Hipoalbuminémia Reveladora: Um Caso de Enteropatia Perdedora de Proteínas Associada a Lúpus Eritematoso Sistémico

Disclosing Hypoalbuminemia: A Lupus Protein-Losing Enteropathy (Lupple) Report

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Resumo:

A enteropatia perdedora de proteínas (EPP) caracteriza-se pela presença de edema generalizado e hipoalbuminemia grave, secundários à perda proteica através do trato gastrointestinal. Os autores reportam um caso de enteropatia perdedora de proteínas secundária a lupus eritematoso sistémico (LES), como a manifestação inicial desta doença.

A doente relatava um quadro pautado por 4 meses de diarreia aquosa, não sanguinolenta, (com um máximo de 10 dejeções diárias), e perda ponderal significativa. Posteriormente desenvolveu marcado edema periférico e *rash* cutâneo malar e maculopapular ao nível do tórax e membros. Analiticamente apresentava anemia, hipoalbuminemia grave, hipocaliémia e hipomagnesémia.

No decurso da investigação foram excluídas proteinúria e outras causas de hipoalbuminemia.

Após resultados como a pesquisa de anticorpos anti-nucleares e anti-ribonucleoproteinas positiva foi assumido o diagnóstico de EPP secundária ao LES. A doente foi tratada com pulsos de Metilprednisolona 1000 mg/dia durante 3 dias, seguido de prednisolona 1 mg/kg/dia, com boa resposta clínica. Após 20 dias, foi adicionada Azatioprina e iniciado o desmame de corticoides.

O presente caso clínico destaca uma EPP como forma de apresentação do LES, cujo diagnóstico pode passar despercebido, tendo em conta a sua raridade, e acarretar um aumento da morbilidade e mortalidade.

Palavras-chave: Enteropatia Perdedora de Proteínas; Hipoalbuminémia; Lúpus Eritematoso Sistémico.

Abstract:

Protein-losing enteropathy (PLE) is characterized by generalised oedema and severe hypoalbuminemia secondary to protein loss from the gastrointestinal tract. We report a case of Lupus protein-losing enteropathy (LUPPLE) as the presenting feature of systemic lupus erythematosus (SLE).

Our patient presented with 4 months of watery, non-bloody, diarrhoea (maximum of 10 stools per day) and significant weight loss. Later she developed severe peripheral oedema, malar and maculopapular erythematous rash in the thorax and limbs. Blood analysis showed anaemia, severe hypoalbuminemia, hypokalaemia, hypomagnesemia.

During the investigation proteinuria and other causes of hypoalbuminemia were excluded and a thorough differential diagnosis regarding the main causes of PLE was made. Positive Antinuclear and anti-ribonucleoprotein antibodies were found and LUPPLE was diagnosed. The patient was started on methylprednisolone pulses 1000 mg/day for 3 days, followed prednisolone 1 mg/kg/day, with great clinical response. After 20 days, azathioprine was added as the tapering of corticosteroids ensued.

This clinical case portraits PLE as a rare form of presentation of SLE that, due to its uncommonness, can result in a missed diagnosis with consequent increase in morbidity and mortality.

Keywords: *Hypoalbuminemia; Protein Losing Enteropathy; Systemic Lupus erythematosus.*

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Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical features.[1]

Protein-losing enteropathy (PLE) is a condition characterized by severe oedema and hypoalbuminemia secondary to protein loss from the gastrointestinal tract.[2] Lupus protein-losing enteropathy (LUPPLE) is a well reported but rare manifestation of SLE.[3] This clinical case portraits this entity as the first manifestation of SLE, with a favourable response to therapy with corticosteroids and azathioprine (AZA).

Case Report

We report the case of a 66-year-old woman, with prior history of essential hypertension treated with olmesartan for the past 2 years. She had, however, suspended the aforementioned drug due to hypotension one month before admission.

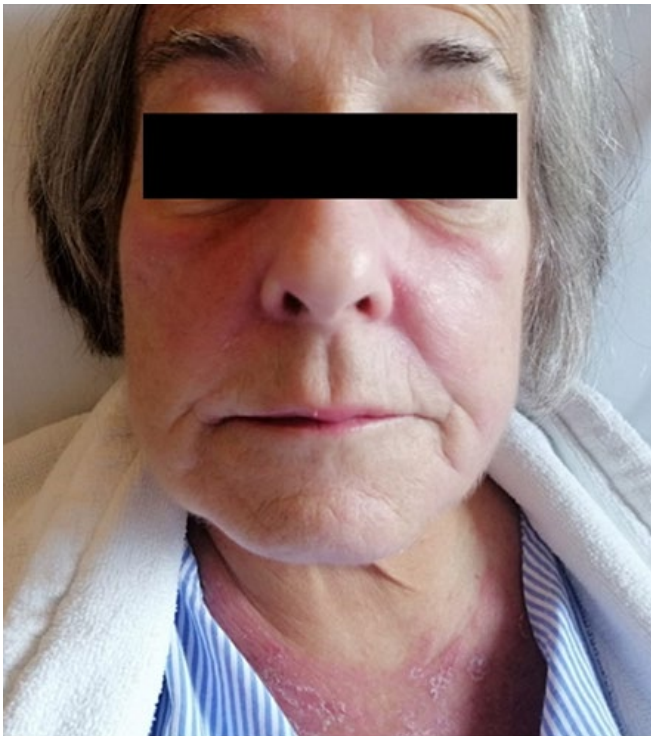

Figure 1

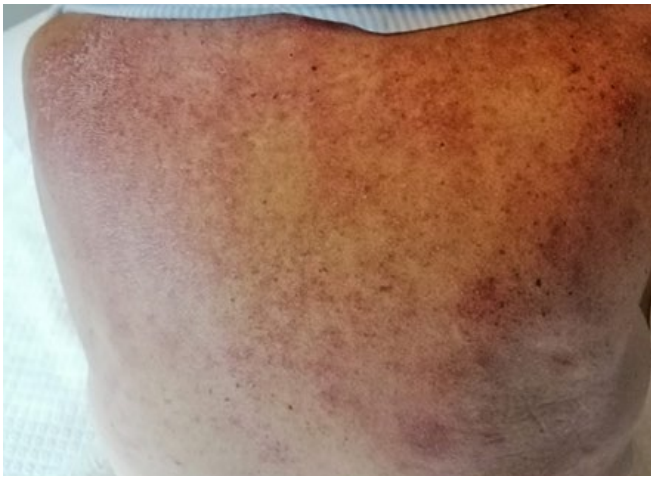

Figure 2

She presented with 4 months of watery, non-bloody, diarrhoea (maximum of 10 stools per day) with a weight loss of 15 kg in that period. Additionally, in the month prior to admission she noticed peripheral oedema mainly on the lower limbs, which was getting progressively worse. The patient denied anorexia or reduced food intake.

On physical examination, she had severe generalized oedema, a malar and maculopapular erythematous rash in the anterior and posterior upper part of the thorax and in the distal extremities of her upper and lower limbs (Figs. 1 and 2). Non-scaring alopecia was also noted.

At this time the blood work showed normocytic normochromic anaemia, severe hypoalbuminemia, hypokalaemia, and hypomagnesemia. Renal function was normal, without proteinuria and there was not evidence of hepatic disfunction (Table 1). Additional investigation revealed a positive antinuclear and anti-ribonucleoprotein antibody (ANA and anti-RNP), a low C3, and positive anti-histone and anti-beta-2 glycoprotein antibodies (anti-ß2GP1).

A computed tomography (CT) of the thorax, abdomen and pelvis, showed pleural effusion, moderate ascites and concentrical wall thickening of the stomach, terminal ileum, and transverse colon. The transthoracic echocardiography revealed a mild pericardial effusion with preserved cardiac function.

At the 10th day since admission, the anaemia and hypoalbuminemia had worsened, and leukopenia ensued. Table 1 shows the initial blood work values in comparison with the same ones on the 10th day after admission.

The patient had no evidence of an infectious aetiology (she had no fever and no raise of inflammatory markers such as leucocytes [4.32x10^{9}/L] and C-reactive protein [1.75 mg/dL]) and endoscopic exams with biopsy were performed to exclude any other major causes of protein losing enteropathy. These revealed only oedema of the ileum and colon mucosa with non-specific inflammatory findings. A skin biopsy of the rash affected area, on the thoracic region, also showed unspecific inflammatory findings.

After exclusion of other causes, protein losing enteropathy was assumed in the context of SLE and treated with corticoids. She was started on methylprednisolone 1000 mg/day for 3 days, followed by a 20-day course of prednisolone 1 mg/kg/day. She was also prescribed a high protein with medium chain triglycerides diet and diuretics. Within a few days the oedema was significantly reduced, the cutaneous manifestations became less evident, and the analytic values shifted towards a normal range (at discharge: haemoglobin 8.3 g/dL and albumin 1.7 mg/dL).

After 20 days prednisolone tapering begun, and AZA was added (starting with 50 mg a day rising to 75 mg/day).

Corticosteroid therapy was suspended 11 months after discharge (slow tapper) and the patient is currently on 75 mg/day of AZA, without any recurrence of the symptom, and normal haemoglobin and albumin.

Discussion

The first and longer lasting symptom in this case was watery diarrhoea and the most prominent laboratory result at admission was severe hypoalbuminemia, resulting in generalized oedema, pleural and pericardial effusion and ascites.

PLE is a condition characterized by severe oedema and hypoalbuminemia secondary to protein loss from the gastrointestinal tract.[2]

Concerning the investigation of protein loss, the patient denied anorexia or reduced food intake, there were no signs of hepatic disfunction and no significant proteinuria in a 24h

Table 1: Laboratory results at the time of admission (2nd column) and at the 10th day of hospitalization (3rd column).

Parameter	Value (admission)	Value (10th day)	Reference range
Haemoglobin	9.8 g/dL	7.5 g/dL	(13.5 - 17-5)
Mean corpuscular volume	83 fL	89 fL	(80 – 100)
Mean corpuscular haemoglobin	29 pg	29 pg	(26 - 34)
Leucocytes	4.32x10^9/L	3.69x10^9/L	(4.00 – 10.00)
Neutrophils	2.50x10^9/L	1.73x10^9/L	(1.80 – 7.00)
Eosinophils	0.10x10^9/L	0.31x10^9/L	(<0.50)
Basophils	0.03x10^9/L	0.02x10^9/L	(<0.10)
Lymphocytes	1.28x10^9/L	1.25x10^9/L	(1.00 – 4.00)
Monocytes	0.41x10^9/L	0.38x10^9/L	(0.20 – 1.00)
International normalized ratio (INR)	1.04		variable
Activated partial thromboplastin time	27.4 seg		(29.0 - 40.2)
Urea	34 mg/dL	29 mg/dL	(21 - 43)
Creatinine	0.64 mg/dL	0.51 mg/dL	(0.55 – 1.02)
Albumin	1.2 g/dL	1.0 g/dL	(3.4 – 5.0)
Sodium	144 mmol/L	143 mmol/L	(136 - 145)
Potassium	2.7 mmol/L	3.5 mmol/L	(3.5 – 5.1)
Magnesium	1.5 mg/dL	3.0 mg/dL	(1.8 – 2.4)
Calcium (albumin adjusted)	9.4 mg/dL	9.0 mg/dL	(8.5 – 10.1)
Phosphate	2.5 mg/dL		(2.5 – 4.9)
Haptoglobin	42 mg/dL		(30-200)
Total bilirubin	0.39 mg/dL	0.40 mg/dL	(0.20 – 1.00)
Conjugated bilirubin	0.11 mg/dL	0.13 mg/dL	(<0.20)
Aspartate aminotransferase	40 UI/L	23 UI/L	(15 - 37)
Alanine aminotransferase	41 UI/L	23 UI/L	(14 - 59)
Gamma-glutamyl transferase	50 UI/L	65 UI/L	(5 - 55)
Lactate dehydrogenase (LDH)	328 UI/L		(81 - 234)
Erythrocyte sedimentation rate	23 mm/h		(<30)
C-reactive protein	1.75 mg/dL	0.78 mg/dL	(<0.60)
Immunoglobulin G (IgG)		706 mg/dL	(700 - 1600)
Immunoglobulin A (IgA)		95 mg/dL	(70 - 400)
Immunoglobulin D (IgD)		83.9 mg/dL	(<100)
Immunoglobulin E (IgE)		232 mg/dL	(<158)
Antinuclear antibodies (ANA)	positive >1280		
Antibodies to ribonucleoprotein (RNP)	strong positive		
Anti-histone antibodies	positive		
Anti-double stranded DNA antibodies (anti-dsDNA)	negative (15.3 UI/mL)		(negative < 100)

Table 1 (cont.): Laboratory results at the time of admission (2nd column) and at the 10th day of hospitalization (3rd column).

Parameter	Value (admission)	Value (10th day)	Reference range
Anti-Smith antibodies (anti-Sm)	negative		
Anti-SSA/Ro antibodies	negative		
Anti-SSB/La antibodies	negative		
Rheumatoid factor	<10.0 UI/mL		(< 14)
Anti-cyclic citrullinated peptide antibodies (anti-CCP)	Negative (1.00 UI/mL)		(negative < 7.0)
Lupus anticoagulant		negative	
Anti-cardiolipin antibodies IgG		weak positive (29 GLP/mL)	(negative < 10)
Anti-cardiolipin antibodies IgM		Negative (6.9 MPL/mL)	(negative < 10)
Anti-cardiolipin antibodies IgA		negative (2.1 MPL/mL)	(negative < 14)
Anti-Beta-2 glycoprotein 1 antibodies IgG		positive (58 U/mL)	(negative < 7)
Anti-Beta-2 glycoprotein 1 antibodies IgM		Negative (2.0 U/mL)	(negative < 7)
Anti-Beta-2 glycoprotein 1 antibodies IgA		Negative (2.4 U/mL)	(negative < 7)
Antineutrophil cytoplasmic antibodies (ANCA)	negative		
Anti-gliadin antibodies	2.5 mg/dL		(2.5 – 4.9)
IgG and IgA	negative		
Anti-endomysial antibody	0.39 mg/dL	0.40 mg/dL	(0.20 – 1.00)
IgG and IgA	negative		
Anti-tissue transglutaminase antibodies	40 UI/L	23 UI/L	(15 - 37)
IgG and IgA	negative		
Human immunodeficiency virus	50 UI/L	65 UI/L	(5 - 55)
(Ag P24 + Ac HIV 1/2)	negative		
Hepatitis B (Ag HBs)	negative		
Hepatitis C (Ab anti-HCV IgM)	negative		
Complement C3		66 mg/dL	(90 - 180)
Complement C4		20 mg/dL	(10 - 40)
Complement activity (CH50)		53 KU/L	(32 - 58)
Fecal alpha 1-antitrypsin concentration	0.10 mg/g feces		(< 0.30)
Stool culture (3 samples)	negative		
Stool examination for ova and parasites	negative		
Clostridioides *difficile toxin*	negative		
24h urine protein	<0.098 mg		(<500 mg for lupus nephritis)

urine sample, rending malnutrition, hepatic disease and nephritis unlikely causes.

PLE can occur as an idiopathic disorder, but it can also develop as a manifestation of several systemic diseases.[3]

PLE is frequently diagnosed by measuring the alpha-1 antitrypsin clearance. An elevated alpha-1 antitrypsin clearance suggests increased enteral protein loss. On the other hand, random fecal alpha-1 antitrypsin concentration is not a reliable test for diagnosing PLE. Unfortunately, in our institution the measurement of alpha-1 antitrypsin clearance is not possible,

so we had to rely on the remainder results and clinical picture.

As in most cases of LUPPLE, thickening of the gastrointestinal tract wall and biopsies with non-specific inflammatory findings were found.[2]

Considering the presented cutaneous features (malar and maculopapular erythematous rash), weight loss, anaemia, and results of the immunologic study with positive ANAs, RNP, anti-ß2GP1 antibodies and low C3, we admitted that PLE was most likely the first manifestation of SLE.

Before any therapy was instituted a thorough investigation was made to exclude the remainder entities that disrupt mucosal permeability or increase exudation of protein rich fluid across the epithelium of the gastrointestinal tract, or that compromise its lymphatic flow.

Throughout the investigation, several diseases were excluded, namely: celiac disease with negative anti-gliadin, anti-endomysial and anti-tissue transglutaminase antibodies and no compatible endoscopic findings; inflammatory bowel disease, since the patient had no typical findings like abdominal pain, bloody stools, fistulas, and no extraintestinal manifestations such as cholangitis, uveitis, or arthralgia; malignancy with no findings on the CT scan or the endoscopic exams suggestive of such aetiology; Whipple's disease regarding the absence of joint symptoms and negative biopsies of the small intestine to periodic acid-Schiff staining and polymerase chain reaction testing for *Tropheryma whipplei*; Ménétrier's disease and Zollinger-Ellison syndrome which diagnosis are also made though upper endoscopy; infiltrative diseases as amyloidosis and sarcoidosis, with no evidence of amyloid on histology on tissue biopsy, and absence of granulomas along the entire gastrointestinal tract along negative serum angiotensin converting enzyme; and intestinal lymphangiectasia since there was no ectasia of the enteric lymphatics.

There was also no evidence of an infectious cause, she had no recent history of travel, remained apyretic for the whole course of the disease, and the *Clostridioides difficille* toxin, stool cultures and examination for ova and parasites all yielded negative results.

A comprehensive review from G. Ianiro *et al* gathered information from 54 patients (11 studies) that developed a sprue-like enteropathy associated with olmesartan treatment. Also L. Marthey *et al* conducted a national survey concerning 32 patients with the same condition. In both studies patient presented with diarrhoea and hipoalbuminemia and recovered after olmesartan withdrawal. It is also an entity with a good response to corticosteroid and/or immunosuppressive treatment.[4,5]

In the present case olmesartan does not seem to be the trigger for the enteropathy since the patient kept worsening even 1 month after this medication was suspended.

The entity drug induced lupus (DIL) was also considered. It can be associated with virtually every drug, occurs after several months or years of continuous therapy, and is in relation with positive anti-histone antibodies.[6] However, upon research, the authors found only one case report linked to olmesartan.[7] Furthermore, in DIL symptoms are usually milder than in SLE and mucocutaneous manifestations are rare. In the present case the symptoms worsened even after one month from the drug suspension, with new onset of non-scaring alopecia and leukopenia rendering SLE the most probable diagnosis.

Most related PLE gastrointestinal manifestations are not as common as other organ involvement such as lupus nephritis. Therefore, it can be clinically missed by internists, rheumatologists, gastroenterologists and nephrologists.[2]

The present case brings into light a rare diagnosis, especially as the presenting feature of SLE, that is more commonly seen in younger individuals. ■

LEARNING POINTS

- Lupus protein-losing enteropathy (LUPPLE) is a well reported but rare manifestation of systemic lupus erythematosus (SLE), and it can be clinically indistinguishable from nephrotic syndrome.
- The delay in diagnosis of SLE can severely increase morbidity and mortality, especially in the presence of hypoalbuminemia due to pleural and pericardial effusion and ascites, which can evolve to life-threatening situations.

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ACR, JC, ARS – Redação do artigo
NM, HV, HC – Revisão do artigo
Todos os autores aprovaram a versão final

Contributorship Statement

ACR, JC, ARS – Article writing
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