135 mcg/dl
Total iron binding capacity (TIBC)	293 mcg/dl	210-440 mcg/dl
Ferritin	156 mcg/L	40-204 mcg/L
Saturation of transferrin	38%	20-50%

Characteristically, a disproportionate rise in the serum alkaline phosphatase (ALP) level in comparison with serum alanine and aspartate aminotransferases (ALT and AST) reflects a cholestatic pattern, whereas an exaggerated elevation in serum aminotransferase level in contrast to ALP indicates hepatocellular injury. Abnormalities in serum bilirubin level or other liver function tests, i.e. albumin or prothrombin time (PT), are not used to distinguish the pattern of hepatobiliary disease; however, this principle is not absolute and should not be extrapolated to all cases. Notably, many patients present with a mixed pattern and elevations in both serum aminotransferases and ALP levels. To resolve this uncertainty, one could use the R value, defined as the ratio of ALT (upper limit of normal) divided by ALP (upper limit of normal). In regard to the amount of R value, the liver injury is stratified into hepatocellular (R>5.0), mixed hepatocellular-cholestatic (2.0<R<0.5), and cholestatic (R<2.0) patterns (1-2).

Given the R value >5.0 in the presented patient, a hepatocellular pattern is predictable. As a result, causes amenable to hepatocellular injury should be included in the differential diagnosis. Common conditions associated with hepatocellular damage include viral hepatitis (hepatitis A, B, C, D, and E), alcohol, drugs (e.g., acetaminophen), autoimmune hepatitis, Wilson disease, nonalcoholic fatty liver disease, and hemochromatosis, among others (3).

A vital question is whether ascending cholangitis, a life-threatening cholestatic condition prompting urgent biliary drainage, should be included in the differential diagnosis of hepatocellular damage. Surprisingly, the answer is yes. Because the first presentation of suppurative cholangitis is hepatic micro-abscesses, the probability of ascending cholangitis for a patient with hepatocellular injury, particularly in accompaniment with a rise in serum bilirubin level, should be kept in mind. Nonetheless, the absence of systemic inflammation markers and biliary duct dilation in ultrasound rules out such diagnosis for MM.

Because of the hepatocellular pattern of liver injury, increased serum autoantibodies (ANA, ASMA), and increased serum immunoglobulin (IgG) level in addition to ruling out other probable differential diagnoses mentioned above, autoimmune hepatitis (AIH) was considered the most likely diagnosis for the present case. To confirm the diagnosis, a liver biopsy was obtained. For the diagnosis of autoimmune hepatitis, histological findings may be characteristic but nonspecific. There are some pathologic diagnostic criteria for autoimmune hepatitis, but they vary considerably according to the grade and stage of disease. Chronic inflammation composed of lymphocytes and a considerable number of plasma cells in portal tracts is a near-constant feature, but during periods of quiescent disease (remission), little portal inflammation is seen. Interface hepatitis is the microscopic characteristic but not specific finding of AIH, which is characterized by a prominent lymphohistiocytic infiltration at the portal tract/parenchymal junction with histologic evidence of liver cell damage. A small number of intraepithelial lymphocytes may be present within the bile duct epithelium, but bile duct destruction and loss are not features of AIH and should alert the pathologist to a possible diagnosis of PBC or overlap syndrome (4-7).

The liver biopsy done in the present case showed an interface hepatitis with prominent lymphohistiocytic infiltration at the portal tract and parenchymal junction

as well as hepatocellular damage, swelling, and disarray, which confirmed the diagnosis of autoimmune hepatitis (Figure 1).

Another question is whether it is well worth the difficulties to evaluate an almost asymptomatic patient for an autoimmune hepatitis. In contrast to the fulminant type of autoimmune hepatitis, there is an indolent and progressive course of the disease which makes searching for the disease invaluable, even in an almost healthy patient.

Based on the guidelines from the American Association of the Study of Liver Diseases (AASLD), an increase in serum aminotransferases following an elevation in serum IgG level and/or positive serological tests in addition to exclusion of other possible differential diagnoses (cholestatic, viral, metabolic, hereditary, and drug-induced liver diseases) are needed to consider autoimmune hepatitis. Subsequently, a histological sample is required to confirm the diagnosis. The main serologic markers that help predict AIH are ANA, SMA, and anti-LKM1 (anti-liver-kidney microsomal) antibodies which are important in children (4-8).

2. What treatment options are available?

Having confirmed the diagnosis of AIH, whether the patient has an indication for treatment should be investigated. Studies have shown that patients who fulfill any of the following criteria should be treated (4-9):

1. AST and/or ALT> 10-fold the upper limit of normal (ULN)
2. Serum IgG> twice the ULN
3. Serum AST and/or ALT> twice the ULN accompanied by (1) disabling symptoms, (2) increased IgG level, (3) elevated direct bilirubin level, and (4) interface hepatitis found on biopsy
4. Histologic findings representing bridging or multiacinar necrosis
5. Liver biopsy revealing cirrhosis
6. Children

MM was started on prednisolone (30 mg daily) and azathioprine (50 mg daily) because of serum aminotransferase levels greater than 10 times the upper limit of normal range (ULN), fatigue, and a liver biopsy consistent with portal lymphoplasmacytic infiltration, interface hepatitis, and mild fibrosis.

Treatment of AIH consists of two phases: induction and maintenance.

Glucocorticoid monotherapy is the preferred initial mode of therapy for AIH. For monotherapy, prednisone or prednisolone is initiated with dosages of 30 mg in mild disease (asymptomatic patients with aminotransferase levels less than 10-fold the upper

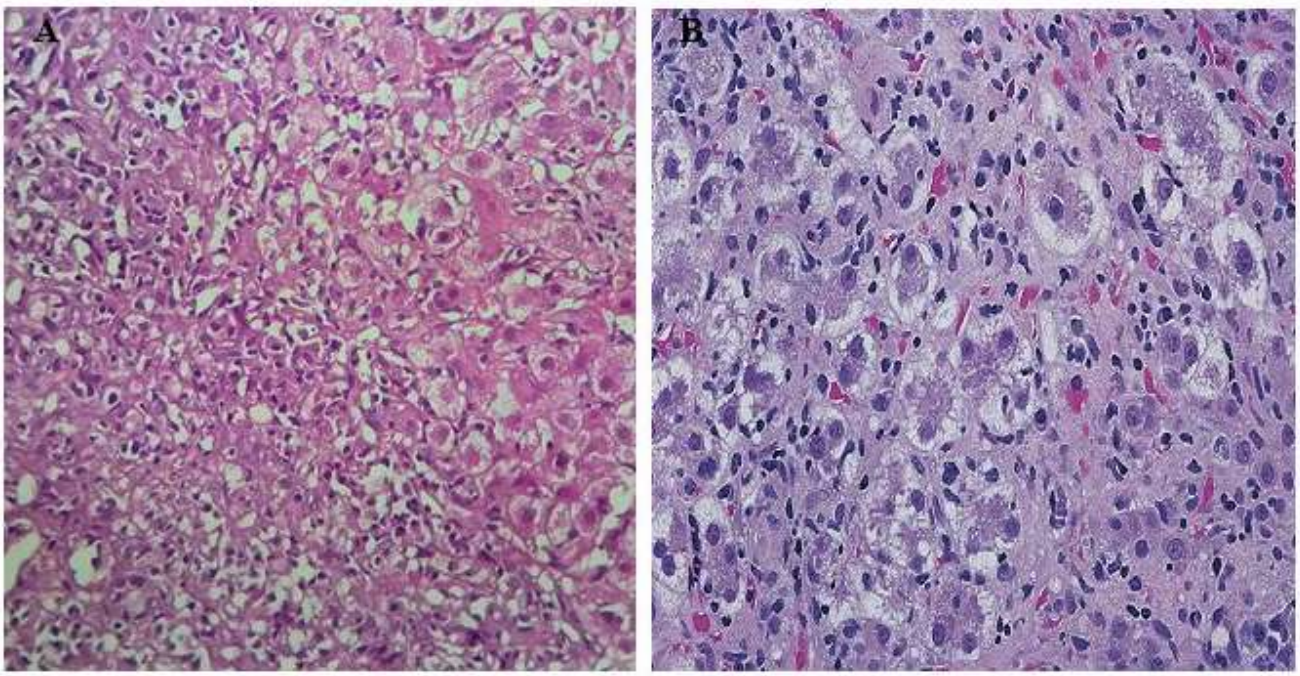

Figure 1. Interface hepatitis in autoimmune hepatitis. Prominent lymphohistiocytic infiltration at the portal tract /parenchymal junction (A), hepatocellular damage, swelling, and disarray (B).

limit of normal) and 40-60 mg in moderate to severe disease followed by a tapering of about 5-10 mg of the dose weekly up to the maintenance dose of 20 mg per day (4-14).

The challenge is for the patients who are not favorable candidates for prednisolone monotherapy, as in the present case who is a young obese female suffering from acne.

In cases at high risk for glucocorticoid side effects (e.g., acne, adrenal suppression, diabetes mellitus and glucose intolerance, myopathy, osteoporosis, peptic ulcer disease, psychosis, seizure, obesity, etc.), combination therapy with azathioprine or 6-mercaptopurine is the treatment of choice (4-14).

Along with combination therapy, 30 mg/day prednisolone and 50 mg/day azathioprine (can be increased up to 2 mg/Kg/day not to exceed 200 mg/day) are administered to reach remission. Having completed a week of simultaneous therapy with prednisolone and azathioprine, prednisolone should be tapered 5-10 mg weekly down to the maintenance dose of 10 mg daily (4-14).

It is also accepted that co-administration of 9 mg/day budesonide with azathioprine (as mentioned above) can be used for cases contraindicated for or intolerant of glucocorticoids. It must be noted that budesonide has a considerable first-pass hepatic metabolism and must not be used in cirrhotic patients (4-6, 13-15).

3. Without treatment, what are we afraid of?

The 5-year survival rate after early medical management of symptomatic AIH cases is reported to be 50%, in contrast to the much lower survival rates of patients who are left untreated. Furthermore, it is estimated that approximately 90% of all patients (symptomatic and asymptomatic) who took proper medication survived 10 years. However, the results are controversial among different studies. Some authors believe that survival is not affected by treatment (16-18).

4. How will I be sure if medication is working? Is there any expected side effect necessitating further tests?

While MM was receiving combination therapy, she was monitored weekly by liver function tests, blood sugar, and complete blood count in addition to her clinical symptoms.

AIH patients who receive medical therapy (glucocorticoid and/or immunomodulators) should be evaluated for treatment responses as well as treatment side effects.

Thiopurines (azathiopurine and mercaptopurine) are said to cause various adverse effects such as bone marrow suppression and hepatotoxicity. Moreover, hyperglycemia is shown to be one of the main side effects of glucocorticoids. To observe these possible adverse effects, complete blood count (not needed in glucocorticoid monotherapy), liver function tests, and blood sugar are monitored (4-15).

To monitor the quality of response to treatment, serum IgG level should be checked weekly for four weeks and then every one to three months. Having completed an 18-month period of treatment, patients should be evaluated for remission by examining resolution of symptoms, normalization of serum aminotransferase levels, normalization of serum bilirubin and gamma globulin levels, and improvement in liver histology (4-15).

It cannot be said that we expect a complete response to treatment. Honestly, treatments are not cure-alls. As presented in the literature, an incomplete response to treatment is seen in about 13% of patients and detected by no improvement in clinical, laboratory, or histologic features after two to three years of appropriate treatment in addition to no worsening in condition and treatment which, reported in approximately 10% of patients, is defined by the development or worsening of cirrhosis and the need for liver transplantation (16-19).

5. What do you expect from the induction therapy? When should therapy end?

Following the treatment of AIH patients, 65-80% of individuals go into remission; 13% and 10% have incomplete remission and no response to therapy, respectively. Approximately 10% of patients show drug-induced side effects that necessitate medication discontinuation. On average, remission is achieved in 18-24 months. Although it is believed that the chance of remission reduces after two years, the remission rate

is estimated to be 65% after 18 months and 80% after three years of treatment. Total remission is defined as improvement of symptoms, biochemical (serum aminotransferases, bilirubin, and IgG), and histological (normal or mild portal hepatitis) abnormalities which commonly are not perceived before 12 months. Histologic remission is usually achieved several months later than biochemical remission. During the remission phase, immunosuppressive drugs should be tapered and changed into maintenance therapy (4-6, 19-21).

6. Is there any need for complementary or non-pharmacological treatment?

Hepatitis A and B virus vaccinations are necessary in patients with AIH who are not already immune (4-6). MM was immune against hepatitis A and B viruses.

Liver transplantation should be considered in AIH patients with acute liver failure, in case there is cirrhosis, decompensated cirrhosis, model of end stage liver disease (MELD) ≥ 15, or hepatocellular carcinoma (in the presence of transplant criteria) (22-23).

MM had no clinical or laboratory evidence of acute liver failure (hepatic encephalopathy, impaired prothrombin time) or cirrhosis (ascites, encephalopathy, impaired prothrombin time, hypoalbuminemia, etc.).

Case study (continued)

Twelve months after treatment initiation, the patient came for consultation regarding the management of her prolonged/persistent elevated liver tests and worsening fatigue. Her blood work revealed (Table 2).

MM asks why her liver tests have remained abnormal, despite her taking the medicine according to doctor's order. Is there another diagnosis? Is another diagnostic evaluation necessary?

7. What complementary diagnostic evaluation is needed? What do you think the diagnosis is?

Given the elevated alkaline phosphatase level, abdominal right upper quadrant ultrasonography was performed to assess hepatic parenchyma and bile ducts. No abnormal finding (especially evidence of intra- and extrahepatic cholestasis) was reported. Because of the possibility of AIH overlap with primary biliary cirrhosis (PBC) in the background of normal extrahepatic bile ducts reported in ultrasound, anti-mitochondrial antibody (AMA) testing was requested, and the results were normal. Next, primary sclerosing cholangitis (PSC) was examined with magnetic resonance cholangiopancreatography (MRCP), which revealed multifocal beaded ducts as well as many dilated intrahepatic ducts.

Various reports have stated the prevalence of AIH-PSC overlap ranges from 1.7-12.5%. In patients who present with AIH, PSC is usually diagnosed some years after onset of initial symptoms (a mean interval of about 5-9 years after symptom initiation with reported cases of up to 15 years) (24-25).

Overlap syndrome should be suspected if alarming features suggestive of PSC, such as pruritus, cholestatic pattern of liver enzymes (elevated alkaline phosphatase), abnormal cholangiography, and absence of response to glucocorticoid therapy, are detected in an AIH patient (26-27).

Identifying characteristic changes in the bile duct cholangiography, including multifocal strictures, intra-/extrahepatic segmental dilations, and exclusion of secondary sclerosing cholangitis, is necessary to provide the definite diagnosis of PSC. Available cholangiography techniques comprise invasive percutaneous transhepatic cholangiography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP), and noninvasive magnetic resonance cholangiopancreatography (MRCP). MRCP is the procedure of choice among the mentioned strategies because of its noninvasive nature (28-29).

Table 2. The Patient's Laboratory Findings 12 months after treatment initiation

Test	Result	Normal Range
White blood cell (WBC)	7200/ µL	4500-11000/µL
Hemoglobin (Hb)	13.8 mg/dl	11-15 mg/dl
Platelet (Plt)	368000	150-450 × 10^3
Prothrombin time (PT)	12 Sec	12-13 Sec
Partial thromboplastin time (PTT)	33 Sec	24-42 Sec
Lactate dehydrogenase (LDH)	486 U/L	150-500 U/L
Serum albumin	4 g/dl	3.8-5.5 g/dl
Blood urea nitrogen (BUN)	13 mg/dl	8-20 mg/dl
Serum creatinine	0.8 mg/dl	0.5-1.1 mg/dl
Aspartate transaminase (AST)	56 U/L	Up to 41 iU/L
Alanine transaminase (ALT)	62 iU/L	Up to 41 iU/L
Alkaline phosphatase (AlkP)	976 U/L	80-306 U/L
Total bilirubin	1.1 mg/dl	Up to1.2 mg/dl
Serum immunoglobulin-G (IgG) level	716 mg/dl	640-1,430 mg/dl

8. What do you think about changing treatment?

Optimal treatment of AIH-PSC is uncertain. In the treatment of these patients, combination therapy with glucocorticoids and other immunosuppressive agents (e.g., azathioprine) with or without ursodeoxycholic acid (UDCA) should be considered (29-30).

9. Does PSC have complications that require screening or complementary diagnostic evaluation?

Because of cholestasis and resulting fat-soluble vitamins malabsorption, advanced PSC patients are at risk for vitamin (A, D, E, and K) deficiencies. Therefore, it is recommended that PSC patients be periodically screened for serum levels of fat-soluble vitamins as well as prothrombin time (PT) for vitamin K evaluation (28-31).

Vitamin and PT serum levels were normal for MM.

Metabolic bone disorder (osteopenia or osteoporosis) is another known complication of PSC patients because of cholestasis and vitamin D deficiency. It should be noted that long-term consumption of prednisolone is another culprit in decreasing bone mineral density among these patients. Bone mineral densitometry (BMD) (e.g., dual-energy x-ray absorptiometry) should be performed at the time of diagnosis and then every 2-3 years (AASLD recommendation) (28-31).

DXA was done for MM and revealed no evidence of osteoporosis or osteopenia (T-score and Z-score> -1).

10. Does PSC increase cancer risk? What are the screening methods?

PSC increases the risk of hepatobiliary cancer (cholangiocarcinoma, gallbladder cancer, and hepatocellular cancer) as well as colon cancer (especially in patients with both PSC and ulcerative colitis) (28-34).

Cholangiocarcinoma and gallbladder cancers should be screened annually by either ultrasound or magnetic resonance cholangiopancreatography (MRCP) plus serum CA 19-9 in patients ≥ 20 years old (32).

In cases of cirrhosis, HCC screening is recommended every 6 months by liver ultrasound with or without serum alpha fetoprotein (33).

PSC patients have an increased risk of colon cancer. This risk is increased when there is simultaneous ulcerative colitis. Therefore, screening colonoscopy should be performed at the time of PSC diagnosis and every 3-5 years thereafter for PSC alone and annually for PSC-UC patients (28, 34).

Having confirmed the PSC diagnosis, MM

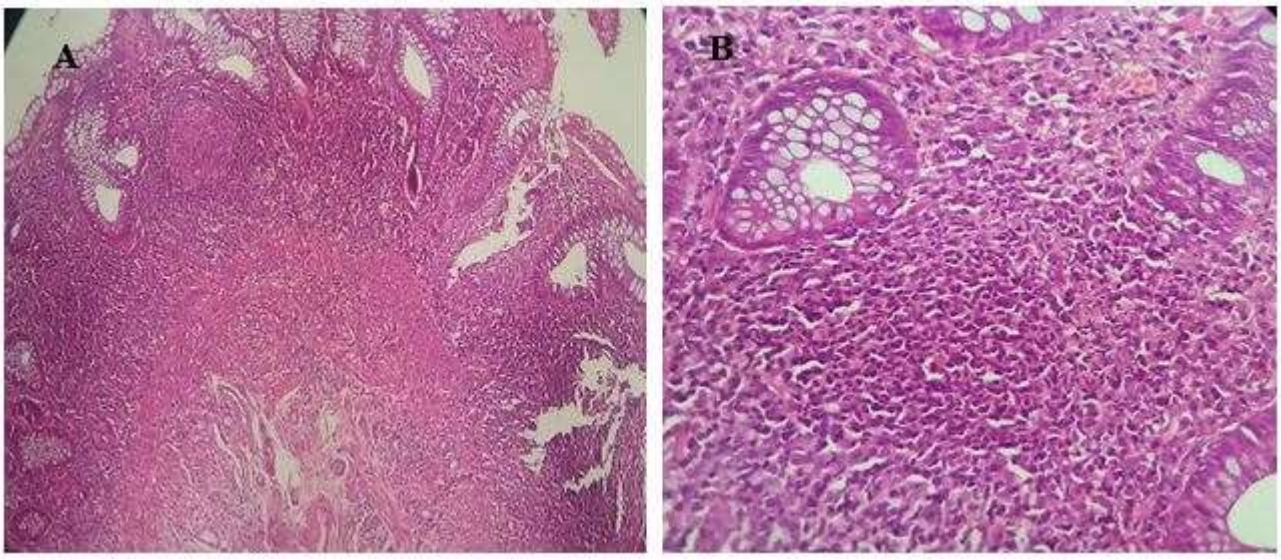

Figure 2. A) Chronic colitis, low-power magnification shows dense lymphoplasmacytic inflammation involves the entire biopsy and a prominent germinal center; some crypts are branched (architectural distortion), indicating previous injury and regeneration. B) Predominantly a lymphoplasmacytic process, dense, homogeneous lymphoplasmacytic inflammation expands and thickens the lamina propria.

underwent a colonoscopy. Colonoscopy revealed mild colitis (mild friability, erythema, and a decrease in vascular pattern) from transverse colon to cecum. The histopathologic features suggested ulcerative colitis (Figure 2).

Evaluation of patterns of injury in colorectal biopsy specimens is best performed at low magnification. The most reliable markers of chronic colitis are crypt architectural distortion and basal plasmacytosis. Crypt architectural distortion is characterized by irregularly arranged, branched, and shortened crypts with loss of mucin content. Basal plasmacytosis filling the space between the base of the crypts and the superficial aspect of the muscularis mucosa is probably the single best marker of chronic colitis. Paneth cell and mucous (pyloric) gland metaplasia are both markers of chronicity. The term activity typically refers to active epithelial injury mediated by neutrophils or eosinophils. Neutrophils may be scattered in the lamina propria or may cause active crypt injury (cryptitis) or form crypt abscess (35,36).

11. Is there a new disease or condition you are looking for through colonoscopy, or it is a part of routine screening for patients being diagnosed with AIH-PSC?

PSC is closely related to inflammatory bowel disease (most often with ulcerative colitis) in up to 90% of patients. As a result, patients with proven PSC should be screened for inflammatory bowel disease (IBD) with colonoscopy (and biopsy). Colon biopsies should be performed for these patients even in normal-appearing mucosa, because patients with IBD and PSC may show active histologic activity despite minimal endoscopic damage (37,38).

In contrast, to the low prevalence of PSC in IBD patients (about 4%) negates the need for routine evaluation for PSC in this group of patients. However, in patients with clinical, laboratory, or imaging findings suggestive of PSC such as unexplained fatigue, pruritus, jaundice, and/or abnormal liver function tests (especially alkaline phosphatase), and/or intra-/extrahepatic biliary ducts abnormality, PSC should be considered (39).

Studies suggest that symptoms as well as endoscopic and histopathologic features of colon involvement may be different in patients with PSC-IBD from patients with IBD only. Generally, patients with ulcerative colitis (UC) alone have more severe symptoms such as mucous/bloody stools and abdominal discomfort, while PSC-UC patients often have asymptomatic or mild symptoms. Endoscopically, pancolitis or right-sided disease is more common in PSC-UC patients. Backwash ileitis and rectal sparing, which are rare in patients with UC alone, are more prevalent in PSC-UC patients. Histologically, colon biopsies from patients with IBD and PSC may show active histologic activity despite minimal endoscopic activity (38-40).

12. Is there a drug added to the treatment regimen to treat ulcerative colitis? What are the adverse effects of this drug and how is it monitored?

Oral mesalazine (3 gr daily) was added to the treatment. The most common side effects of aminosalicylates (5-ASAs) are watery diarrhea, abdominal pain, headache, and nausea. Nephritis is a rare side effect, but patients must be monitored for it. Monitoring is performed by measuring serum creatinine and blood urea nitrogen (BUN) levels at week 6 and months 6 and 12 after initiation of 5-ASAs therapy and annually thereafter (38-42).

It is recommended that 6 to 12 months after achieving clinical remission, patients be evaluated clinically and endoscopically. Simultaneous measurement of noninvasive inflammatory markers (i.e. CRP and fecal calprotectin that correlate with the degree of mucosal healing) is useful (38-42).

13. Does UC have complications that require screening or complementary diagnostic evaluation? Do UC patients need preventive care?

Patients with UC should receive calcium (1000-1200mg) and vitamin D (600 IU) daily.

Metabolic bone disorders (osteopenia or osteoporosis) are complications of UC, so bone mineral density (BMD) (e.g., dual-energy x-ray absorptiometry) should be measured in patients with increased risk of osteoporosis (males >50 years, post-menopausal females, glucocorticoid use with a dose of 7.5 mg/day or higher> 3months, history of fragility fracture). If low

bone mass is reported, the patient should take calcium (1200 mg) and vitamin D (800-1000 IU) daily. If a patient has osteoporosis, oral bisphosphonate (e.g., alendronate) is the preferred drug (43-46).

UC patients are at risk of anemia, which is caused by a variety of factors, including chronic disease, iron deficiency, folate or B12 deficiency, and/or drug-induced anemia (e.g., thiopurines). Therefore, it is recommended the CBC be checked every 6-12 months (41).

All IBD patients (who are taking or intending to start immunosuppressive agents) must receive inactivated (non-live) seasonal influenza and pneumococcal vaccines. Other inactivated vaccines (e.g., hepatitis A, hepatitis B, meningitis, human papillomavirus, herpes zoster, tetanus, diphtheria, and pertussis) should be received based on the guidelines for the general population. Live vaccines (e.g., intranasal influenza, shingles, varicella, yellow fever, measles, mumps, and rubella), however, are contraindicated in immunosuppressed patients (45-49).

14. Does UC increase cancer risk? What are the screening methods?

UC increases the risk of colon cancer; an even higher risk is expected for patients with both PSC and UC.

The time to start screening for colon cancer with colonoscopy depends on the extent to which the colon is involved by disease and the duration of the disease from onset. Colonoscopy should be started 8-10 years after UC diagnosis in patients with extensive colitis (i.e. extending proximal to splenic flexure), 15-20 years after UC diagnosis in patients with left-sided colitis (i.e. distal to splenic flexure), and it should be repeated every 1-3 years thereafter. Simultaneous occurrence of PSC and IBD urges screening colonoscopy to be performed at the time of diagnosis and then annually thereafter. It must be noted that proctitis alone does not require colon cancer screening (49-51).

Annual cervical cancer screening (pap test and/or primary HPV testing based on age) is recommended in UC (IBD) women on immunosuppressive therapy (51,52).

IBD patients who have taken or are currently taking immunomodulators (e.g., thiopurines) or biologic agents (e.g., anti-TNF drug) are at increased risk of skin cancer (both melanoma and non-melanoma).

Table 3. Medical therapy regimen for MM.

Agents	dose	Side effect monitoring
Azathioprine	50mg once-daily	Cell blood count, liver function tests, blood sugar, should be checked weekly for four weeks and then every one to three months.
Prednisolone	10mg once-daily	
Mesalazine	1000mg thrice-daily	Serum creatinine and BUN at 6th week, 6th month, and 12th month after starting mesalazine and then annually.
Vitamin D	600 IU once-daily	
Calcium	1000 mg once-daily	

Table 4. Preventive care for MM.

Preventive care	Interval
BMD (DXA)	Every 2-3 years
Complete blood count	Every 6-12 months
Colonoscopy, CRP and fecal calprotectin	In 6 to 12 months after achieving clinical remission
Seasonal inactive influenza vaccine	Annually
Pneumococcal vaccine	The 13-valent pneumococcal vaccine (PCV13) followed ≥8 weeks later by the 23-valent pneumococcal polysaccharide vaccine (PPSV23). PPSV23 is repeated every 5 years.
Other inactivated vaccines (e.g. hepatitis A, hepatitis B, meningitis, human papillomavirus, herpes zoster, and Tetanus, diphtheria, pertussis) should receive be based on the guideline like general population.	

Table 5. Cancer screening for MM.

Type of cancer	Screening method	Interval
Colon cancer	Colonoscopy	Annually
Cholangiocarcinoma	MRCP + serum CA 19-9	Annually
Gallbladder cancer	US or MRCP	Annually
Skin cancer	Dermatologist skin examination	Annually
Cervical cancer	Pap test and/or HPV primary testing	Every 3 years

Annual skin examination is recommended in such patients (53-54).

Take home message

15. What is the final diagnosis, and what is your recommendation for medication regimen, drug monitoring, preventive care, and cancer screening?

The final diagnosis is AIH-PSC-UC. Azathioprine, mesalazine, prednisolone, and calcium and vitamin D supplementation were started for MM. She was advised to adhere to expected drug side effects monitoring, a preventive care plan, and the cancer screening program (Table 3-5).

Conflict of interests

The authors declare that they have no conflict of interest.

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