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Systemic capillary leak syndrome and autoimmune diseases: A case series☆

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ABSTRACT

Objectives: Systemic capillary leak syndrome (Clarkson's disease) is a rare entity characterized by recurrent and unpredictable attacks of capillary leakage of plasma fluid and proteins throughout the endothelium. Some cases are secondary. We describe the rare association between secondary capillary leak syndrome (SCLS) and autoimmune diseases.
Methods: We conducted a nationwide, retrospective, observational, and collaborative study throughout the hospital units of the Club des Rhumatismes et Inflammations network (CRI) between March and August 2015. Inclusion criteria were patients with (1) capillary leakage episodes characterized by edema and elevated hematocrit, low albumin count without proteinuria, or other cause of protein loss; and (2) definite autoimmune diseases according to international classification criteria.
Results: The clinical and biological data of five patients (three women) were reviewed. Median age was 43.2 (17–55) years. Four patients had Sjögren syndrome. One of them also fulfilled the criteria for systemic sclerosis ($n = 1$). The fifth patient had polymyositis. During the 37.2 months of median follow-up (5.4–201), we recorded a total of 24 attacks, yielding an attack incidence of 91/100 patient-years. Laboratory tests revealed that three patients had anti-SSA/Ro antibodies. Only one patient had a monoclonal blood component (IgGκ). Three patients needed ICU support; one died during a flare.
Conclusions: We reported the first case series of a rare association of SCLS and autoimmune diseases, supporting the idea of some immune mediation in the pathogenesis of the former disease.

Introduction

Idiopathic systemic capillary leak syndrome—currently known as Clarkson's disease—is a rare disorder (about 200 reported cases), with poor prognosis (20% of mortality). It is characterized by recurrent and unpredictable attacks of fluid and proteins leakage in the interstitial compartment. Capillary leak attack is manifested at the onset by hypotension, hemoconcentration, and paradoxical hypoalbuminemia [1]. The syndrome can be idiopathic (Clarkson's disease) or secondary [2]. Causes of secondary capillary leak syndrome (SCLS) include malignant hematological diseases (lymphoma, myeloproliferative disorder, and hemophagocytic

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lymphohystiocytosis), infectious diseases (arbovirus infections and hemorrhagic fevers, brucellosis, and sepsis), and medications [IL-2, granulocyte colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), gemcitabine, and bortezomib] [3–5]. However, very little is known about the occurrence of capillary leak syndrome in autoimmune diseases.

We reported here the first series of patients with autoimmune diseases who experienced capillary leak attacks. We analyzed their clinical and biological features, and followed the evolution of both diseases by observing therapeutics applied and recurrence of attacks during all the available follow-ups.

Methods

Study design and data collection

Between March and August 2015, we performed a nationwide, retrospective, and observational study through the French society of internal medicine Societé Nationale Française de Médecine Interne (SNFMI) and the French network called "Club des Rhumatismes et Inflammation" (CRI), bringing together up to 2300 autoimmunity expert members from France, Belgium, Switzerland, Canada, Algeria, Morocco, and Tunisia.

Patients inclusion and exclusion criteria

Patients had been followed up between December 1991 and May 2015. To be included in the study, they had to fulfill the following criteria: (1) capillary leakage with one or more episodes of edema and weight gain (≥ 1 kg), low blood pressure count (systolic blood pressure < 100 mmHg), hemoconcentration (elevation of hematocrit above normal values), and/or low albumin count (≤ 35 g/L) in exclusion of other causes (chronic cardiac insufficiency, nephrotic syndrome, exudative enteropathy, angioedema with C1q deficiency, Gleich syndrome, neuroendocrine related syndrome, ovarian hyperstimulation, drugs, and toxic angioedema); and (2) autoimmune disease according to international ACR/EULAR classification criteria. All observations were reviewed by a single investigator (A.G.) and were collected using a standardized and anonymized data form.

All the data were collected in accordance with French ethical policies.

Statistical analysis

Data are presented as median (range) or counts (percentage). Tests have been carried out using the version 3.2.2 of the R software (R-project.org).

Results

Clinical and biological data

We reviewed clinical data on three women and two men (Supplementary material). The median age at diagnosis was 43 years (17–55). During a median follow-up of 37 months (5–201), a total of 24 attacks with a median of 3 (2–14) attacks per patient were recorded, yielding a risk of attack of 91/100 patient-years. Triggers associated in the flare included infection, cold exposure or physical effort, and flare of autoimmune disease (Table). Prodromal symptoms were different from one patient to another, but occurred in all patients and were relatively stereotyped in the same patients (Table and Supplementary Table S1). Median maximal weigh gain was 14 kg (3.4–30.4 kg) ranging from 6% to 52% of usual personal dry weight count.

Table
Main characteristics of the patients with capillary leak syndrome and autoimmune disease

Epidemiology	
Median age at diagnosis—years (min; max)	43.2 (16.9; 55.1)
Sex ratio (F/M)	1.5 (3/2)
Median follow-up—months (min; max)	37.2 (5.4;201)
Capillary leak syndrome	
Number of attacks	
Median number by patient	3 (2;14)
Incidence (100 patient-years)	91
Promoting factors	5/5
ENT infection	1/5
Digestive infection	1/5
Flare of autoimmune disease	1/5
Physical effort	2/5
Prodromal symptoms	4/5
Asthenia	2/5
Weakness	4/5
Abdominal pain, vomiting, diarrhea	1/5
Thirst and/or oliguria	3/5
Severity of the disease	
Need for ICU support	3/5
Fatal attack	1/5
Serological findings	
Positive ANA in IIF HEp-2 test ($\geq 1/160$)	3/5
Positive anti-SSA/Ro antibody	3/5
Positive anti-SSB/La antibody	1/5

Abbreviations: SD, standard deviation; M, male; F, female; ENT, ear nose and throat; ICU, intensive care unit; ANA, antinuclear antibody; IIF, indirect immunofluorescence; HEp-2, human epithelial-2 cells.

In all cases, diagnosis of autoimmunity was made concomitantly with the first manifestations of SCLS.

We found three patients with significant antinuclear antibodies ($\geq 1/160$) by indirect immunofluorescence (IIF) on HEp-2 cells. All, but one patient, fulfilled the criteria for Sjögren syndrome and 3/5 had anti-SSA/Ro antibodies (Table). One patient also had anti-SSB/La antibody. One patient had systemic sclerosis associated with Sjögren and one had polymyositis (proven by muscle biopsy), though no specific autoantibody of myositis was found. Only one patient had a monoclonal component (IgGκ). The patient with polymyositis also had rhabdomyolysis (which occurred during a flare of myositis). For two patients, the vascular endothelial growth factor (VEGF) measured during a flare was elevated.

Treatments

Four patients received one or several prophylactic treatments such as IVIG ($n = 4$), diuretics ($n = 3$), steroids ($n = 2$), chemotherapy protocol vimblastine melphalan, carmustine, cyclophosphamide, and prednisone (VMBCP) ($n = 1$), theophylline ($n = 1$), methotrexate ($n = 1$), or D-penicillamine ($n = 1$) (Supplementary Table S2).

For the treatment of the underlying autoimmune disease, patient received immunosuppressive drugs ($n = 3$), hydroxychloroquine ($n = 1$), or methotrexate ($n = 1$) (Supplementary Table S2).

Immunosuppressive therapies allowed simultaneous control of autoimmunity and flare of capillary leakage for the patient with polymyositis (3). He relapsed when steroids and methotrexate were tapered. One patient (1) also relapsed when steroids were tapered under 5 mg/day (Supplementary material).

In the four patients treated with IVIG (1–2 g/kg), the median number of infusions was 30 (9–135) with relapse occurring within 4 months following discontinuation in three patients.