

Case Report

Protein-losing enteropathy and IgA nephropathy in a man with systemic lupus erythematosus: a case report

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Abstract: Protein losing enteropathy (PLE) is a rare gastrointestinal manifestation of systemic lupus erythematosus (SLE). The causes of non-lupus nephropathies associated with SLE were rarely described. Here we presented a case of oedema with ascites from severe hypoalbuminaemia secondary to lupus-associated PLE. Renal biopsy revealed IgA deposits in isolated mesangium, consistent with the pathological feature of primary IgA nephropathy (IgAN). Moreover, a full clinical remission was achieved with a course of intravenous cyclophosphamide therapy.

Keywords: Systemic lupus erythematosus (SLE), protein-losing enteropathy (PLE), IgA nephropathy (IgAN), CA125

Introduction

Protein-losing enteropathy (PLE) is generally diagnosed in patients with hypoproteinaemia after other causes, such as malnutrition, proteinuria and impaired protein synthesis due to cirrhosis are excluded. It is a rare condition characterized by a loss of serum protein into the gastrointestinal tract resulting in hypoproteinaemia, which manifests as oedema, ascites, malnutrition, and pleural and pericardial effusions. Primary IgA nephropathy (IgAN), the most frequent primary glomerulopathy in the world population, was rarely described in association with systemic lupus erythematosus (SLE). In the present study, we reported a case of SLE-associated PLE and IgAN with severe hypoalbuminaemia secondary to lupus in a man.

Case report

A 46-year-old Chinese male was admitted in March 2017 with a three-month history of progressive anasarca. Three months ago, the patient received a diagnosis of IgAN based on the pathology report of mesangial hypercellularity with isolated IgA deposits in his renal biopsy sample. The patient did not respond to a month of corticosteroid therapy. Two months before the present admission, he defaulted corticosteroid treatment because of gastric

ulcer, and received angiotensin receptor blockers (ARB) instead. In his visit to the clinic of another institution on February 2017, he complained gradual abdominal distension, generalized swelling, and a 7.0-kg weight gain. There was no arthralgia, oral ulcer, butterfly malar rash or alopecia. Laboratory investigations revealed a normal full blood count and creatinine level, and the urinary protein was 0.6 g/24 h. He was found hypoalbuminaemic with serum albumin of 12 g/L (normal range 35-50 g/L). His serology profile demonstrated positive for antinuclear antibody (ANA) and hypocomplementemia. The CA125 level was markedly raised to 2929 IU/mL (normal range 0-30 IU/mL). Ascetic fluid assessment showed a low fluid protein, suggesting a transudate. Cytology tests found suspected low-differentiated adenocarcinoma cells on two separate occasions. The abdominal CT scan with contrast and PET-CT scan demonstrated no tumor but polyserositis. Electronic gastroscopy showed healing ulcers. According to the American College of Rheumatology's revised criteria in 1997, the patient did not meet the diagnosis of SLE because only positive ANA, polyserositis, and a biopsy-proven IgAN were detected. Since Malignant tumor cannot be ruled out, the patient received low dose prednisone treatment and was admitted into our hospital in March 2017.

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On admission, he complained of serious abdominal distension and intermittent diarrhea for three years. His anti-ds-DNA level was within the normal range, and anti-U1RNP and anti-Smith antigen were positive. A test for ANA was positive at a dilution of 1:1000, with a speckled pattern. Complements (C3 and C4) were low at 0.62 g/L (normal range 0.8-1.6 g/L) and 0.07 g/L (normal range 0.16-0.38 g/L), respectively. Cytomegalovirus, hepatitis B and C were negative in serological tests. The CA125 levels were markedly raised at 3575 IU/mL (normal range 0-30 IU/mL). A serum albumin was 12.45 g/L (normal range 35-50 g/L). Values for 24-hour urine-protein excretion were within 0.5 g. Given the concern of a malignant tumor, the patient underwent a Laparoscopic exploration, in which a normal enterocoelia without any intra-abdominal tumor deposits nor evidence of infection were shown.

During the admission in April 2017, his diagnosis was changed to probable systemic lupus erythematosus (SLE) based on the presence of polyserositis, hypocomplementaemia, high titre ANA and positive anti-Smith antigen, according to the SLICC Revision of the ACR Classification Criteria in 2009. A diagnosis of lupus associated protein-losing enteropathy (LUPLE) was made after other causes of hypoalbuminaemia, such as malnutrition, proteinuria and impaired protein synthesis due to cirrhosis were ruled out. A Technetium 99m-labelled (99mTc) human serum albumin (HSA) scintigraphy or faecal alpha-1-antitrypsin clearance (FAAC) test, which would have confirmed the diagnosis, was not available at our hospital. The patient received a seven-day course of intravenous methylprednisolone (80 mg daily), followed by a course of intravenous cyclophosphamide weekly at 1 g per week for two weeks and 50 mg of oral prednisolone daily at approximately 1 mg/kg per day. The planned second dose of cyclophosphamide was completed in May 2017. He did well during the following 2 months but complained about painful knee arthritis on his last review in June 2017. His ascites were minimal, serum albumin was 41 g/L, ANA remained positive in low titer, and CA125 has been tapered to a low level.

Discussion

SLE, a multi-organ, autoimmune disease, mainly affects women. The peak age at onset ranges from 20-40 years. Males with SLE represent

4-22% of all SLE patients and are misdiagnosed easily for special clinical manifestation and serological results [1]. Studies have shown that serositis is a more prominent clinical manifestation and auto-antibody positive rate is lower in male compared with female SLE patients [1, 2]. It is known that the usage of the new SLICC classification criteria relative to the current ACR classification criteria resulted in fewer misclassifications (49 versus 70) and led to greater sensitivity (94% versus 86%) [3]. We have performed well in the case, i.e. the male SLE patient with ascites, positive ANA and hypocomplementemia, using the new classification criteria.

PLE was manifested as a severe hypoalbuminemia due to plasma protein leaking into gastrointestinal tract. Causes of PLE include erosive gastrointestinal lesions (sarcoidosis, ulcerative colitis, pseudo membranous enteritis, gastrointestinal lymphoma, peptic ulcer), non-erosive gastrointestinal lesions (celiac disease, microscopically colitis, rheumatic disease), and disorders involving increased central venous pressure or mesenteric lymphatic obstruction (intestinal lymphatic vessels dilated disease, congestive heart failure, portal hypertension, after intestinal lymphatic fistula and peritoneal sclerosis) [4].

SLE is a rare cause of PLE, the possible mechanism underlying which may be associated with intestinal mucosa or vascular injury and increased capillary permeability of intestinal mucosa mediated by cytokines or complement as well as intestinal lymphangiectasia because of extrusion of oedematous interstitial [5]. Some patients also have hypoglobulinemia because immunoglobulin can also leak into the intestinal lumen [6]. 99mTc-labelled HSA scan Radiolabelled albumin and faecal clearance of alpha 1-antitrypsin (a1-AT) are classical approaches that have been used for the diagnosis of protein malabsorption and intestinal losses [7, 8]. However, both approaches were not available in our hospital. The patient was diagnosed with SLE because of hypoalbuminemia. However, inadequate intake, proteinuria, liver dysfunction or thyroid dysfunction were not found in the patient. Therefore, PLE should be taken into account.

CA-125, recognized by murine monoclonal antibody OC125, has been proposed as a marker for carcinoma. However, CA-125 elevation

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was observed in many physiologic and pathologic conditions including pregnancy, during menses, and ascites [9, 10]. It can be detected immunohistochemically in the mesothelial cells of the peritoneum, pleura, and pericardium [9].

Serositis, a classification criterion for SLE, can be present in the form of peritonitis, pleuritis, and pericarditis with accompanying fluid accumulation, all of which may result in the elevation of CA-125. It was reported that CA125 was detected in 15% of SLE patients in a Hungarian cohort [11]. Furthermore, a study showed that serositis and disease duration of SLE were two clinical variables significantly associated with elevation of serum CA125 level [12].

Lupus nephritis (LN), the most common visceral manifestation of SLE, is characterized by cellular proliferative lesions, wire-loop lesions and deposits of immunocomplex (prevalently IgG) and complement fractions (C1q, C3, C4). These deposits are often localized in the basal membrane of glomerular capillary [13]. IgA nephropathy (IgAN), the most common cause of glomerulopathy in general population [14], was rarely coexisted with SLE but shares some common pathogenesis. There is strong evidence that activation of the complement system contributes to glomerular injury in IgAN [15, 16]. Complement component 3 (C3) is commonly observed in the same distribution as IgA in kidney biopsies. The presence of anti-C1q antibodies and antiendothelial cell antibodies in both LN and IgAN patients suggests that some similar pathogenic mechanisms exist [16, 17]. Furthermore, mucosal immune is participated in initiation of IgAN and LN [18, 19]. From systems genetics perspective, a study suggests many of the alleles that are risk alleles for SLE are protective alleles for IgAN [20]. The SLE patient in the current case, IgAN was detected in the renal biopsy with few proteinuria and normal renal function, indicating a very mild renal lesion. IgAN may be an expression of lupus patients with a tententially less aggressive renal involvement.

An abnormally increased level of circulating poorly O-galactosylated IgA1 and the subsequent IgA1-containing immune complexes in mesangial deposition lead to the development of IgAN, which is derived from mucous mem-

brane [18, 21]. In healthy adults, the mucosal immune system accounts for about 80% of the immune system, and the secreted IgA (sIgA) of intestinal mucosal played a primary role in humoral immunity [18, 22]. Various studies imply that dysregulated intestinal mucosal immunity caused by dietary components, intestinal microbiota, and intestinal diseases promote the production of sIgA. SIgA is then deposited in the glomerular mesangium, eventually leading the development of IgAN [23]. It is reasonable to postulate that the tonsillectomy, a simple way of removing part of pathogens of IgAN, should be able to reduce mucosal-associated immune system. However, results obtained from the previous studies are still inconclusive.

A study demonstrated circulating plasmablasts can be used as a marker for mucosal immune reactions in SLE. IgA is expressed by 48% of plasmablasts in SLE with varying co-expression patterns. Consistent with mucosal homing, some SLE plasmablasts migrated towards the mucosal chemokine CCL28 and secreted polymeric IgA, which indicate an overly activated mucosal immune system in patients with SLE [19].

The SLE patient in the current case suffered from protein-losing enteropathy. We would surmise that abnormal function of intestinal mucosa contributes to concomitant IgAN.

The new SLICC classification criteria may be more accurately correlate with male SLE, which normally lack of typical clinical manifestations. CA125, relative to a tumor marker, is more appropriately regarded as a proof of serositis in SLE patients. PLE is an uncommon gastrointestinal manifestation of SLE, with a so far unexplained hypoproteinemia. It may be not a hapenstance for the co-exist of IgAN and PLE in SLE because mucosal immunity acts a common pathogenesis.

Disclosure of conflict of interest

None.

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