Generalized megaviscera of lupus: Refractory intestinal pseudo-obstruction, ureterohydronephrosis and megacholedochus

Frederick D Park, Jeffrey K Lee, Ganga D Madduri, Pradipta Ghosh

Frederick D Park, Jeffrey K Lee, Ganga D Madduri, Department of Medicine, University of California San Diego, San Diego, California 92103, United States

Pradipta Ghosh, Division of Gastroenterology and Hepatology, University of California San Diego, San Diego, California 92103, United States

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Correspondence to: Pradipta Ghosh, MD, Department of Internal Medicine, Division of Gastroenterology, University of California, San Diego School of Medicine, George Palade Laboratories for Cellular and Molecular Medicine, 9500 Gilman Drive, La Jolla, California 92093-0651, United States. prghosh@ucsd.edu

Telephone: +1-858-8227633 Fax: +1-858-8227636

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have termed this rare clinical syndrome generalized megaviscera of lupus (GML). Although the SLE disease-activity parameters responded to aggressive immunomodulative therapy in our patient, clinical evidence of peristaltic dysfunction persisted in all involved viscera. This is a variation from the favorable outcomes reported previously in SLE patients with GML and we attribute this poor clinical outcome to disease severity and, most importantly, delayed clinical presentation. Since inflammation followed by atrophy and fibrosis are key aspects in the pathogenesis and natural history of GML, the poor response in our patient who presented late in the clinical course may be the result of 'burnt out' inflammation with irreversible end-stage fibrosis. Thus, early recognition and timely initiation of treatment may be the key to recover visceral peristaltic function in patients with GML.

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Abstract

Dilated dysfunction involving multiple visceral organs has been reported in patients with systemic lupus erythematosus (SLE). Chronic intestinal pseudo-obstruction (CIPO) resulting from intestinal smooth muscle damage has presented in conjunction with ureterohydronephrosis and, more rarely, biliary dilatation (megacholedochus). While the molecular pathogenesis is largely unknown, observed histopathologic features include widespread myositis, myocyte necrosis in the intestinal muscularis propria with subsequent atrophy and fibrosis, preserved myenteric innervations and little vasculitis. High dose immunosuppression usually results in resolution of symptoms with recovery of smooth muscle function, indicative of an autoimmune etiology. We report a patient with SLE who presented with intestinal pseudo-obstruction, ureterohydronephrosis and megacholedochus, and present images that illustrate megaviscera simultaneously involving all 3 visceral organs. Since the co-manifestation of all 3 is unusual and has been reported only once previously, we

INTRODUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a rare but important clinical syndrome as it causes 20% of chronic intestinal failure in adults and 15% in children^[1]. It is characterized by ineffective intestinal propulsion with signs and symptoms similar to

mechanical bowel obstruction including abdominal distension, pain, nausea, vomiting, obstipation and sluggish bowel sounds, but the absence of an occluding lesion of the intestinal lumen. CIPO is idiopathic in the vast majority of cases, but secondary causes can include virtually any disease process that affects structures involved in intestinal motility, including intestinal myocytes and the extrinsic and intrinsic neural networks. The management of CIPO has been challenging, and long-term outcomes often disappointing^[1]. In contrast, CIPO in systemic lupus erythematosus (SLE) patients has shown an excellent response to immunosuppressive therapy when initiated early, consistent with an autoimmune etiology^[2-5]. While the pathophysiology of CIPO in SLE remains unclear, the frequent concurrence of ureterohydronephrosis (67% in one case series)^[3,4,6] and histopathologic evidence of intestinal leiomyocyte damage^[3-5] suggest a systemic autoimmune process targeting smooth muscle cells. Here we describe a patient with SLE who presented with refractory intestinal pseudo-obstruction, ureterohydronephrosis and megacholedochus in the setting of delayed immunosuppressive therapy. This triad of gastrointestinal, genitourinary, and hepatobiliary hollow viscera dilatation and dysmotility has been described to co-manifest in lupus only once previously^[6]. We term this rare and likely under-recognized clinical syndrome Generalized Megaviscera of Lupus (GML). An understanding of the pathophysiology of these processes is needed to avoid poor outcomes resulting from either unnecessary procedures and interventions or a delay in the diagnosis and/or initiation of treatment. We review the literature and discuss the pathophysiology.

CASE REPORT

A 46-year-old Japanese-American female presented to our hospital with a 4-mo history of worsening arthralgias, abdominal discomfort, distension and obstipation. Her past medical history was notable for SLE diagnosed in 1993, which was complicated by disseminated encephalomyelitis, malabsorption syndrome, and biopsy-confirmed membranous glomerulonephritis. In the past, she has been treated with steroids and immunomodulators; however, because of adverse reactions to several of these medications, frequent changes were made to her treatment regimen. This resulted in poor compliance and resultant breakthrough episodes of disease exacerbations affecting various organ systems. Most recently, she was being treated with mycophenolate mofetil (CellCept®) and oral prednisone which she self-discontinued 8 mo prior to admission.

Physical examination revealed a distended tender abdomen with hypoactive bowel sounds. Laboratory tests were notable for elevated acute phase reactants, proteinuria, and acute renal insufficiency. An abdominal plain film X-ray series (Figure 1A-C) showed multiple air-fluid levels and distended loops of the large (up to

8 cm in diameter) and small (up to 3 cm in diameter) bowel without any obvious structural basis for luminal obstruction. Computed tomography (CT) of the abdomen (Figure 1D and E) confirmed the plain film findings but also showed ascites and fecalization of the luminal contents within the small bowel. Unlike lupus enteritis, the bowel wall in this case was neither thickened nor edematous^[1]. Her symptoms and radiographic findings were consistent with an intestinal pseudo-obstruction. Supportive therapy was initiated with placement of a nasogastric tube in low intermittent suction, intravenous (IV) fluid, and pain medications. The patient was started on a course of tegaserod maleate (Zelnorm®) for 2 wk and 2 doses of neostigmine, with little improvement. In addition, she was also treated with enemas (glycerol, magnesium sucrate and water) and promotility agents (metoclopramide and erythromycin). A decompressive colonoscopy was attempted but the procedure was aborted at the level of the transverse colon because of poor visibility as a result of hard fecal matter and an increased risk of perforation. A gastrografin enema was performed after the colonoscopic procedure, which demonstrated aperistaltic distal colon and contrast filling within a narrow lumen surrounded by stool that was cleared during the attempted colonoscopy (Figure 1C).

The abdominal CT scan also revealed intra- and extra-hepatic biliary tree dilatation (Figure 1E). To investigate this further, magnetic resonance cholangiopancreatography (MRCP) was performed and confirmed the presence of dilated bile ducts, without any structural basis for luminal obstruction (Figure 2). The common bile duct was dilated up to 2 cm without filling defects, calculi, or masses. The patient had no jaundice or right upper quadrant pain and her liver function tests remained within the normal limits throughout her hospital stay.

Regarding her acute renal insufficiency, she was started on IV fluid but her renal function did not improve despite adequate hydration. CT and MR images revealed bilateral hydronephrosis and hydroureters (Figure 1D, Figure 3B and C) without any structural obstruction. Obstructive uropathy resulting from lupus cystitis was entertained as a diagnosis and emergency placement of bilateral double-J ureteral stents was carried out in an attempt to decompress the genitourinary system. Despite optimal positioning of the stents, there was no improvement in the ureterohydronephrosis or her renal function. A voiding nephro-uretero-cystogram confirmed the persistence of dilated aperistaltic ureters bilaterally (Figure 3A and B). Treatment with cyclophosphamide (Cytoxan®) for presumed lupus cystitis also failed to produce any improvement. She continued to have modest urine output but nonetheless eventually required hemodialysis.

Full thickness biopsies from the genitourinary or gastrointestinal viscera were not performed in view of her poor clinical condition. She was treated with conventional immunomodulating therapies consisting of high dose IV methylprednisolone (Solu-Medrol®) and

Figure 1 Megabowel: X-ray radiography (A-C) and computerized tomography scan (D, E) of the abdomen revealed the presence of distended loops (stars) of the small and large bowel (megabowel) in the absence of any luminal obstruction.

Figure 2 Megacholedochus: magnetic resonance cholangiopancreatography revealed the presence of a distended common bile duct (megacholedochus, arrowheads) without any evidence of luminal obstruction.

mycophenolic acid (Myfortic®) along with parenteral nutrition, promotility agents, antibiotics, aggressive correction of electrolytes, and hemodialysis for presumed lupus flare with multiple organ involvement. She was discharged after improvement of her ascites, arthralgias, proteinuria and serum acute phase reactants. At 6 mo follow-up there was persistent dysfunction in all 3 organ systems without recovery of peristaltic function; however at no point during the clinical course was there any evidence of encephalopathy, cardiomyopathy, or any involvement of skeletal muscles either clinically or biochemically.

DISCUSSION

We have described a patient with SLE who presented with abdominal distension, obstipation and renal

insufficiency with various imaging modalities revealing diffusely dilated hollow viscera in the absence of structural obstruction involving the genitourinary, hepatobiliary and gastrointestinal systems. Since these signs and symptoms are non-specific, it is important that all other possible diagnoses are entertained. The presentation as hydronephrosis in isolation deserves expert consultation and exclusion of other common causes e.g., lupus cystitis. Similarly, biliary tract dilation could occur as a result of coexisting liver diseases or as a direct consequence of an autoimmune phenomenon such as vasculitis. Hepatic artery vasculitis is known to give rise to a similar radiographic appearance but is usually accompanied by symptoms, resulting in abnormalities in liver function, and responds to systemic immunomodulation. Associated hepatobiliary diseases, e.g., autoimmune hepatitis, nodular regenerative hyperplasia, cryptococcal infection, should be considered in the differential diagnosis when isolated involvement of the biliary tract is seen. Involvement of multiple hollow visceral organs should raise suspicion of a generalized autoimmune smooth muscle injury, as in our case. Intestinal pseudo-obstruction is a very rare complication in SLE patients, but hydronephrosis are a frequent concurrent finding in these patients. The case presented here is among the first to show an additional visceral organ dilatation - megacholedochus. These findings suggest a truly rare, but likely under-recognized clinical syndrome we term generalized megaviscera of lupus (GML), which we define as hollow visceral dilatation and dysfunction present concurrently in more than one organ system in a patient with SLE, with intestinal pseudo-obstruction the most common manifestation.

Figure 3 Hydronephrosis and megaureters: the presence of distended ureters (megaureters, arrowheads) was appreciated during a voiding nephro-uretero-cystogram (A, B) whereas hydronephrosis (stars) was detected by magnetic resonance imaging of the abdomen (C) as well as during the nephrogram (B).

We reviewed the anecdotal reports of patients with apparent GML in an attempt to further our understanding of the pathophysiology of this phenomenon. An overview of the pathological analysis of the gastrointestinal tract in lupus patients with CIPO revealed the following characteristics: widespread myocyte necrosis in the muscularis propria with active inflammatory cell infiltrate^[5], severe atrophy and fibrosis of the muscularis^[3,5], active serositis with serosal thickening and fibrosis^[5], little or no evidence of vasculitis or injury to bowel innervation^[3,5], and absence of thromboembolic disease^[4,5]. It is notable that intestinal myonecrosis is observed without significant lupus vasculitis, often involving smooth muscle dysfunction in another organ system. These findings argue for the existence of a systemic circulating factor causing smooth muscle injury by a mechanism other than vasculitis (although the histopathologic basis for concomitant hydronephrosis and megacholedochus are yet to be determined). A good clinical response to immunosuppressive treatment has led some to hypothesize that the intestinal myopathy may be a direct result of an autoimmune phenomenon in the bowel wall^[5], and a common autoantibody against smooth muscle cells has been proposed^[4]. It has been shown that autoantibodies against proliferating cell nuclear antigen (PCNA) have been detected exclusively in SLE patients and 2 cases were presented in which patients with this antibody in systemic sclerosis developed CIPO^[7]; whether PCNA autoantibodies play a role in GML, however, remains unclear. Dense T-lymphocytic infiltrates with degeneration limited to the muscularis propria is considered the histopathologic hallmark of autoimmune enteric myositis causing CIPO in young children without lupus^[8-10]. The location of intestinal myocyte damage is similar in SLE-associated CIPO, but dense T-cell infiltrates have not been observed; thus it is unclear whether the same disease process is involved. Autoimmune enteric neuropathy has been considered in the etiology of SLE-associated CIPO, but neuronal structures have generally been preserved on histopathology^[3,5], making this less likely. It has also been suggested that serositis can cause paralytic ileus,

and this may be a secondary cause of intestinal pseudo-obstruction in SLE^[4]. Further studies will be needed to elucidate the pathogenic mechanism behind the development of GML.

In prior anecdotal reports, medical management that effectively led to improvement of GML, including remission of intestinal pseudo-obstruction and urinary symptoms, included a combination of high dose corticosteroids, immunomodulators and supportive care (parenteral nutrition, oral antibiotics, and pharmacological stimulation of small bowel motility)^[2-5]. We had expected improvement and remission with similar management of our patient. Unfortunately, although there was improvement in the clinical and biochemical indicators of lupus exacerbation, e.g., ascites, arthralgias, proteinuria and serum acute phase reactants, she continued to show signs and symptoms of biliary dilatation, worsening of renal function, persistence of bowel distension and required parenteral nutrition and hemodialysis. This was concerning because of persistent generalized smooth muscle dysfunction causing aperistaltic megaviscera. While the clinical course is the best way to monitor treatment response, histopathologic reversal with immunosuppressive therapy has been documented for myositis-related intestinal pseudo-obstruction^[11]. A delay in initiation of therapy has been associated with failure to regain functional peristalsis and was correlated with histopathologic progression to fibrosis and atrophy of the intestinal wall, and secondary impairment of the myenteric plexuses^[12]. Progression to atrophy and fibrosis of the muscularis propria was also observed in a case of suspected non-compliance with immunosuppressive therapy in an SLE patient with CIPO^[5]. Similarly, we presume that in the setting of delayed intervention and medication non-compliance, our patient developed advanced irreparable tissue destruction including myonecrosis, fibrosis and atrophy, resulting in failure of peristalsis to return despite treatment with high dose pulse steroids during her inpatient stay.

Our report emphasizes that timely diagnosis and intervention is crucial in the management of GML for the return of peristaltic activity in the various visceral organs involved. Appropriate imaging of the

gastrointestinal, genitourinary and hepatobiliary tracts should be obtained early in the investigation. It is also vital to recognize intestinal pseudo-obstruction as the cause of the symptoms and signs in order to avoid unnecessary and invasive interventions, which may confer extra risks and lead to further damage. Neostigmine was administered twice to our patient, and caused increased crampy abdominal pain and discomfort but failed to improve gut motility. Given that neostigmine acts at the myoneural junction upstream of the damaged myocyte, it is unlikely to help in this setting. Moreover, ureteral stenting has been utilized in lupus cystitis but is largely without benefit in the setting of aperistaltic ureters; this procedure caused multiple complications in our patient including ascending urinary tract infections and hematuria. The Gastroenterology service was consulted repeatedly to perform endoscopic retrograde cholangio-pancreatography (ERCP) for evaluation of her dilated biliary ducts. Biliary tree dilatation is without consequence, especially with normal liver function tests and reflects aperistalsis within the bile duct system. However, knowledge of this is essential to avoid unnecessary invasive procedures such as ERCP and/or biliary stenting. In our patient, a more conservative imaging modality, MRCP, was equally useful to rule out structural obstruction and avoided ERCP related risks. Overall, it seems that early recognition of generalized visceral organ dilatation in lupus patients, consistent with the syndrome GML, is helpful for gastroenterologists, urologists, and rheumatologists to initiate supportive care and early immunomodulation to restore peristaltic function as well as to avoid invasive procedures which may not address the basic pathophysiologic process involved.

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