

# **Autoimmune gastrointestinal complications in patients with Systemic Lupus Erythematosus: case series and literature review**

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## **Declaration of interest**

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**Abstract**

The association of Systemic Lupus Erythematosus (SLE) with gastrointestinal autoimmune diseases is rare, but has been described in the literature, mostly as case reports. However, some of these diseases may be very severe, thus a correct and early diagnosis with appropriate management are fundamental. We have analysed our data from the SLE patient cohort at University College Hospital London, established in 1978, identifying those patients with an associated autoimmune gastrointestinal disease. We have also undertaken a review of the literature describing the major autoimmune gastrointestinal pathologies which may be coincident with SLE, focusing on the incidence, clinical and laboratory (particularly antibody) findings, common aetiopathogenesis and complications.

**Keywords:**

Systemic Lupus Erythematosus, Lupus enteritis, Crohn's disease, ulcerative colitis, autoimmune hepatic disease, acute pancreatitis, gastrointestinal involvement.

## **Introduction**

Systemic Lupus Erythematosus (SLE) can affect virtually every organ and system in the body (1). Gastrointestinal (GI) symptoms are common in SLE patients, occurring in up to 50%. They are usually mild and most are caused by viral or bacterial infections or adverse reactions to therapy (1–3). Although SLE related gastrointestinal involvement is not as common that in the skin, joints or kidney, early and accurate diagnosis and treatment are essential to improve the prognosis (1,3).

We have reviewed the literature describing the major autoimmune gastrointestinal diseases associated with SLE and also analysed data from our own SLE patients, followed in a dedicated clinic since 1978. Out of 675 SLE patients, we have identified 29 (4.3%) with an associated autoimmune gastrointestinal disease: 16 with autoimmune hepatitis (AIH), two with primary biliary cirrhosis (PBC), five with ulcerative colitis (UC), two with Crohn's disease (ChD), one with celiac disease (CD), four with lupus enteritis and three with autoimmune pancreatitis (Table 1). Four SLE patients with AIH also had a concomitant autoimmune gastrointestinal disease.

## **Lupus Enteritis**

Lupus enteritis is a rare cause of abdominal pain in patients with SLE, but it increases the mortality if it is not promptly treated (4).

In the British Isles Lupus Assessment Group (BILAG) index 2004 (5), lupus enteritis is defined as either vasculitis or inflammation of the small bowel, with supportive image and/or biopsy findings.

The pathogenic mechanism is not fully understood, but seems to be the consequence of an inflammatory process occurring in the wall of small vessels, caused by the deposition of circulating immune complexes and complement activation (6).

The incidence of intestinal vasculitis in patients with SLE has been reported to range from 0.2 to 14% (7–14) (Table 2). In a review of the literature, Sultan *et al.* found that 0.4% of 266 lupus patients (then in our cohort) had intestinal vasculitis (11), while Vitali *et al.* reported the incidence from a large group of 704 patients with SLE at 1.1% (12).

However, the incidence increases in patients presenting with abdominal pain. Medina *et al.* (9) found that 37% of 51 SLE patients with acute abdomen had pathological lesions related to vessel inflammation.

Although the underlying lesion in most cases is a vessel arteritis or venulitis, vasculitis is not found in all SLE patients presenting with abdominal pain. In a large study, Drenkard *et al.* (10) looked specifically for vasculitis in a cohort of 540 lupus patients and described only one patient with mesenteric vessel inflammation.

Several reports have showed an association between the GI involvement in SLE patients and antiphospholipid antibodies (aPL), due to mesenteric thrombosis (9,15).

Therefore, the term “lupus enteritis” rather than vasculitis was introduced, which highlights the wide spectrum of the disease (16).

The clinical picture of lupus enteritis is non-specific and usually presents as acute abdominal pain with sudden onset and severe intensity (17). It is sometimes accompanied by symptoms and signs of impaired intestinal motility.

In our cohort, we identified four patients with lupus enteritis. The initial symptom was abdominal pain in all cases. Diarrhoea occurred in two. Three of them also developed nausea and vomiting. SLE was diagnosed before the lupus enteritis in three of our patients. In one case, the abdominal vasculitis was the first SLE manifestation. All four had antinuclear antibodies (ANA) and three were positive for anti-ds DNA antibodies. In addition, low complement levels were recorded in these patients and may have been related to complement activation and leuco-occlusive vasculopathy.

Intestinal vasculitis tends to occur in patients with active disease in other organs and systems. Buck *et al.* (18) found that only patients with high lupus activity were diagnosed with lupus mesenteric vasculitis. Thus, in those patients with a high SLE Disease Activity Index (SLEDAI) abdominal pain is more likely to be due to lupus than as an un-related condition. Medina’s study (9) investigated the relationship between the aetiology of abdominal pain in 51 patients with SLE and the disease activity using the SLEDAI score, which contains no abdominal items in contrast to the BILAG index.

They found that patients presenting with GI vasculitis or thrombosis had higher SLEDAI scores than patients with non-SLE related acute abdomen.

However, Lee *et al.*(13) reported no correlation between the occurrence of lupus enteritis and the SLEDAI index and the laboratory data, except for the leukopenia.

Diagnosis is based on typical CT findings (focal or diffuse bowel wall thickening, oedematous and dilated loops of bowel, abnormal bowel wall enhancement which is also called “target sign”, mesenteric oedema, engorgement of mesenteric vessels also known as “the comb sign” and ascites) in SLE patients with acute abdominal pain. (19,20)

However, some CT abnormalities can also be seen in patients with pancreatitis, mechanical bowel obstruction or peritonitis, and may mimic intestinal ischemia. Abdominal ultrasound can be useful to confirm bowel oedema or ascites. We performed an abdominal CT scan and an ultrasound examination in our patients. All of them had bowel wall thickening. The ileum was the site most commonly affected. The target sign was present in one patient. None had mesenteric vascular thrombosis on CT scans.

Although colonoscopy with a biopsy can be useful to confirm the diagnosis, there are no pathognomic histopathologic findings. An oedematous and inflamed intestine, especially in the submucosa, is often observed. It is associated with fibrinoid necrosis of subserosal vessels and leukocytoclasia on the vascular wall. Occasionally, vasculitis can cause ulceration, gangrene and perforation (1). In our cohort, colonoscopy was

performed in three patients. The duodenum appeared oedematous in one patient. Colonoscopy and histology was normal in the other two cases.

Unfortunately, due to the rarity of the mesenteric vasculitis and the lack of controlled trials, management is based on anecdotal clinical experience. Lupus enteritis is typically responsive to high dose of steroids (9,11,21). Immunosuppressive treatment is usually reserved for severe cases or those with recurrent enteritis. Successful treatment of GI vasculitis with cyclophosphamide in patients with SLE has been reported (22,23).

In case reports, beneficial effects of Rituximab in SLE patients with diffuse involvement of the GI tract have been described(17,24). Azathioprine can be used as steroid-sparing in responsive patients(11).

Early diagnosis and appropriate immunosuppressive therapy may avoid possible severe complications. Surgical intervention for potential bowel ischemia should be considered. Early intervention within 24-48 hours positively influences the prognosis of these patients (9).

However, in our series, no patients developed complications and surgical intervention was not needed. All our patients were treated with high dose prednisolone with subsequent tapering. In two of them with more severe disease, Rituximab combined with cyclophosphamide was used with good outcome. Azathioprine as a steroid sparing drug was added with complete resolution of their GI symptoms in the remaining two patients.

### **SLE and Inflammatory bowel disease (IBD)**

The coexistence of these diseases may be difficult to diagnose given that some GI features are present in both diseases and because some of the therapies used in IBD may cause drug-induced lupus (1,3,25). GI symptoms, laboratory analyses and imaging may appear similar in both IBD and SLE. Clearly getting the correct diagnosis has significant implications for treatment and prognosis (3,26). IBD may develop before or after the diagnosis of SLE (3). The association of SLE and UC is very uncommon and only documented in a limited number of case reports (26–30). The estimated prevalence of UC in SLE patients is around 0.4% (1,3,11,25,31).

Concomitant ChD has been reported even less frequently(1,3,11,29). The thoughtful review by Zizic (32) and our own study(11) have concluded that, in general, acute GI manifestations rarely occur in isolation in SLE. The differential diagnoses of both acute and chronic abdominal manifestations in patients with SLE are wide.

In an SLE patient with abdominal pain serious complications including intestinal vasculitis must be excluded. However, it is essential to be aware of the SLE association with IBD, particularly if GI symptoms develop in a well-controlled patient. In these cases a colonoscopy with biopsy should be performed (25,27). Similarly, in patients



with IBD and various extra-intestinal manifestations the coexistence of SLE should be considered (26,29).

The use of anti TNF alpha inhibitors in IBD patients seems to have a role in the formation of antinuclear antibodies and/or anti-dsDNA antibodies. However, these antibodies are not generally associated with clinical symptoms and signs of autoimmunity, and the role that TNFalpha has in SLE is controversial. True cases of SLE in IBD patients treated with TNFalpha inhibitors have been rarely reported (3).

Anti-TNF-associated lupus shares common serological and epidemiological characteristics with SLE making differentiation difficult. Temporal association between therapy and symptoms and resolution of these symptoms after the discontinuation of the anti-TNF agent are the most important clues to differentiate these two diagnoses (30). It is well known that specific alleles can confer susceptibility to multiple inflammatory diseases in humans (33). Although it is possible that SLE and IBD share immunological or genetic defects, data on a truly common genetic susceptibility are controversial.

Three loci, the CARD15/NOD2 gene, the discs large homolog 5 gene (DLG5), and the IBD5 locus on 5q31 (IBD5), have been validated as giving susceptibility to IBD. The 16q12–13 region, which contains the CARD15 gene variants associated with IBD, has been linked to SLE (33).

However, a study of 189 Spanish SLE patients (34) and a study of 188 Hong Kong Chinese SLE patients (35) failed to show association between these CARD15 alleles and SLE. More studies are thus needed to resolve this issue.

In 1964, Dubois *et al.*(31) reported an association between SLE and UC in two of his 520 patients (0.4%) and in 2002 Hallegua *et al.*(4) found this co-existence in two of his 464 patients.

In 2006, Nitzan *et al.* (36) reviewed ten cases (nine cases in the literature and one reported case) of patients with SLE and IBD. In most cases, SLE was diagnosed prior to IBD (70%) and usually at an earlier age than patients with SLE alone. At the time the second disease was diagnosed the first disease was not usually active. Those patients reviewed tended to have less photosensitivity, less arthritis, and less serositis than patients with SLE alone. None of the patients (70% females) had neurological or renal involvement. Every patient was anti-dsDNA antibody positive. In these patients, both diseases had a benign course, 60% having UC and 40% ChD.

In 2010, 27 cases of SLE related UC had been reported (1). The majority had a good response to treatment with steroids associated with azathioprine or hydroxychloroquine. The prognosis of SLE-related IBD is generally good (1,3).

In 2012, Yamashita *et al.*(28) reviewed seven cases of SLE complicating ChD (6 literature cases and one case report). In most patients, ChD developed after the SLE diagnosis. All patients experienced diarrhoea and were anti-dsDNA antibody positive.

In 2012 and 2013, Katsanos *et al.*(3,29)described cases of ChD associated with SLE in the literature and one with ChD and subacute cutaneous lupus erythematosus, typically in young patients and usually with ChD as the preceding diagnosis. Two patients had lupus nephritis as a complication and one showed positive renal response to infliximab. In our SLE clinic we have had five patients with co-existing UC. Four of these patients were already reported in a previous study (25). Female gender was more frequent (80%) and all patients had a positive anti-dsDNA antibody. In three cases SLE diagnosis was prior to the UC. The difference between the diagnoses was 5-14 years. All UC diagnoses were biopsy proven. All patients were treated with steroids and disease-modifying anti-rheumatic drugs (DMARDs) and only one patient had biological therapy. We report one death, a UC/SLE patient with concomitant AIH who died of liver failure after liver transplantation.

Two female patients in our clinic concomitantly developed SLE and ChD (both biopsy proven). One patient had positive anti-dsDNA antibody and the ChD diagnosis was made before the SLE diagnosis. The other also had AIH (both GI diagnoses made after the SLE) and sadly died of liver failure.

### **SLE and Celiac Disease**

CD has been associated with multiple autoimmune pathologies; however the link with SLE is rare and mainly based on case reports (37–40). In 2010 only 17 cases had been

reported in the literature (1), but the true prevalence of CD associated with SLE is unclear because of the limited data.

The symptoms of CD are generally well controlled with a gluten-free diet and refractory cases resolve with steroids (1,11,38). In general, the prognosis is good (1). CD can occur either before or after the SLE diagnosis. In a majority of the patients, serum anti-gliadin (AG) antibodies are positive and duodenal biopsy is compatible with CD (1). Some patients have been diagnosed with CD, even though they lack biopsy proof, because they do have CD specific antibodies. In 2001, Rensch *et al.* (41) reported that 23.3 % of 103 SLE patients had a positive AG antibody, while none had positive anti-endomysial antibody. None of the AG positive patients had endoscopic or histological support of CD indicating that the presence of these AG antibodies in patients with SLE is commonly a false positive result (42).

In 2004, Marai *et al.* (40) did a case-control study composed of 100 patients with SLE, and 120 healthy people. Anti-transglutamine antibodies were found at a low rate in SLE patients and most of them did not have CD. Thus, serological screening for CD is not recommended in SLE, unless there is a clinical suspicion of CD.

Freeman (38) in 2008 evaluated 246 patients with biopsy-defined celiac disease for a previous diagnosis of SLE, based on the revised criteria of the American Rheumatological Association. They found six patients (2.4%), four females and two males. The mean age at diagnosis of celiac disease was 44.7 years and SLE 50 years. In

all patients, the diagnosis of SLE was made after the diagnosis of CD. All patients had a good response to gluten-free diet with histological normalization of the small intestinal biopsies. Ludvigsson *et al.*(43) reported in 2012 the increased risk of SLE in 29,000 patients with biopsy-verified CD. Patients with CD had a 3-fold increased risk of SLE compared to the general population. The excess risk remained more than 5 years after the CD diagnosis; however the absolute risk was low. The authors estimated that not more than two individuals with CD out of 1000 would develop SLE in the ten years following CD diagnosis.

In 2013, Picelli *et al.*(44) search for GI organ-specific auto-antibodies in 194 patients with SLE and 103 healthy controls. 14.4% of SLE patients had positive antibodies, which was significantly different from the control group (0.97%.  $p < 0.001$ ). However, only the anti-endomysium antibodies were associated with SLE and with the presence of discoid lesions.

The underlying mechanism for a link between CD and SLE is not known. Both diseases have an autoimmune aetiopathogenesis and share HLA-B8 and HLA-DR3 histocompatibility antigens (1,39–41,45,46).

Increased interleukin-21, an interleukin that has an important role in the differentiation and function of B cells(47), may be another essential mechanism (48).

Nakou *et al.*(49) demonstrated four-fold higher IL-21 mRNA and increased levels of intracellular IL-21 in peripheral blood CD4+ T cells in patients with active SLE. Fina *et*

*al.*(50) reported high levels of IL-21 RNA and protein expression in duodenal samples from patients with untreated CD. Einarsdottir *et al.* (51) showed an increased risk of CD with elevated IL-21 levels. However, further studies are needed to prove this hypothesis.

In addition, autoimmune enteropathy should be considered in the differential diagnosis of malabsorption with small bowel villous atrophy. This disease is rarely observed in adults and is usually associated with a predisposition to autoimmune disorders. The diagnosis of this condition is based on five criteria: chronic diarrhea for more than 6 weeks, malabsorption, specific histological findings, exclusion of similar disorders, and the presence of specific antibodies such as anti-enterocyte and anti-goblet cell antibodies (52).

In our series, only one female was diagnosed with concomitant SLE and CD (biopsy proven). She had negative anti-dsDNA antibody and interestingly she had also an inflammatory muscle disease. The presence of gut epithelial cell antibodies was not investigated in this patient because of typical CD histologic features and complete response to gluten free diet.

### **SLE and acute pancreatitis**

Since the first report by Reifenstein in 1939 with a fatal outcome (53), pancreatitis complicating SLE has been widely recognized, although it is a rare complication. It has been described in several case reports and small series (54–63).

The estimated rate of SLE-related pancreatitis is 0.7-4% (1,64). However, this rate may be an underestimate because SLE patients may have a ‘subclinical’ type of pancreatitis, with elevation of pancreatic enzymes in the absence of clinical symptoms. In our cohort, we found that SLE-related pancreatitis was rare (3/675 patients; 0.44%).

Acute pancreatitis usually occurs early in the course of SLE. 60% of patients develop pancreatitis within the 2 years of disease onset and in 22% of cases this is the first clinical presentation. (65)

In our series, pancreatitis presented as the initial manifestation of SLE in 2 of 3 patients and after 2 years of disease onset in the remaining one. All SLE-related pancreatitis cases had abdominal pain. In one patient it was associated with nausea, anorexia and diarrhoea.

The diagnosis of lupus-associated pancreatitis should only be made after excluding other mechanical and toxic-metabolic causes of pancreatitis. Suggested pathogenic mechanisms responsible for pancreatic injury in SLE include vasculitis leading to ischemic necrosis of the pancreas (58), aPL-related thrombosis of pancreatic arteries or arterioles (62,66), intimal thickening/proliferation (67) and immune complex deposition

with complement activation in the wall of pancreatic arteries (68). Acute pancreatitis has also been associated with anti-La antibody positivity, cutaneous vasculitis and hypertriglyceridemia(64). One of our patients had cutaneous vasculitis. All cases were anti-La negative with triglyceridemia in the normal range. Interestingly, as pancreatitis is a known complication of primary Sjögren's syndrome, we found anti-Ro positivity in all of our three patients. Among the general population, steroids and azathioprine have been implicated as potentially cause of acute pancreatitis (69). However, in patients with SLE this association is less clear. Pascual-Ramos *et al.*(70) could not find a correlation between corticosteroid or azathioprine administration and the development of pancreatitis. Moreover, studies have demonstrated that immunosuppressive therapy with these medications decreases the mortality (71).

Lupus activity may be an important cofactor predisposing to pancreatitis. Pascual-Ramos *et al.* (70) compared the SLEDAI score between the 24 patients with pancreatitis associated with mechanical or toxic-metabolic aetiologies, and the "idiopathic" pancreatitis group (17 patients) in which no apparent cause other than SLE was identified. The disease activity was significantly increased in the patients with idiopathic pancreatitis.

Immunosuppressive therapies such as azathioprine or cyclophosphamide in combination with steroids may be initiated if the clinician suspects lupus-related pancreatitis. It has been claimed that, in severe cases, plasmapheresis and intravenous gamma-globulin



infusion may be also helpful (1). In our small series, pancreatitis was well controlled with treatment.

### **SLE and Auto-Immune Hepatitis**

Abnormal liver function tests are common in the lupus patient. Patients with SLE have a 25–50% chance of developing liver enzyme abnormalities in their life time (72). Hepatotoxic drugs, coincident viral hepatitis and non-alcoholic fatty liver disease are the main causes of liver disease in SLE (73). There is controversial evidence on a role for SLE in triggering an asymptomatic ‘hepatopathy’, which is characterized by a mild increase in serum liver enzyme levels (74–76). However, there are also overlaps with the autoimmune liver diseases (AILD), such as AIH and PBC (77,78). AIH and PBC are both immunologically mediated disease, but with different clinical, biochemical and serological characteristics. Hepatocyte damage is the dominant feature of AIH (79), whereas PBC is characterized by cholestasis, the expression of biliary epithelial cell (BEC) pathology(80).

However, it is important to differentiate AIH from PBC, as the treatment is different: the corticosteroid therapy of AIH might have a negative impact on the calcium metabolism of PBC patients(81).

The association between AIH and lupus was first described in the 1950s and was incorrectly referred to as “lupoid hepatitis”(82,83), that has caused confusion between the two entities.

To complicate the picture, at the beginning of 1980, Runyon *et al.*(84) published a retrospective review of the spectrum of liver disease in 238 patients with SLE. They found liver disease in 21% of patients, based on abnormal liver histologies or, in some cases, elevation of liver enzymes twice the upper limit of normal (ULN). Moreover, they described liver biopsies of 33 lupus patients that showed different types of liver damage. SLE was thought to be the only explanation for these liver abnormalities, namely cirrhosis and a “canalicular cholestasis” profile. Markers to rule out hepatitis C did not exist at that time.

These controversial findings prompted other researchers to confirm these results. One year later, a similar incidence was reported by Gibson *et al.* (74). No obvious cause for liver abnormalities other than SLE could be identified in 19 out of 81 patients (23%). Liver histology of seven of these patients revealed portal inflammation in five, steatosis in one and active chronic hepatitis in the remaining patient.

Pathologically, a wide variety of lesions have been reported in the liver of SLE patients (Table 3). However, histological examination revealed characteristic lesions only in patients with ‘lupoid hepatitis’(85), while histopathological features in patients with lupus hepatitis are miscellaneous and non-specific. These findings confirm that ‘lupoid

hepatitis' and lupus hepatitis are distinct. In 2008, Chowdhary *et al.* (86) reported a strong association between SLE and AILD. 20% of SLE patients out of 40 showed evidence of AIH and 6 of them had PBC. In 2011, Efe *et al.* (87) reported a survey of 147 patients with SLE and found 36 cases with elevated transaminase levels; 13.8% of these patients had findings consistent with AIH. According to the international autoimmune hepatitis group, the AIH current diagnostic criteria include the histological features of hepatitis, elevation of serum Immunoglobulin G (IgG), demonstration of characteristic auto-antibodies and the absence of viral hepatitis (88). Female predominance and occurrence in the fourth decade of life are characteristic (89). Recently, the AIH has been sub-classified according to antibody profile (90). Type 1 AIH is associated with positive ANA and anti-smooth muscle antibody (SMA). It is also related with multisystem manifestations such as facial rash, arthralgia, haematological disorder, fibrosing alveolitis and renal tubular acidosis. Type 2 AIH is characterized by anti-Liver Kidney Microsomal (LKM) antibody positivity and seems to be more 'organ-specific' (77).

The other interesting finding in patients with AILD is the anti-dsDNA antibody positivity, which is usually known as a specific marker for SLE. In particular, the concomitant seropositivity for AMA and anti-ds DNA is highly suggestive of AIH/PBC overlap syndrome (91,92). Moreover, in a retrospective study of 504 SLE patients,

Zheng *et al.* (93) reported an higher prevalence of lupus hepatitis in patients with active SLE than in those with low disease activity (11.8% vs 3.2%).

A correlation between chronic active hepatitis with the presence of antibody to ribosomal P protein has also been described (94,95). However, the association is still controversial and more data to support the role of anti-ribosomal P antibodies in AIH pathogenesis are needed. Moreover, female predominance, genetic susceptibility, hypergammaglobulinemia, ANA positivity and response to immunosuppressive therapy suggest that similar immunologic mechanisms are responsible for the development of both these autoimmune diseases.

In our cohort, we identified 16 cases with SLE-AIH overlap syndrome (2.3%), 15 females and one male. A lupus patient had concomitant features of both hepatic and biliary damage.

Every patient had positive ANA and 13 patients had a positive anti dsDNA-antibody. The dominant manifestation was elevation of serum liver enzymes. 11 out of 16 SLE-AIH overlap patients had mild symptoms associated with liver injury, such as fatigue, abdominal pain and nausea. 87.5% of these SLE-AIH overlap patients had arthritis, 50% skin rash and 37.5% mouth ulcers.

5 patients (31.3%) developed target organs manifestations due to SLE (neurologic involvement, serositis and nephritis).

While antibodies can be strongly overlapping in SLE and AIH, liver biopsy represents the key feature to distinguish AIH in patients with SLE from non-specific lupus hepatic involvement.

Liver histopathology compatible with AIH shows specific changes, such as interface hepatitis, rosetting of hepatocytes, emperipolesis and fibrosis(89).

Interestingly, in our previous report we found that the prevalence of AILD in juvenile SLE patients is higher compared with adult patients and the AIH preceded the diagnosis of SLE in the juvenile group (77). In this current series, the median age at presentation was 23 years (range: 6-67 years) and AIH was diagnosed before age 16 in six patients.

Treatment strategies are determined by the predominant disease. The recommended treatment for both, AIH and SLE, is immunosuppressive therapy. The standard treatment for AIH comprises high dose of prednisone, which is often successful. Azathioprine should be added to the therapeutic regimen as a steroid sparing agent or in refractory cases(96).

In our series, after receiving standard treatment of steroids and/or immunosuppressive agents, most of the patients' elevated transaminase levels fell to normal. Three patients died of hepatic failure and one of liver malignancy six years after the AIH/PBC overlap syndrome was diagnosed.

## **SLE and Primary Biliar Cirrhosis**

Culp *et al.*(97) reported that 84% of 113 PBC patients had at least one other auto-immune illness associated. The co-existence of PBC with keratoconjunctivitis sicca, CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, Raynaud's and AIH is well recognized. In contrast, the association of PBC with SLE is rare and based on case reports (98–100).

Matsumoto *et al.* (101) analyzed liver histology of 73 SLE patients. PBC was identified as the main cause of liver disease in only 2.7% of them.

Chowdhary *et al.* (86) evaluated 40 SLE patients with liver enzyme abnormalities and found that the incidence of PBC, confirmed by biopsy, was 7.5% (3 patients).

Takahashi *et al.*(102) reported PBC as cause of liver dysfunction in 2.4% of 123 SLE patients with liver dysfunction.

A large-scale study by Gershwin *et al.* (80) reported 27 (2.6%) of 1032 PBC patients also had SLE.

Efe *et al.*(87) studied 71 AIH/PBC overlap patients to find the prevalence of extrahepatic autoimmune disease (EHAD) in these patients. 31 patients (43.6%) had EHAD, of whom 2 (2.8%) had SLE. The authors suggested an extended autoimmune screening in patients with AIH/ PBC overlap.

More recently, Floreani *et al.* (103) assessed the connexion between PBC and other autoimmune conditions and the impact of EHAD on the natural history of PBC. Of 361 PBC patients studied, 221 (61.2 %) had at least one EHAD; 8 of them (3.6 %) had SLE.

Female gender was the only factor significantly associated with positivity for EHAD and there was no difference on survival after the diagnosis of PBC between patients with and without EHAD.

Shizuma (104) reviewed 34 cases of SLE associated with PBC described in the English and Japanese scientific literature and Japanese proceedings. 97% (33/34) were females, and in 69% PBC was diagnosed before SLE. In five cases the diagnosis were simultaneously made.

Most of the reported cases of SLE with PBC were ANA and anti-mitochondrial antibody (AMA) positive. However, antibody profiles are not always useful to support the diagnosis or predict the risk for overlapping disease. ANA was found in 33% of the patients with isolated PBC. In contrast, the presence of anti-mitochondrial antibodies in SLE patients is restricted (1%), but may help predict the course of disease (100).

In PBC patients, anti-dsDNA and anti-ribosomal-P antibodies have been reported in 22% and 5%, respectively (105).

The role of genetic factors in this co-occurrence is not yet established. Osteopontin (OPN), a soluble ligand with pleomorphic immunologic activities that have a vital role in inflammation and immunity, may be a link. OPN which was highly expressed in a SLE model mouse (106), is also involved as a chemoattractant cytokine in the recruitment of macrophages and T lymphocytes in the formation of liver granulomas in PBC patients (107). Han *et al.* (108) confirmed the bond between OPN and SLE.

In our clinic two female SLE patients have developed PBC. Both had the SLE diagnosis before the PBC and have positive ds-DNA antibodies. Treatment with steroids and DMARDs was used in both. One of these patients had an overlap syndrome (AIH/PBC) and sadly died of hepatocellular carcinoma, six years after the overlap syndrome had been diagnosed.

### **Conclusion**

This report highlights the main associations of autoimmune GI diseases in SLE. We have reviewed all lupus patients in our cohort at University College London Hospital followed from 1978 to 2015 and we have compared our SLE cases with concomitant autoimmune GI complications with the results of a literature review. Although these associations are rare, the clinician should be aware of the co-existence of these diseases. As in any disease, early recognition and appropriate treatment benefit the patient.

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