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Nephrotic Syndrome and Protein-Losing Enteropathy in A Patient with Suspected Systemic Lupus Erythematosus — A Case Report

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Abstract

We report a 57-year-old female patient with suspected systemic lupus erythematosus presented with general anasarca, pleural effusions, hypercholesterolemia and severe hypoalbuminemia. First, nephrotic-range proteinuria was revealed and membranous glomerulonephritis was diagnosed and successfully treated. She developed diarrhea 2 years later with similar clinical presentations but this time no proteinuria was found. Primary protein-losing enteropthy, a rare complication of systemic lupus erythematosus, was diagnosed after other causes of gastrointestinal protein loss were excluded. Complete remission was achieved with steroid therapy. This case is unusual by the presentation of the same clinical pictures with different etiologies. Hypoalbuminemia and general anasarca need further investigation if renal protein loss was not found. (J Intern Med Taiwan 2005; 16: 139-145)

Key Words ：Systemic lupus erythematosus, Hypoalbuminemia, Hypercholesterolemia, Nephrotic syndrome, Protein-losing enteropthy

Introduction

Hypoalbuminemia can be attributed to conditions of (1) decreased synthesis such as poor protein intake or liver disease, or (2) excessive protein loss. Excessive protein loss generally occurs because of nephrotic syndrome or protein-losing enteropathies (PLE). There are numerous conditions associated with gastrointestinal loss of proteins, among which the most common are congestive heart failure, intestinal lymphangiectasia, lymphoma, specific small- and large-bowel enteropathies, abdominal tuberculo-

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sis and retroperitoneal tumors[1].

Gastrointestinal manifestations of systemic lupus erythematosus (SLE) are uncommon. Recently, it has been reported that SLE can be a cause of protein-losing enteropthy[2-4]. This association is rare with a total about 20 cases having been reported in the English literature. Here we report another case of PLE associated with SLE, besides, this case is unusual by the preceding similar clinical manifestation of hypoalbuminemia due to class V lupus nephritis.

Case Report

A 57-year-old woman was first admitted to Shin Kong Wu Ho-Su Memorial Hospital in January 1997 because of generalized edema, exertional dyspnea and malaise for 1 week. Three months prior to admission, the patient gradually experienced puffy eyelids, abdominal fullness and general weakness. She had no history of fever, arthralgia or skin rashes. On admission, moderate bilateral pretibial edema and puffy eyelids were noted and her blood pressure was 130/70 mmHg, pulse rate 90/min with regular rhythm, and temperature 36.6 ℃. Urinalysis showed 3+ protein with insignificant sediment. The 24-hour urine protein was 3870 mg. Hemoglobin was 12.1gm/dl, white blood cell count was 4500/mm^3 with normal classification, platelet count was 297000/mm^3 and bleeding time (Duke) was 1 minute. Blood urea nitrogen (BUN) was 9 mg/dl, serum creatinine (Cr) was 1.0 mg/dl, serum albumin 1.6 gm/dl, globulin 2.8 gm/dl, total cholesterol 267 mg/dl, triglyceride 281 mg/dl, AST 30 U/L and ALT 12 U/L. Creatinine clearance was 77 ml/min. The serum complements were within normal range and the tests for antinuclear antibody (ANA), anti-DNA antibody, anti-HCV antibody and HBs antigen were negative. A chest X-ray showed pulmonary infiltration and moderate right pleural effusion, but the heart was normal. Renal ultrasonagraphy showed normal renal size (right 10.6cm, left 12.2cm) with smooth surface and slightly hyperechoic cortex.

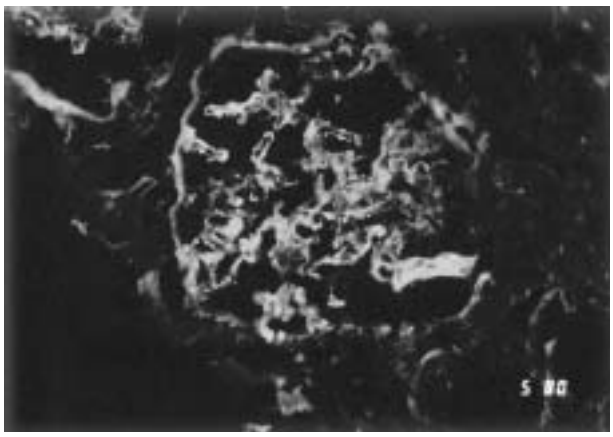

Fig. 1. Renal biopsy. Immunofluorescence microscopy revealed IgG deposits along the glomerular capillary walls, mainly subepithelial, and in the mesangium (x 250).

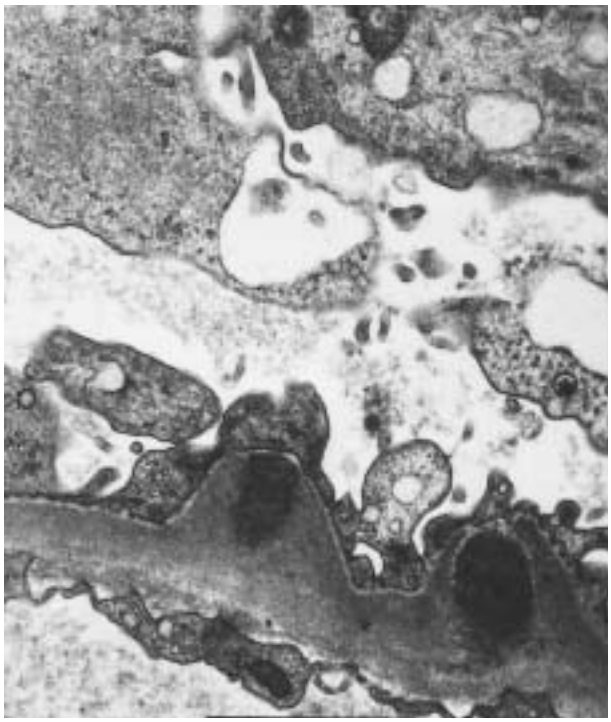

Fig. 2. Renal biopsy. Electron microscopy showed global effacement of foot process, scattered deposition of electron-dense materials in subepithelial regions (x 15000).

Renal biopsy was performed on the fifth day of admission. Light microscopy revealed membranous glomerulonephritis. Immunofluorescent examination revealed diffuse global granular IgG deposition in capillary wall and mesangium (Fig.1) and trace focal segmental granular deposition of IgM, IgA, C1q, C3, C4 in mesangium. Electron microscopy showed global effacement of foot process, scattered

deposition of electron-dense materials in subepithelial and mesangial regions (Fig. 2). Under the diagnosis of membranous glomerulonephritis, stage 1, with nephrotic syndrome, the patient was treated with albumin, furosemide and prednisolone 60mg per day. Her condition improved and discharged on the eighth day of admission.

After discharge, she was regularly followed in our out patient clinic. The edema waxed and waned. A test for ANA 6 months later showed 1: 640x, speckled type positive, but the C3 and C4 level was still within the normal range. Lupus nephritis, class V, was suspected, however, she was lost in the next 2 years. This patient visited us again in June 2000 with the complaints of diarrhea, abdominal fullness and legs edema. Hypoalbuminemia, hyperchlosterolemia were found, ANA showed 1:1280x but the symptoms were resistant to diuretics, so she was admitted again on August 2000.

During admission, her blood pressure was 130/60 mmHg, pulse rate was 82/min with regular rhythm, and temperature was 36.5 ℃. Hemoglobin was 12.2gm/dl; white blood cell count was 4800/mm^3 with normal classification; platelet count was 258000/ mm^3. BUN was 8 mg/dl, Cr was 0.9 mg/dl, serum albumin 1.0 gm/dl, globulin 2.4 gm/dl, total cholesterol 317 mg/dl, triglyceride 226 mg/dl, AST 16 U/L and ALT 8 U/L. However, urinalysis showed no proteinuria and 24-hour urine protein was 54 mg. Renal ultrasonagraphy showed normal renal size (right 9.8cm, left 11.3cm) with smooth surface and good cortex. The serum C3 was 64.1 mg/dl (normal 69-137), C4 was 20.7 mg/dl (normal 9-33), but anti-DNA was negative. Because the diarrhea and hypoalbuminemia persisted in spite of aggressive therapy, protein-losing enteropathy was suspected. A protein losing study with Tc-99m human serum albumin was performed and showed increased radioactivity in ileum at 6.5 hour and colon at 24 hour (Fig. 3). Under the impression of systemic lupus erythematosus with protein-losing enteropathy, pulse methylprednisolone 1gm daily was given for 3 days followed by prednisolone 50 mg per day. Her diarrhea improved dramatically and the edema disappeared, so she was discharged with stable condition. Her serum albumin was 4.2 gm/dl, globulin 3.0 gm/dl, total cholesterol 181 mg/dl, triglyceride 149 mg/dl, BUN 8 mg/dl and Cr 0.9 mg/dl four months after discharge.

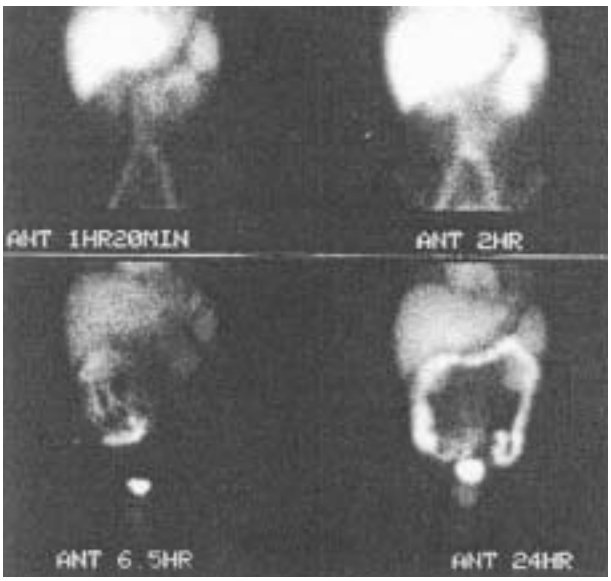

Fig.3. Tc-99m labeled human serum albumin scintigraphy showed increased radioactivity in ileum at 6.5 hour and entire colon at 24 hour.

Discussion

The patient first presented as nephrotic syndrome due to a membranous glomerulonephirtis (class V of WHO morphologic classification of lupus nephritis [5]). It is known that patients with the membranous form of lupus nephritis often have low or undetectable ANA titers [6]. Moreover, antibody to native DNA is markedly reduced in SLE patients with membranous compared to proliferative glomerulonephirtis, and is almost exclusively non-precipitating [7]. This phenomenon is compatible with our patient's manifestation, because her ANA was not detected until 6 months after the diagnosis of nephrotic syndrome and her anti-DNA was persistently negative. In SLE, low levels of non- precipitating antinuclear antibody favor the presence of circulating unbound antigen; the latter is known to be capable of binding non-im-

munologically to glomerular basement membrane and promoting in situ subepithelial immune deposits formation [8].

There are numerous conditions associated with gastrointestinal loss of protein. The most frequently cause is congestive heart failure due to constrictive pericarditis, and forms of lymphatic obstruction, such as intestinal lymphangiectasia, lymphoma, Whipple's disease, abdominal tuberculosis and regional enteritis [1,2,9,10]. Intestinal lymphatic obstruction occurs either directly (eg, intestinal lymphangiectasia) or indirectly through high venous pressure on lymphatic flow (eg, constrictive pericarditis) in these conditions. Leakage from dilated lymphatics resulted in the direct loss of proteins, lipids, and lymphocytes [1,9,10]. The resultant clinical findings are characteristic. Hypoalbuminemia, hypoglobulinemia, and lymphocytopenia with low or normal serum cholesterol occur, frequently with steatorrhea. Other causes of PLE are generally the direct result of intestinal mucosal disruption such as tropical sprue and regional enteritis.

The association of SLE and PLE was first reported by Waldmann et al [9]. in 1969. There are now 22 reported cases of PLE associated with SLE in English literature. Four cases were associated with other commonly recognized causes of PLE, ie, pericardial effusion and intestinal lymphangiectasia [4,9-11]. The remaining 18 cases [2,3,12-26] and our case appeared to be primary protein-losing enteropathies associated with SLE. Young females are predominant in these patients. Diarrhea is present about 50% of the cases. In the recent survey of the 14 patients with SLE who presented only with PLE[2], all of whom were diagnosed as having SLE on the basis of a positive ANA. None of these patients, including the one in our report, presented with any of the typical symptoms of SLE, such as malar rash, renal failure, pericarditis, pleural effusions, or vasculitis [2,3]. It is of interest that SLE had not been previously diagnosed in one half patients, although some symptoms suggestive of the disease were frequently present months or years before diagnosis. Thus, severe hypoalbuminemia due to PLE may be the first manifestation of SLE.

The clinical presentation of PLE due to SLE differs markedly from that due to lymphatic obstruction, suggesting a completely separate pathophysiology[2]. Steatorrhea was absent in all eight cases in which fecal fat was measured, and serum cholesterol levels were abnormally high in 70% of the reported cases. Lymphocytopenia is associated with SLE protein-losing enteropathy in only 10% of cases. In 8 of 8 cases, total serum globulin levels were normal. This pattern is consistent with a selective loss of low-molecular-weight proteins. These findings all suggest a mechanism independent of lymphatic leakage, and are consistent with the inability to demonstrate intestinal lymphangiectasia in small- and large-bowel biopsy specimens.

The actual pathophysiologic mechanism underlying lupus-associated PLE is unknown. Theories include intestinal lymphangiectasia and direct disruption of intestinal mucosa [4,9-11], but these causes are unlikely due to the majority of cases in which lymphangiectasia and ulcer is absent. The important characteristic of this disease is that increased capillary permeability will permit the loss of protein-rich fluid from the microvascular bed to intestinal interstitial tissue, and leakage of colloid into the intestinal lumen [15,18,23]. The resulting hyperlipidemia resembles the clinical presentation of nephrotic syndrome, in which loss of proteins or lipid-clearing macromolecules stimulates hepatic lipoprotein synthesis and inhibits lipoprotein catabolism[24]. Although intestinal vasculitis is the most likely cause of lupus-associated PLE, confirmation of its causative role is still lacking. Intestinal venulitis has been described in one patient by Weiser et al., when a full thickness of jejunal biopsy was obtained[15]. However in all other patients where small intestinal biopsy has been performed, vasculitis has not been demonstrated[2-4,10,12,16-23]. There is currently few information as to why only

a small patients group develop PLE, especially when the majority of those who are affected lack obvious vasculitic changes or immune deposits on intestinal biopsy.

Lupus-associated PLE should be considered in any young female presenting with hypoalbuminemia and edema, with or without a diagnosis of SLE. If the 24-hour urine protein did not reach the nephrotic range, a protein-losing enteropathy should be considered. Intravenous administered chromium 51-tagged albumin is the gold standard test to assess gastrointestinal protein excretion[9]. Technetium 99m-labeled albumin and indium 111-labeled plasma transferrin have also been used successfully and are more widely available[27,28], as in our case. Although 24-hour stool α_1-antitrypsin clerarance has recently been described as a convenient nonisotopic diagnostic test, its reliability remains in doubt[23]. Once excessive fecal protein excretion is found, steatorrhea, lymphopenia, and hypoglobulinemia suggest the presence of direct or indirect lymphatic obstruction. Intestinal biopsy will demonstrate the presence of dilated lymphatics and provide a definite diagnosis when mucosal abnormalities are present. If steatorrhea, lymphopenia, and hypoglobulinemia are not present, a positive antinuclear antibody and hypercholesterolemia strongly suggest the diagnosis of primary SLE-associated PLE.

The treatment of choice to primary SLE-associated PLE is steroids. The response of PLE to steroids is nearly uniform. Among 19 treated patients, only 2 cases[4,10] were steroid resistant. Cyclophosphamide was successful if the steroids failed. The longest follow-up reported in the literature has been 4 years[16], with an average follow-up of 20 months. Relapse occurred in at least 30% of patients when the medication was tapered or withdrawn. Nevertheless, steroid tapering is usually successful and one patient was able to discontinue treatment completely.

In summary, we report here a case of suspected SLE with both nephrotic syndrome and protein-losing enteropathy. These two conditions share the common clinical features: hypoalbuminemia, hypercholesterolemia and general anarsarca, but with different sites of protein loss. The association of PLE should be considered in all patients with SLE having edema and hypoalbuminemia without renal protein loss, as the condition is readily treated with steroids and the overall prognosis is good.

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疑似全身性紅斑性狼瘡合併腎病症候群及蛋白質流失性腸病變——一病例報告

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摘　要

我們報告一位五十七歲之女性疑似全身性紅斑性狼瘡患者，其表徵爲全身水腫，肋膜積水，高膽固醇血症和嚴重的低白蛋白血症。首先，病人被發現有大量蛋白尿，腎臟生檢診斷爲膜性腎絲球炎並接受成功的治療。但兩年後病人又出現相同的臨床表徵並伴有腹瀉現象，然而此次未發現蛋白尿。在排除其他腸胃道蛋白質流失的原因後，我們診斷她爲全身性紅斑性狼瘡合併罕見的原發性蛋白質流失性腸病變，並在類固醇治療後達到完全緩解。本病例的特殊處在於不同之病灶表現出幾乎完全相同的臨床症狀。嚴重的低白蛋白血症和全身水腫卻未合併有重度蛋白尿之患者，需要我們做進一步之鑑別診斷和探討。