Gastrointestinal Vasculitis in Systemic Lupus Erythematosus: A Successful Treatment with Belimumab

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Abstract

Introduction: Gastrointestinal (GI) vasculitis among systemic lupus erythematosus (SLE) patients is a rare manifestation confounded with non-specific clinical symptoms and laboratory parameters which delay diagnosis leading to increase morbidity and mortality. This is a case report of a patient with of GI vasculitis who was successfully treated with belimumab

Case presentation: We describe a case of a Chinese descent, 24-year-old female who was diagnosed with SLE presenting as malar rash, arthritis, intermittent fever, positive antinuclear antibody (ANA), high titer anti double-stranded DNA and low serum complement. She had gastrointestinal manifestations of colicky abdominal pain, vomiting and diarrhea, with computed tomography scan findings of diffuse mucosal edema involving both small and large intestines, with "target" sign strongly suggestive of GI vasculitis. She initially showed good response to methylprednisolone pulse therapy, but with recurrence of abdominal pain after three months. Repeat abdominal CT showed perforated viscus at the ileal segment with pneumoperitoneum, requiring emergency exploratory laparotomy and colostomy placement. Subsequent clinical course was marked by intolerance to oral steroid requiring regular administration of high dose intravenous steroids. Belimumab was started months after surgery and maintained for two years now. She was successfully shifted to oral prednisone, tapered to lowest dose and underwent uneventful intestinal reanastomosis with closure of colostomy.

Discussion: Gastrointestinal (GI) vasculitis is one of the most serious gastrointestinal complications SLE presenting as acute abdominal pain. Our patient was diagnosed based on abdominal CT scan which led to an accurate diagnosis and prompt treatment. Supportive measures, surgery, and belimumab impacted the outcome of this patient.

Conclusion: Gastrointestinal (GI) vasculitis in SLE has a good outcome with early diagnosis and intervention. Our patient responded well with surgery, steroid and belimumab, a fully human recombinant immunoglobulin G (IgG) 1λ monoclonal antibody. This case report showed that belimumab is a good alternative treatment for lupus GI vasculitis.

Keywords: gastrointestinal vasculitis, systemic lupus erythematosus, sle, lupus

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune inflammatory disease with protean clinical manifestations. Virtually every system and organ can be affected by SLE.[1] The gastrointestinal tract is one of the most commonly affected systems in SLE and common manifestations are anorexia, nausea, and vomiting which are seen in around 50% of these patients.[2] Among the gastrointestinal (GI) manifestations in SLE, lupus GI vasculitis is a rare presentation (0.2%–9.7%) but it is more common in SLE patients with abdominal pain (29%–65%).[3] CT scan findings are helpful in diagnosing GI vasculitis and in facilitating early medical treatment. If symptoms do not improve after medical treatment, or if necrosis and perforation of the intestines are highly suspected, surgical intervention should be considered.[4] Belimumab, a fully human monoclonal antibody directed against B lymphocyte activating factor (BLys) has been used with success on SLE patients who are serologically active. We discuss here a case of GI vasculitis in SLE who successfully improved with the novel use of belimumab.

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Case Presentation

A 24-year-old female was admitted due to a two-week history of colicky abdominal pain, vomiting, and watery diarrhea. Physical examination revealed hyperactive bowel sounds, flabby, distended, with epigastric and left upper quadrant tenderness. She was also noticed to have erythematous, non-pruritic, papules and patches on zygomatic areas overlying the bridge of her nose, cervical

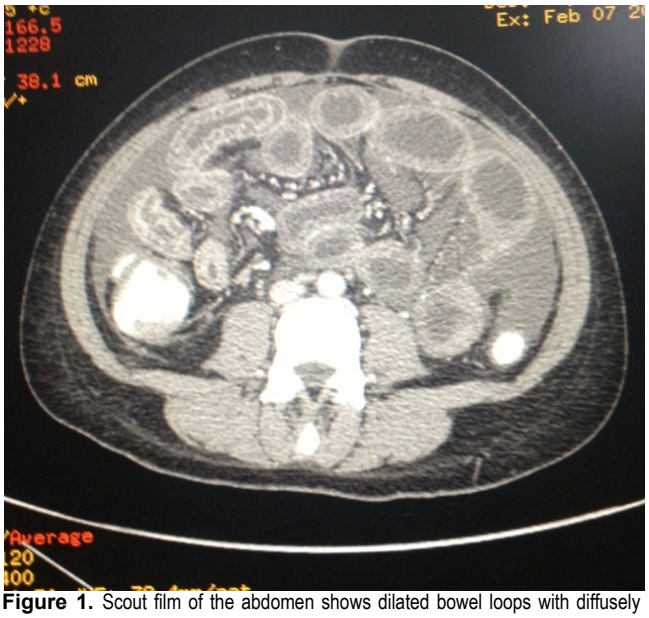

Figure 1. Scout film of the abdomen shows dilated bowel loops with diffusely thickened small intestinal wall

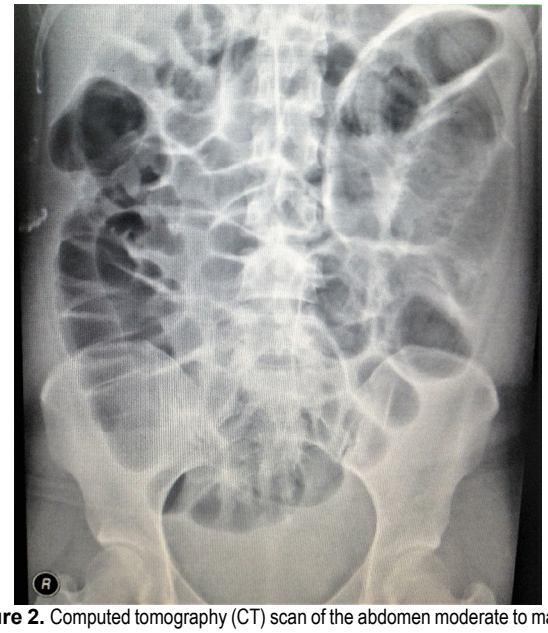

Figure 2. Computed tomography (CT) scan of the abdomen moderate to massive ascites

lymphadenopathy, mottling on lower extremities and arthritis of hand joints. Retrospective history revealed a two-week history of intermittent fever and joint pains. She was treated with metronidazole for presumed infectious colitis.

Her laboratory work-ups showed the following: anemia with hemoglobin 11.7 mg/dL; leucopenia 3,600/cu' mm and bilateral pleural effusion on chest X-ray. Further tests were done due to worsening abdominal pain, non-bilous vomiting and increasing abdominal girth. Abdominal supine radiograph (Figure 1) and abdominal CT scan revealed moderate to massive ascites and a diffusely thickened small intestinal wall (Figure 2).

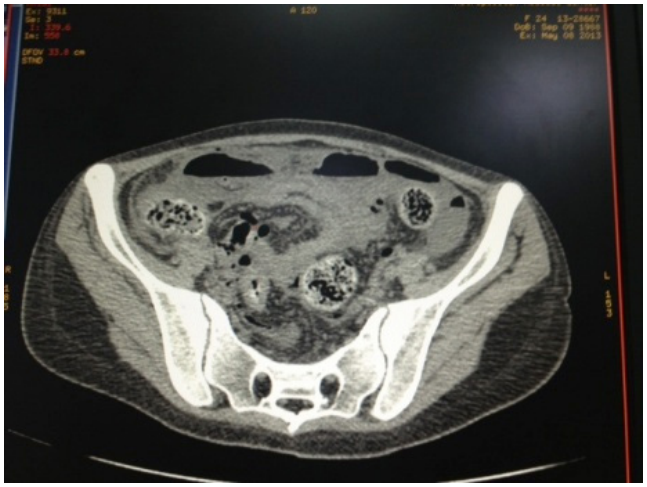

Figure 3. CT scan of the whole abdomen

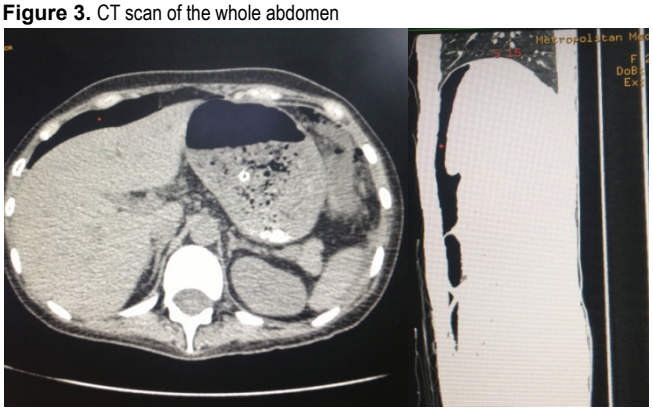

Figure 4a and 4b. Perforated viscus at the ileal segment of the small bowel with surrounding inflammatory reactions, ascites and pneumoperitoneum

A consideration of connective tissue disease prompted a request for the following: antinuclear antibody (ANA) titer which was positive at 1:320 (homogenous), tests for antibodies to double-stranded DNA was positive at 1:20, C3 was down at 0.32 (NV 0.8-1.9) and anti-Ro was positive. Urinalysis showed protein +2, random urine protein 263.5 mg/dL (NV 0-119), urine creatinine 223.40 mg/dL (NV 30-125). She underwent pulse therapy with methylprednisolone one gram for three consecutive days after which hydrocortisone 100 mg IV was initiated and eventually tapered to oral prednisone 60mg/day and hydroxychloroquine 200mg/tab twice a day. She was discharged improved with regular follow-ups.

Two months after hospitalization, she was readmitted due to severe generalized abdominal pain associated with hypotension and tachycardia. Abdominal examination was significant for multiple petechial, maculopapular rashes, absent bowel sounds, rigid and distended abdomen with generalized direct and rebound tenderness on palpation. Pneumoperitoneum and distention of small bowel loops were seen on scout film of the abdomen. CT scan of the whole abdomen also showed perforated viscus (Figure 3) at the ileal segment of the small bowel with surrounding inflammatory reactions, ascites, and pneumoperitoneum (Figure 4). The

patient underwent emergency exploratory laparotomy, segmental resection of terminal ileum and closure of distal ileal stump with colostomy placement on the right. During surgery there was voluminous intraperitoneal intestinal fluid and a 150cm gangrene on the ileal segment with multiple perforations.

She was given IV hydrocortisone 300mg/day and after resuming regular diet an attempt to wean hydrocortisone to oral prednisone 60mg/day resulted in adrenal insufficiency. She was discharged improved after two months with hydrocortisone 300mg/day.

A month after discharge from the second admission, she was apprised for cyclophosphamide infusion for the treatment of her GI vasculitis but due to concerns of possible adverse effects of the drug on reproductive health, she was instead given belimumab (Benlysta®), a fully human monoclonal antibody directed against B lymphocyte stimulators. It was given at a recommended dose of 10mg/kg and infusions of the same dose were given at days 0, 14, 28 and then at four-week interval thereafter. The patient has been having belimumab infusions for two years now and slow tapering of IV steroids to oral prednisone 5mg/day was achieved. The patient is also maintained on hydroxychloroquine (Plaquenil®) 200mg a day, dabigatran (Pradaxa®) 75mg once a day, calcium and vitamin D one tablet twice daily.

Last June 2015, re-anastomosis of intestines and closure of colostomy were done successfully and she was able to defecate normally thereafter.

Discussion

It is a challenge for clinicians to immediately determine the cause of GI symptoms in lupus patients because more than half of them are caused by adverse reactions to medications and viral or bacterial infections.[5, 6] GI vasculitis in lupus has been described in many terms such as lupus mesenteric vasculitis (LMV), mesenteric arteritis, lupus enteritis, lupus arteritis, lupus vasculitis, intra-abdominal vasculitis and acute gastrointestinal syndrome.[1] GI vasculitis is one of the most serious gastrointestinal complications SLE presenting as acute abdominal pain.[7] The symptoms of GI vasculitis vary from mild, nonspecific abdominal pain, bloating or loose stool, to necrosis and intestinal perforation which manifest as severe extensive gastrointestinal bleeding or acute surgical abdomen. Other manifestations of include anorexia, nausea, vomiting, dysphagia, hematemesis, postprandial fullness, diarrhea, and melena.[1]

In determining lupus GI vasculitis three cardinal imaging signs on abdominal CT can be seen: (1) bowel wall thickening of greater than 3 mm (target sign) and dilatation of intestinal segments, (2) engorgement of mesenteric vessels ("comb sign"), and (3) increased attenuation of mesenteric fat.[8] In our patient, imaging was the key in leading to the correct diagnosis of GI vasculitis and the final diagnosis was made by fulfilling all three imaging signs.

Initial treatment for GI vasculitis is high-dose intravenous methylprednisolone and complete bowel rest. Even in patients who show a good initial response to treatment, relapse is common.[9] As in the case of our patient GI vasculitis recurred and this time resulted to perforation and gangrene of the ileum. Emergency exploratory laparotomy resulted to improved outcome and survival as supported in the study of Medina et al.[10] Recurrent GI vasculitis mostly involve the jejunum and the ileum. The rectum is rarely involved, because of collateral circulation.[4]

It is also essential to note that in this case the shifting of hydrocortisone to oral steroid resulted to adrenal insufficiency probably due to physiological changes that affected the absorption of oral steroid reducing its effect after the terminal ileal resection.

Finally this case is considered important because of the new treatment given to control the patient's GI vasculitis. Although successful outcomes were noted using cyclophosphamide in GI vasculitis, this patient considered belimumab due to concerns of possible adverse effects of the drug on reproductive health. Belimumab is a fully human recombinant immunoglobulin G (IgG) 1λ monoclonal antibody to soluble B-lymphocyte stimulator (BLys) also known as B-cell activating factor (BAFF).[11] This drug has specificity and affinity for BLys which is a key survival cytokine for B lymphocytes[12] which is overexpressed in patients with systemic lupus erythematosus and other autoimmune diseases.[13] It was developed with the goal of inhibiting the binding of soluble circulating BLyS to its three target receptors: BLyS receptor 3 (BR3; also known as BAFF-R), transmembrane activator–1 and calcium modulator and cyclophilin ligand–interactor (TACI), and B cell maturation antigen (BCMA).[14] Belimumab was approved in March 2011 for the treatment of SLE, thus becoming the first FDA-approved medication for SLE in the past 50 years. This patient was serologically active thus the good response to belimumab as was proven in clinical trials wherein serologically positive patients responded to this treatment better than serologically negative patients.[13] Normalization of C3 and anti-ds DNA in this patient was achieved six months after Belimumab infusion and up to present time.

Conclusion

Gastrointestinal vasculitis in SLE is a life-threatening condition where early diagnosis and prompt treatment is critical to improving the overall outcome. The use of

belimumab in this patient resulted in reductions in disease activity without an observed increased risk of infection or major adverse events. Continued clinical studies in belimumab or into BLyS-targeted SLE therapy will one day aid in defining its role in managing the heterogeneity of SLE. As far as we know this is the first reported case of the use of belimumab for GI vasculitis in SLE.

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Conflict of interest: The authors have nothing to disclose

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