Journal of Community Hospital Internal Medicine Perspectives

Volume 12 | Issue 6 Article 11

2022

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Recommended Citation

Halilu, Fatima; Qureshi, Anum; and Nash, Brenton (2022) "Lupus Enteritis in the Absence of a Lupus Flare. A Case Report and Review of Literature," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 12: Iss. 6, Article 11.
DOI: 10.55729/2000-9666.1129
Available at: https://scholarlycommons.gbmc.org/jchimp/vol12/iss6/11

Journal of Community Hospital Internal Medicine Perspectives

Manuscript 1129

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CASE REPORT

Lupus Enteritis in the Absence of a Lupus Flare. A Case Report and Review of Literature

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Abstract

Lupus enteritis is a rare manifestation seen in systemic lupus erythematosus (SLE). Its diagnosis can be challenging as symptoms frequently overlap many gastrointestinal disorders, imaging findings are not specific, and endoscopic features are infrequently diagnostic. Moreover, enteritis can occur in isolation without other systemic manifestations or even elevated inflammatory markers.[1] Here is presented the case of a 22-year-old female with known SLE manifested by lupus nephritis complicated by end-stage renal disease who presented with abdominal pain. She had leukocytosis with thickened bowel loops, ascites, "target sign", "comb sign" and patent abdominal vessels on CT imaging. The differential diagnoses considered ranged from infectious gastroenteritis to systemic vasculitis. Her infectious workup was negative while inflammatory markers and autoimmune workup did not support active lupus flare. Having ruled out alternative etiologies, steroid dosing was increased in consultation with rheumatology. Subsequently, her abdominal pain responded supporting a diagnosis of lupus enteritis. The case was perplexing in light of her non-specific presenting symptoms and the absence of laboratory evidence of active lupus flare which delayed the diagnosis. This case illustrates how the diagnosis of lupus enteritis continues to remain a challenge.

Keywords: Lupus enteritis, Systemic lupus erythematosus (SLE), Target sign, Steroids

1. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by the formation of autoantibodies. Nearly every organ system in the body can be affected by SLE with the most affected organ systems being the integumentary, musculoskeletal, renal, cardiovascular, hematologic, and central nervous system. Its incidence is estimated at 23.2 cases per 100,000 persons in North America with African American females being the most affected group.[2] The initial presentation of SLE is widely heterogenous which can make recognition challenging. To standardize diagnosis; the American College of Rheumatology (ACR) devised criteria requires 4 out of 11 parameters be met for diagnosis. The 11 criteria are malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, antinuclear antibody (ANA) and disorders of renal, neurologic, hematologic, or immunologic systems. This was recently revised in 2019 in conjunction with the European League against Rheumatism (EULAR) to produce the latest guidelines.[3]

Abdominal pain and other gastrointestinal complaints are frequently encountered in SLE, but these are usually the result of infection brought on by immunosuppression, medication side effects, or even unrelated gastrointestinal comorbidities.[4] SLE-related gastrointestinal involvement is rare, presentations range from oral ulceration, serositis, pancreatitis, hepatobiliary manifestations to lupus enteritis, protein-losing enteropathy, and intestinal pseudo-obstruction.[5,6] Despite advancements in the treatment of SLE, specific diagnostic criteria for lupus enteritis remain poorly defined. We present the case of a 22-year-old SLE patient that presented with non-specific abdominal complaints who is eventually diagnosed with lupus enteritis. The path to her diagnosis was marred with diagnostic challenges and further confounded by the lack of

Received 12 June 2022; revised 10 September 2022; accepted 22 September 2022.
Available online 7 November 2022

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https://doi.org/10.55729/2000-9666.1129

inflammatory or autoimmune markers to suggest an acute lupus flare.

2. Case presentation

A 23-year-old African American female with a known history of SLE complicated by end-stage renal disease, type 2 diabetes mellitus, and psychogenic non-epileptic seizure presented to the emergency department (ED) with a one-day history of abdominal pain, nausea, non-bilious emesis, and diarrhea. She noted fatigue and worsening lower extremity swelling but denied having arthralgias, arthritis, rashes, or ulcers. Pertinent details of her lupus history included stage IV lupus nephritis with current home medications of prednisone, mycophenolate mofetil, and hydroxychloroquine.

On presentation, the patient's vitals were as follows: temperature 37.0 °C, blood pressure 224/169 mmHg, heart rate 96 bpm, and respiratory rate 16/min with 100% oxygen saturation on room air. On examination, her abdomen was mildly distended, diffusely tender to palpation with guarding, but no rigidity or rebound tenderness. She had 2+ pitting edema of her bilateral lower extremities. Her laboratory results on admission (Table 1) were notable for leukocytosis with neutrophilia, hyperkalemia, markedly elevated BUN and creatinine, and mildly elevated procalcitonin. CT abdomen pelvis showed diffusely dilated and thickened bowel loops without obstruction, "target sign," "comb sign," and considerable ascites without evidence of ischemia (see Figs. 1–5).

Her hyperkalemia and markedly elevated BUN and creatinine were the result of a recently shortened dialysis session and raised concern that uremia and incomplete dialysis could account for her nausea, diarrhea and hypertensive urgency. She received urgent hemodialysis for hyperkalemia of

Table 1. Laboratory results on admission.

Labs	Day of admission	Reference
WBC	12.72 × 10^3/μL	4–11 × 10^3/μ L
Neutrophil Total	9.44 × 10^3/μL	2.00–8.00 × 10^3/μL
Neutrophil %	74.2%	–
Hemoglobin	13.5 g/dL	12.5–15 g/dL
Platelet	299 × 10^3/μ L	140–400 × 10^3/μ L
Sodium	135 mEq/L	133-145 mEq/L
Potassium	5.9 mEq/L	3.3–5.1 mEq/L
Chloride	95 mEq/L	96-108 mEq/L
Bicarbonate	20.6 mEq/L	22-29 mEq/L
Anion Gap	19.4	5–16
BUN	75 mg/dL	6–23 mg/dL
Creatinine	11.75 mg/dL	0.5–1.00 mg/dL
Glucose	195 mg/dL	70–115 mg/dL
Phosphate	7.8 mg/dL	2.6–4.5 mg/dL
Albumin	4.9 g/dL	3.2–5.2 g/dL
Total protein	7.9 g/dL	5.9–8.4 g/dL
Total Bilirubin	0.4 mg/dL	<1.0 mg/dL
AST	15 IU/L	4–31 IU/L
ALT	9 IU/L	4–31 IU/L
ESR	31 mm/h	<20 mm/h
CRP	0.41 mg/dL	<0.05 mg/dL
Lipase	20.8 IU/L	16–63 IU/L
Lactic acid	1.2 mmol/L	0.5–1.9 mmol/L
Procalcitonin	0.16 ng/mL	≤0.10 ng/mL

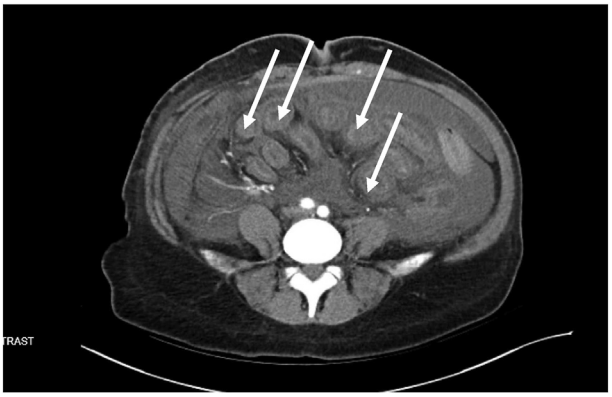

Fig. 1. Axial view of CT abdomen with contrast showing target sign.

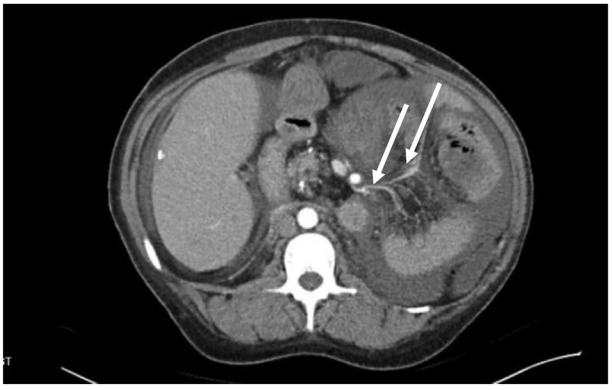

Fig. 2. Axial view of CT abdomen showing comb sign.

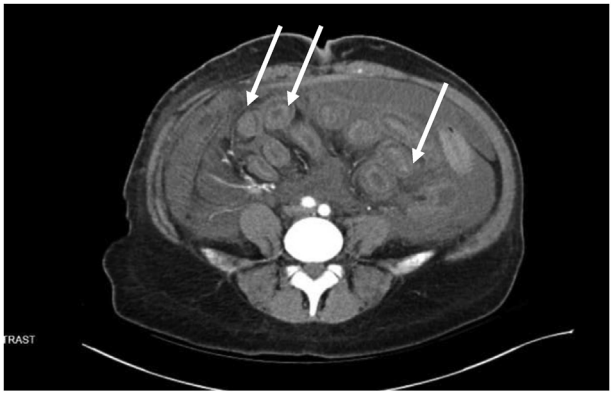

Fig. 3. Axial view of CT abdomen showing Coomb sign.

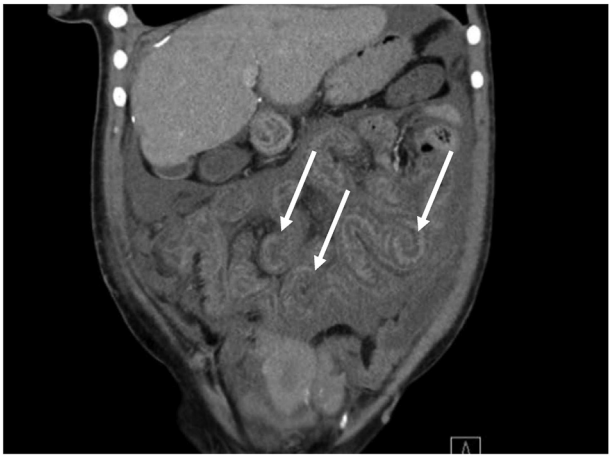

Fig. 4. Coronal view of CT abdomen showing target sign.

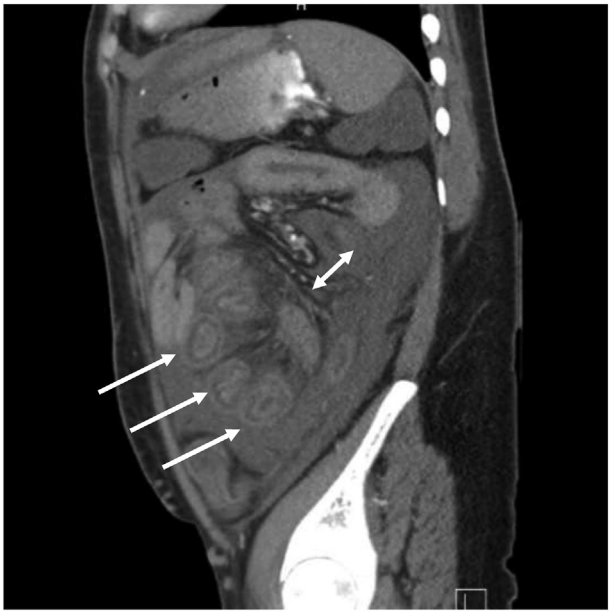

Fig. 5. Sagittal view of CT abdomen showing target sign (single arrow) with hint of Comb sign (double arrow).

5.9 mEq/L and EKG findings consistent with hyperkalemic emergency with reduction in pedal edema but her abdominal symptoms persisted.

Diabetic ketoacidosis was entertained as a cause of her abdominal pain, but her glucose was only mild elevated, acetone was negative and her mild anion gap metabolic acidosis was more easily explained by uremia given its resolution post dialysis. The patient was placed on bowel rest and general surgery was consulted. Surgery did not feel that her presentation or imaging represented pathology that would require surgical intervention. They raised the question of infectious enteritis. Workup for an infectious etiology was negative including *Clostridioidies difficil*e.

A paracentesis was performed prior to the initiation of antibiotics to further characterize the patient's newly discovered ascites. Fluid analyses showed 531 white blood cells/cumm with a 65% lymphocytic predominance, serum ascitic albumin gradient (SAAG) was <1.1 and gram stain and cultures were negative (Table 2).

Given the radiographic appearance of the patient's bowel with target and comb sign, lupus enteritis was considered highly likely, and rheumatology was consulted.

Inflammatory markers – ESR and CRP were minimally elevated with normal C4 levels and borderline low C3 that were not typical of her past active lupus flares. Additional autoimmune evaluation showed high titers of ANA, elevated anti-dsDNA, and anti-Ro (Table 3).

CT angiography of abdomen undertaken to evaluate for mesenteric thrombosis/arteritis showed patent intraabdominal vessels without thrombi.

Table 2. Ascitic fluid analysis.

Labs	
Gross appearance	Clear yellow
Protein	4.3 g/dL (serum protein 7.0 g/dL)
Albumin	3.1 g/dL (serum albumin 4.1 g/dL)
SAAG	1.0
Gram Stain	Few PMNs, no organisms seen
Culture	No growth
Cytology	Predominantly histiocytes, few mesothelial cells, few acute and chronic inflammatory cells

Table 3. Autoimmune laboratory results.

		Reference
Complement C3	73.3 mg/dL	76–100 mg/dL
Complement C4	29.5 mg/dL	15–46 mg/dL
ANA titers	1:320	Negative <1:40 Elevated >1:180
ANA pattern	Nuclear homogenous pattern	
Anti mitochondrial antibody	Negative	
Anti-dsDNA	1:20	<1:10
Anti-smooth muscle/RNP (Ribonucleoprotein)	<1.0 Negative	
anti-Ro/SSA	>8.0	Negative <1.0
Anti-La/SSB	<1.0 Negative	Negative <1.0
Rheumatoid Factor	<14 IU/mL	<14 IU/mL
Anti-Scl (scleroderma)	<1.0 Negative	Negative <1.0
Anticardiolipin antibody		
IgM	<2.0	<20.0 APL-U/mL
IgG	<2.0	<20.0 APL-U/mL
IgA	<2.0	<20.0 APL-U/mL
Anti-beta 2 glycoprotein		
IgM	70	<20 SMU
IgG	<9	<20 SMU
Lupus anticoagulant with reflex	Not detected	

Incidentally, it was noted that the bowel wall edema and the volume of ascites had improved compared to her previous imaging obtained on admission. After ruling out most of the alternative diagnoses with persisting nausea and abdominal pain, lupus enteritis seemed the likely diagnosis and her prednisone dose was increased to 1 mg/kg/day with continued improvement of abdominal pain. Further endoscopic evaluation was deferred, and she was discharged on a steroid taper with outpatient rheumatology follow up where she continues to do well.

3. Discussion

The gastrointestinal manifestations of SLE were first alluded to by William Osler in 1895, but it was not until 1980, when the duo of Hoffman and Katz succinctly described lupus enteritis.[7,8] The British Isles Lupus Assessment Group (BILAG) in 2004 defined lupus enteritis as "vasculitis or inflammation of the small bowel, with supportive image and/or biopsy findings".[9] The pathophysiology behind lupus enteritis is thought to be the deposition of immune complexes with subsequent complement activation leading to edema in bowel wall.[10] The most involved sites are the ileum and jejunum. Studies estimate the rates of lupus enteritis to range from 0.2 to 5.8% among patients already diagnosed with SLE, with a mean onset of 34 months from the time of lupus diagnosis.[4] In addition, isolated presentations of lupus enteritis as the initial presentation of SLE have been described.[11,12] Koo et al. in their retrospective review of radiographically confirmed lupus enteritis found an 85% female prevalence and a median age of 34 years.[13] The initial presenting signs and symptoms of abdominal pain, nausea, vomiting, anorexia, and diarrhea are commonplace and may not elicit clinical suspicion. Additionally, ongoing immunosuppressive treatment can mask gastrointestinal (GI) symptoms. Zizic et al. in their retrospective review of 140 SLE patients found the presence of vasculitis, thrombocytopenia, or rheumatoid factor to be associated with an increased risk of developing lupus enteritis, all of which were absent in our patient.[14] In the medical literature, lupus nephritis has been strongly associated with lupus enteritis with an estimated 65% co-existence such as in our patient.[15,1]

Laboratory testing is valuable in supporting a diagnosis of lupus enteritis. The levels of inflammatory markers are variable, but CRP is frequently normal and complement levels are usually low in 70% of cases.[15] Autoantibodies are more reliable, with ANA titers elevated in 92%, positive anti-dsDNA in 80% and 20% seropositivity for anti-smith antibodies.[10] While, our patient did have elevated titers of ANA and anti-dsDNA with normal CRP, her complement titers were not low as her past typical lupus flares had. Luis et al. noted similar findings of non-elevated ESR and CRP with modestly elevated anti-dsDNA titers in their retrospective analysis of 7 patients with lupus enteritis.[1] These autoimmune and inflammatory markers can be helpful but, are not a requirement for diagnosis as isolated lupus enteritis can occur without clinically active lupus as was seen in this case.[15]

Unfortunately; the criteria for lupus enteritis has not been defined by ACR and past attempts to produce normograms or predictive models have yielded conflicting results.

Liu and colleagues produced a normogram consisting of 11 features to help predict lupus enteritis, these are; age, albumin, anion gap, D-dimer, platelet count, ANCA, C4, anti-SSA (Sjogren syndrome-related antigen A), anti-ribosomal P protein (Rib-P), anti-ribonucleoprotein (RNP).[16] The last four variables had the strongest correlation with C4 being a protective factor while anti-SSA, anti-Rib-P and anti-RNP were risk factors with anti-RNP being the strongest risk factor.[16] Our patient only had 1 of 11 predictive markers and that was anti-SSA. Conversely, Zhang and colleagues' predictive normogram for diagnosis of LE found elevated D-dimer, low C3 and anti-SSA to be positively predictive.[17] Similarly, Lee et al. in their retrospective review of 175 SLE patients categorized into lupus enteritis (n = 17), non LE related abdominal pain and SLE without abdominal pain only found leukopenia to correlate with occurrence of lupus enteritis.[18] They did not find SLE Disease Activity Index (SLEDAI) or other laboratory parameters including complement, ESR, CRP, lupus related antibodies or antiphospholipid antibodies to correlate with risk of lupus enteritis.[18] Comparable results were obtained by Kwok and colleagues in their retrospective review of 87 SLE patients with abdominal pain including lupus enteritis (n = 41) found SLEDAI and anti-endothelial cell antibody to be significantly higher in patients with LE.[19] They did not find a significant correlation with other laboratory parameters except pre-existing antiphospholipid syndrome which increased risk of recurrent LE.

With such discrepant findings computed tomography (CT), the imaging modality of choice has become increasingly helpful. The classic finding of target and comb signs are frequently seen as described by Byun and colleagues in their retrospective review of 39 abdominal CT imaging of SLE

patients.[20] Target sign occurs as a result of bowel edema while comb sign results from engorgement of small bowel vessels.[4] Unfortunately, these image findings are not exclusive to lupus enteritis as the target sign can be seen in mesenteric vein thrombosis, inflammatory bowel disease (IBD) and bowel ischemia. Our patient had no thrombus on CT angiography of abdomen, bowel ischemia was highly unlikely in the absence of hematochezia and IBD was not entertained given acute nature of diarrhea. Other commonly encountered imaging patterns include ascites and mesenteric fat stranding.[1] Pathology in lupus enteritis is of low yield and frequently not diagnostic, therefore endoscopy is not a requirement for diagnosis and mostly reserved for cases where the diagnosis remains uncertain.[15] Janssens et al. in their systematic review of 150 cases of lupus enteritis revealed endoscopy was only carried out in 34 cases with macroscopic findings of bowel edema, hyperemia, and ischemia with or without ulceration or necrosis. Microscopic findings from endoscopically or surgically obtained tissue revealed cellular infiltration of submucosa and muscular layers, hemorrhage with occasional vasculitis.[15] We did consider enteroscopy for our patient but deferred, as endoscopy was unlikely to change management. Alternative diagnoses were considered unlikely, and the patient was exhibiting both clinical and radiological improvement with time and steroids (see Figs. 1–5).

The treatment of choice for lupus enteritis is immunosuppression with steroids. The optimum dose, route of administration, and duration of steroids vary based on the severity of presentation. When diagnosed early, lupus enteritis responds well to immunosuppression with symptoms resolving rapidly upon steroid initiation, but some may show a poor response in which case additional immunosuppressive agents such as mycophenolate and cyclophosphamide have been utilized with benefit.[1] Early diagnosis saves patients the burden of invasive workup. Late diagnosis has the potential to be catastrophic with estimated mortality rates of 11% in SLE-related acute abdominal pain6. Untreated lupus enteritis can progress to bowel ischemia, infarction, bleeding, and even perforation.[20]

Prognosis is good when the diagnosis is made early and high dose steroids are started in a timely manner but occasionally patients may have a recurrence. A recurrence rate of 28% was reported by Koo and colleagues with higher recurrence seen with colon or urinary tract involvement defined by contrast enhancement and wall thickening on CT imaging.[13]

4. Conclusion

Lupus enteritis should be considered among the top differentials when SLE patients present with non-specific abdominal complaints. A high index of suspicion is required as there are no pathonognomic clinical features, laboratory markers, or imaging findings and endoscopy is frequently non-diagnostic.

Acknowledgment

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no potential conflict of interest to declare.

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