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CASE REPORT

Autoimmune Lupus Enteritis with Pan Gastrointestinal Involvement in an Adult Patient with Systemic Lupus Erythematosus: Complete Response to Belimumab

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Abstract

Autoimmune lupus enteritis in systemic lupus erythematosus (SLE) is a rare manifestation that comprises of gastrointestinal tract inflammation with supportive images and/or biopsy findings. We report a unique case of widespread lupus enteritis occurring late in the disease process and in isolation without additional features of active SLE but in the presence of SLE serological activity. There was no clear evidence of active mesenteric vasculitis, intestinal pseudo-obstruction, protein-losing enteropathy, or coagulopathy by imaging or histopathology. This is the first reported case of an SLE patient with pan-gastrointestinal involvement of lupus enteritis responding to Belimumab, with complete resolution of the gastrointestinal syndrome and no further recurrence of gastrointestinal events. Rapid diagnosis and prompt immunomodulatory treatment of lupus-related enteritis are critical to avoid potentially life-threatening complications.

Keywords: Autoimmune enteropathy, Systemic lupus erythematosus, Lupus enteritis, Gastrointestinal lupus, Belimumab

1. Introduction

About 40–50% of patients with systemic lupus erythematosus (SLE) may experience gastrointestinal (GI) issues at some point in their lives, which can progress rapidly during a lupus flare.[1,2] Medication side-effects, infections, or co-morbidities account for a majority of these issues, with only 2–30% attributed to active SLE per se.[3] SLE-related causes include but are not limited to lupus enteritis, intestinal pseudo-obstruction, protein-losing enteropathy, peritoneal inflammation (serositis), pancreatitis, paralytic ileus, and autoimmune 'lupoid hepatitis'.[1,2]

Lupus enteritis is rare, with a global incidence is 0.2–14.2%.[4] The small bowel tends to be frequently impacted, but pan-gastrointestinal involvement is rare.[5] Computed tomography (CT) imaging is primarily used for the diagnosis of this condition. Early diagnosis and treatment with glucocorticoids and immunosuppressive therapy are crucial to improving clinical outcomes and avoiding life-threatening complications. Here we describe a unique case of lupus enteritis with pan-gastrointestinal involvement in an adult patient with SLE who had a complete resolution of widespread enteropathy with Belimumab.

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2. Case presentation

A 31-year-old woman presented with epigastric pain, vomiting, and watery diarrhea of one-week duration. The patient denied recent travel, sick contacts, or new dietary or medication triggers. It is worth noting that the patient had experienced similar symptoms of epigastric pain and diarrhea intermittently over the previous eight months, which had led to three hospitalizations during that period. Fecal studies, including stool for ova and parasites, stool cultures, and clostridium difficile toxin, carried out during those hospital admissions had all resulted in negative for infection.

The past medical history was significant for SLE, for which the patient was taking hydroxychloroquine. The initial presentation of SLE was 15 years prior and included discoid skin lesions, arthralgia, neutropenia (absolute neutrophil count: 1.3 $\times$ 10^3/mcL), and severe thrombocytopenia (platelet count: 52 $\times$ 10^3/mcL). Persistent serological activity was noted during outpatient follow-up visits, with low serum complement levels (C3 and C4) and high titers of anti-dsDNA and anti-cardiolipin antibodies (IgG) [refer to baseline results, Table 1].

The physical examination was negative for abdominal tenderness or bruits. There was no active synovitis, petechial lesions, or active lupus dermatitis. Chronic discoid skin lesions were noted.

The laboratory results revealed pancytopenia. Serum chemistry was unremarkable. Serum amylase and lipase were negative. The C-reactive protein was elevated to 1.3 mg/dL. Coagulation parameters (PT/INR and PTT) were within normal limits. Work-up for infectious causes included stool for ova and parasites, stool cultures, and clostridium difficile toxin, all of which were negative. Serologic testing for celiac disease was negative. C3 and C4 complement protein levels were low. Positive results for serum antinuclear antibodies were observed at dilutions >1:1280 (normal <1:40) with a speckled pattern. Anti-double stranded DNA (dsDNA), anti-Sjögren's syndrome-related antigen A (Anti-SSA), anti-U1-ribonucleoprotein (anti-U1-RNP), anti-cardiolipin (IgG and IgM), and anti-B2-glycoprotein- I (IgA) antibody titers were elevated. Anti-myeloperoxidase (anti-MPO) and anti-proteinase 3 (anti-PR3) antibodies were within the normal range. The pertinent laboratory results obtained during the current hospital admission are summarized in Table 1 and compared with their baseline values recorded during outpatient visits.

CT abdomen with contrast demonstrated wall thickening in the distal esophagus, gastric body and antrum (arrows, Fig. 1. A, E), duodenum (arrow, Fig. 1. F), proximal bowel loops, colon (arrows, Fig. 1. D, arrowhead, Fig. 1. F), and rectosigmoid region (arrow, Fig. 1. B). The classic "target sign," characterized by colonic wall thickening and mucosal hyper enhancement is visualized (arrows,-Fig. 1. D). Minimal mesenteric vascular engorgement and inflammatory vascular stranding (comb sign) was noted around the proximal bowel loops (highlighted in white, Fig. 1. E and arrowhead, Fig. 1. G). CT angiography of the abdomen revealed a normal caliber aorta with a patent celiac artery, superior mesenteric artery (SMA), and inferior mesenteric artery (IMA). Upper gastrointestinal endoscopy demonstrated mild inflammation in the entire stomach and the first and second portions of the duodenum. A diffuse area of moderately vascular pattern and decreased mucosa was seen in the sigmoid colon and the rectum on sigmoidoscopy. Histologic evidence of mild acute inflammation was noted in the biopsy specimens from the esophagus and the gastric antrum. An acute on chronic enteritis pattern was noted in the duodenum (Fig. 2. A and B). Sigmoid colon biopsies showed mild, reactive changes with no evidence of inflammatory bowel disease or microscopic colitis. The imaging findings and the absence of infectious or other inflammatory etiology during the work-up pointed to the diagnosis of lupus enteritis.

Table 1. Laboratory workup this hospital admission compared with the baseline during previous outpatient follow-up visits.

Laboratory result	This admission	Baseline	Reference Range	Laboratory result	This admission	Baseline	Reference Range
WBC	3.0	4.0−5.0	4.5−11 $\times$ 10^3/mcL	**CRP**	1.3	<0.5	<1 mg/dL
Hgb	8.2	11−11.5	11.9−15.7 g/dL	**Anticardiolipin IgG**	31	10−25	<14 GPL U/mL
Platelets	99	120−140	153−367 $\times$ 10^3/mcL	**Anticardiolipin IgM**	58	20−41	<12 MPL U/mL
C3	57	88−118	90−165 mg/dL	**dsDNA antibody**	237	17−40	0−9 IU/mL
C4	10	13−17	14−44 mg/dL	**ANA titer**	>1:1280	1:160−1:640	<1:40
ESR	>120	60−80	0−25 mm/h				

WBC: white blood cells; Hgb: hemoglobin; C3, C4: complement proteins; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; dsDNA: double-stranded deoxyribonucleic acid; ANA: antinuclear antibodies; 1 GPL unit is 1 μg of IgG antibody. 1 MPL unit is 1 μg of IgM antibody.

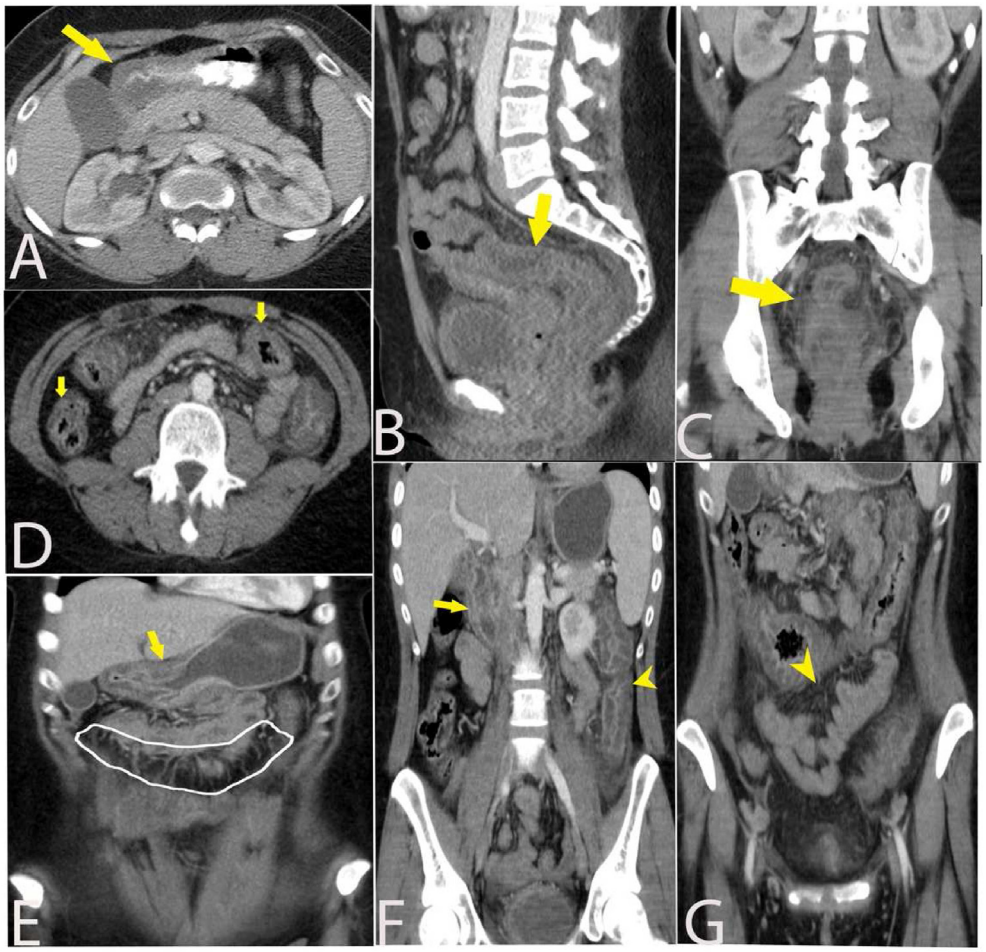

Fig. 1. Patient with a history of systemic lupus erythematosus presenting with abdominal pain. CT of the abdomen and pelvis with iodinated intravenous contrast shows diffuse circumferential wall thickening and edema of the gastric wall (arrow, A), most prominent at the pylorus. There is mild diffuse circumferential wall thickening of the colon prominent at the rectosigmoid region (arrow, B) with peri colonic fat stranding (arrow, C) and small ascites. CT with iodinated IV contrast performed eight months later for abdominal pain again shows similar findings, including diffuse wall thickening and edema involving the stomach (arrow, E), duodenum (arrow, F), and colon (arrowhead, F), including rectosigmoid. Colonic wall thickening with mucosal hyperenhancement, known as the "target sign," is visualized (arrows, D). Diffuse mesenteric edema and engorgement, known as the "comb sign" (highlighted in white, E and arrowhead, G) with small ascites, is noted.

High-dose intravenous steroids and Belimumab injections were initiated. The patient responded favorably and has continued to remain in sustained remission for more than six years now. The improvement with immunosuppressants provided additional confirmation of our diagnosis.

3. Discussion

Lupus enteritis is defined as either vasculitis or small-bowel inflammation with accompanying radiological and/or histological evidence.[6] Clinical manifestations range from resembling mild gastroenteritis to acute abdomen, depending on the severity and duration of vascular inflammation. The SMA territory is involved in 80–85% of the cases, with jejunum and ileum being the most frequently affected regions.[7] While it is not uncommon for multiple vascular territories to be involved, the entire gastrointestinal tract is rarely affected.[5] As far as we can determine, this is only the second documented case of pan-gastrointestinal lupus enteritis reported in the literature.

It is postulated to result from organ-specific manifestation of systemic inflammatory response syndrome (SIRS) that accompanies a lupus flare. It is best explained by the Shwartzman phenomenon in which excessive complement activation in tandem with immune complexes and primed endothelial cells are presumed to induce neutrophil–endothelial cell adhesion and leuko-occlusive vasculopathy. The resultant effect is widespread damage to microvasculature and increased vascular permeability.[8] Additionally, a thrombotic model was described wherein the circulating anti-phospholipid antibodies predispose to mesenteric vessel thrombosis. These two

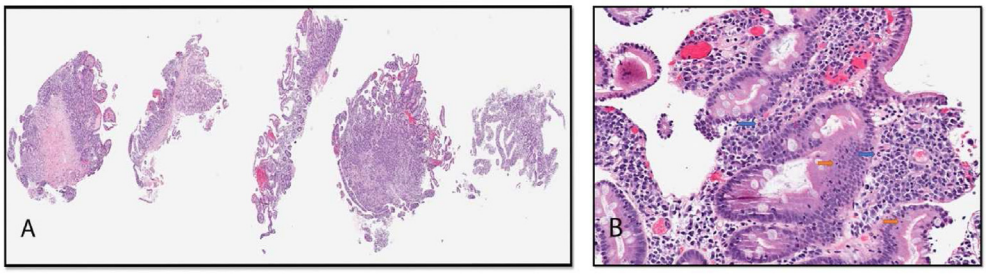

Fig. 2. A. This low power image shows several duodenal biopsies from the same patient. It is clear from this magnification that the villous architecture is intact. However, the lamina propria is more cellular than a healthy specimen. 2B. A higher magnification image of the duodenal biopsy reveals neutrophils (blue arrows) within the lamina propria and apoptotic bodies in the glands, indicating active inflammation and glandular injury. There is also an increase in the plasma cells within the lamina propria, indicating chronicity. This pattern of inflammation is consistent with acute chronic enteritis. Though this is nonspecific, autoimmune lupus enteritis is within the differential diagnosis in the appropriate clinical context. (20x).

pathways can mutually activate each other, resulting in worsening cascades of vasculitis and thrombosis.[9]

Early diagnosis with CT abdomen is pivotal to avoiding sequelae, including bowel ischemia, perforation, and hemorrhage.[2] Imaging findings include dilated bowel, focal or diffuse bowel wall thickening, abnormal bowel wall enhancement (double halo or target sign), mesenteric edema, engorged mesenteric vessels (Comb sign), and increased attenuation of mesenteric fat, and ascites.[1,2,10] Definitive diagnosis requires endoscopy and biopsy demonstration of vasculitis in the mesenteric arterioles. A negative biopsy does not rule out the diagnosis because the submucosa is challenging to access. While the histology, in this case, was inconclusive, the classic CT findings, in conjunction with the clinical presentation, were suggestive of lupus enteritis.

Immune modulatory treatment is often initiated with high-dose intravenous corticosteroids. Immunosuppressive therapies such as cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, rituximab, and intravenous immunoglobulin are usually reserved for severe or recurrent cases.[6,7] Belimumab is a monoclonal antibody directed against B-cell survival factor (BAFF) authorized for the treatment of non-renal lupus. Phase III trials have shown it to be successful in terms of reducing overall disease activity and the incidence and intensity of flares without worsening of patients' overall condition or the development of significant disease activity in new organ systems.[11,12] It is not commonly attempted for the treatment of lupus enteritis. However, we were able to successfully treat a case of pan-gastrointestinal lupus using Belimumab, making it the first of its kind.

Conflict of interest

The above authors have no potential conflicts of interest or sources of financial support.

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