Antiphospholipids Syndrome Complicated by a Systemic Capillary Leak-Like Syndrome Treated With Steroids and Intravenous Immunoglobulins

A Case Report

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Abstract: This report describes the onset of systemic capillary leak (SCL)-like syndrome in a 30-year-old woman with antiphospholipids syndrome (APS) during puerperium.

Twelve hours after a cesarean section, she presented a sudden fever and abdominal pains followed by dyspnea, severe edema of the limbs and pelvis.

Computer tomography shows congestion of interstitial pulmonary parenchyma, pericardial and pleural effusion, edema of intestinal wall and of visceral adipose tissue, and pericardial lymphedema. Laboratory tests showed neutrophilic leukocytosis, hypoalbuminemia, and an increase of erythrocyte sedimentation rate and C-reactive protein. Because fever and raised inflammation parameters are not observed in idiopathic capillary leak syndrome (SCLS; Clarkson disease), a diagnosis of SCL-like syndrome was made.

Albumin solution, high-dose methylprednisolone and intravenous immunoglobulins (IVIG) infusion were administered with a rapid improvement of her clinical condition.

The prompt treatment with steroids and IVIG likely prevented the life-threatening shock syndrome that can occur in SCLS, with acute hypotensive attacks, and severe limbs edema requiring fasciotomy.

All clinical and laboratory findings supported autoinflammation as the underlying pathogenic mechanism of the syndrome. The data indicate that SCL-like syndrome can be considered a novel clinical syndrome, which can complicate APS.

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Abbreviations: aCL = anticardiolipin antibodies, ANA = antinuclear antibodies, APS = antiphospholipid syndrome, CAPS = catastrophic antiphospholipid syndrome, CRP = C-reactive protein, CT = computed tomography, ENA = extractable nuclear antigen, ESR = erythrocyte sedimentation rate, IVIG = intravenous immunoglobulins, SCL = systemic capillary leak, sPAP = systolic pulmonary arterial pressure.

INTRODUCTION

Idiopathic systemic capillary leak syndrome (SCLS; Clarkson disease) features transient, severe hypotensive shock, hypoalbuminemia, and anasarca. It is caused by a reversible microvascular barrier dysfunction characterized by the leakage of fluids and macromolecules (up to 900 kDa) into the extravascular compartment.1,2 This very rare condition was recognized for the first time as a distinct clinical entity by Dr Bayard Clarkson in 1960.7 Most of the cases reported in the literature were associated to a serum monoclonal component,1,2,4-6 none of which was reported in the context of antiphospholipid syndrome (APS). The 5-year overall survival rate of SCLS has been estimated to range between 59% and 97%, depending on complications related to the acute phase of the disease characterized by severe limb edema, often requiring fasciectomy and by severe hypotensive shock, requiring intensive care therapy.4,5

Herein, we report the case of a young woman affected by APS who, after a cesarean section, rapidly developed widespread peripheral and internal tissues edema with no apparent cause, a condition resembling an SCLS.
the 38th week of gestation. The newborn was alive and vital (weight 2300 g, APGAR index 8). Twelve hours after delivery, despite prophylactic therapy with metronidazole benzoate, levofloxacin and cefazolin, she rapidly developed a continuous remitting fever of up to 39°C, with chills and abdominal pain in the epigastrium and mesogastrium. On physical examination, blood pressure was 100/60 mm Hg and heart rate 70 beats per minute; the abdomen was painful on palpation of all quadrants; visible mucous membranes were dehydrated. She was given supportive therapy with electrolytic solutions and rifaximin. On the second day after delivery she complained of sudden dyspnea and severe edema of the pelvis and of proximal and distal parts of the limbs. Computed tomography (CT) pulmonary angiography, CT angiography of the abdominal vessels, and abdominal x-ray excluded signs of pulmonary embolism, arterial and venous thrombosis of abdominal vessels and intestinal occlusion. Chest–abdomen–pelvis CT showed interstitial pulmonary parenchymal congestion, bilateral pleural effusions associated with atelectasis, cardiomegaly, congestion of the liver with periporal edema, peritoneal effusion, distension of the gall-bladder, and ileal and colonic loops. Edema of the entire intestinal wall and of perivisceral adipose tissue was observed (Figure 1, panel A). Transthoracic Doppler echocardiogram revealed a mild enlargement of the whole heart, a slight dilatation of the inferior vena cava, minor mitral valve prolapse, an estimated pericardial effusion of 200 to 500 mL, an estimated systolic pulmonary arterial pressure (sPAP) of 25 mm Hg, mild mitral and tricuspid regurgitation and normal systolic function (EF 60%). Other findings included neutrophilic leukocytosis, increased erythrocyte sedimentation rate (ESR), D-dimers, C-reactive protein (CRP) and fibrinogen, red blood cell count at the lower normal limits, normochromic normocytic anemia with no schistocytes, along with a decreased potassium, albumin concentration, and platelets count (Table 1). ANA positivity (titer: 1:640) and the presence of lupus anticoagulant were detected. Microbiological cultures, virological tests, and procalcitonin were negative. 24-hour urine protein was 300 mg.

Based on these data, a diagnosis of a systemic capillary leak (SCL)-like syndrome was made. Albumin solution and methylprednisolone (60 mg/day) were added to the previous therapy. Intravenous immunoglobulins (IVIG) infusion (0.4 g/kg/day for 5 days) were started on the seventh day. After a few days her clinical conditions rapidly improved, and she developed marked polyuria. Hemoglobin, leukocytes, albumin, potassium, D-dimers, and inflammatory indices gradually returned to normal (representative results in Figure 1, panel B). At 3 months follow-up, she was in good health and laboratory tests were normal. Finally, the enoxaparin was switched to acetylsalicylic acid.

**DISCUSSION**

Transient, severe hypotensive shock, anasarca, and hypoalbuminemia in the absence of nephrotic proteinuria are typical features of SCLS. Some of the signs of SCLS were present in our patient, namely edema of the peripheral and...
internal tissues, hypoalbuminemia (Table 2).8,9 The normal pro-
calcitonin values, the absence of nephrotic proteinuria, negative
blood microbiological cultures along with the results of vir-
ological tests and transthoracic Doppler echocardiogram ruled
out a number of clinical conditions which could have mimicked
SCLS. These included nephrotic syndrome, sepsis, or heart
dysfunction.1,4 Even so, the diagnosis of SCLS “sensu stric-
tiore” could not be formulated because of the presence of high

| Analysis          | Values (IS)       | Normal Range          |
|-------------------|-------------------|-----------------------|
| Blood             |                   |                       |
| Erythrocytes      | 4.08 × 10^{12}/L  | (4.00–5.20)           |
| Leukocytes        | 15.29 × 10^{9}/L  | (3.54–9.06)           |
| Neutrophils       | 0.96              | (0.40–0.70)           |
| Lymphocytes       | 0.03              | (0.20–0.50)           |
| Monocytes         | 0.01              | (0.04–0.08)           |
| Eosinophils       | 0                 | (0.0–0.6)             |
| Basophils         | 0                 | (0.0–0.02)            |
| Hemoglobin        | 95 g/L            | (120–158)             |
| Hematocrit        | 0.29              | (0.35–0.44)           |
| MCV               | 88.1 fl           | (79–93.3)             |
| MCHC              | 329 g/L           | (323–359)             |
| Platelets count   | 124 × 10^{11}/L   | (165–415)             |
| Creatinine        | 73.33 μmol/L      | (44–80)               |
| Urea nitrogen     | 2.17 mmol/L       | (2.5–7.1)             |
| Glucose           | 3.7 mmol/L        | (3.6–5.3)             |
| AST               | 19 U/L            | (12–37)               |
| ALT               | 52 U/L            | (20–96)               |
| Lipase            | 355 U/L           | (73–393)              |
| Total bilirubin   | 15.3 μmol/L       | (5.1–22)              |
| Albumin           | 21 g/L            | (40–50)               |
| Potassium         | 2.9 mmol/L        | (3.5–5.0)             |
| Sodium            | 147 mmol/L        | (136–146)             |
| Chloride          | 112 mmol/L        | (102–109)             |
| ESR               | 66 mm/1h          | (1–20)                |
| CRP               | 204 mg/L          | (<10)                 |
| NT-proBNP         | 1794 ng/L         | (<125 up to 75 years) |
| Troponin T        | <0.015 μg/L       | (0–0.01)              |
| D-dimers          | 1794 ng/mL        | (<300)                |
| PT                | 12.2 s            | (12.7–15.4)           |
| PTT               | 37.3 s            | (26.3–39.4)           |
| TT                | 18.2 s            | (15.3–18.5)           |
| Functional Antithrombin III | 0.76 U/L | (0.7–1.30) |
| Fibrinogen        | 8.48 g/L          | (2.3–4.96)            |
| Total protein     | 51 g/L            | (67–86)               |
| C3                | 1.04 g/L          | (0.83–1.77)           |
| C4                | 0.2 g/L           | (0.16–0.47)           |
| Procalcitonin     | 0.1 μg/L          | (<0.1)                |
| Urine             |                   |                       |
| pH                | 6.5               | (5.0–9.0)             |
| Glucose           | 0 mg/dL           | (0–10.0)              |
| Protein           | 100 mg/dL         | (<30)                 |
| Hemoglobin        | 0.00 mg/dL        | (0–0.03)              |
| Ketones           | 15 mg/dL          | (0–5)                 |
| Bilirubin         | 0.00 mg/dL        | (0–0.2)               |
| Urobilinogen      | 0.2 mg/dL         | (0.2–1)               |
| Leukocytes        | 0 Leu/μL          | (0–25)                |
| Urinary sediment abnormality | None |
| Blood gas analysis|                   |                       |
| pH                | 7.45              | 7.35–7.45             |
| pCO2              | 29.90 mm Hg       | 35–45                 |
| pO2               | 74.00 mm Hg       | 80–100                |
| HCO3^-            | 20.20 mmol/L      | 21–29                 |

ALT = alanine transaminase, AST = aspartate transaminase, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, MCHC = mean corpuscular haemoglobin concentration, MCV = mean corpuscular volume, PT = prothrombin time, PTT = partial thromboplastin time, TT = thrombin time.
fever and increased inflammation parameters (neutrophilic leukocytosis, ESR, CRP, and D-dimers), which are not usually observed in SCLS. Therefore, the diagnosis of SCL-like syndrome was made.

SCLS has been reported to be mostly associated with monoclonal gammopathies of undetermined significance, typed as IgG kappa in 89% of cases, that have a mortality rate ranging between 35% and 70%. There has been 1 report of the syndrome occurring as the clinical presentation of Kawasaki disease. The pathogenic mechanisms underlying microvascular barrier dysfunction are unknown. It is thought that in some patients with TNF inhibitors during acute episodes, the improved clinical condition obtained in some patients with TNF inhibitors during acute episodes, and the use of IVIG both in the acute phase and as disease prophylaxis, support this view. A similar conclusion can be reached for the syndrome described here, in which the presence of high fever, neutrophilic leukocytosis and high serum CRP levels, besides the prompt response to steroids and IVIG, supported autoinflammation as the underlying pathogenic mechanism. The same pathogenic mechanism has also been recognized as responsible for catastrophic APS (CAPS), a rare but severe complication of APS, characterized by a sudden onset of multi-organ failure due to widespread microthrombosis, puerperal fever and increased inflammation parameters (neutrophilic leukocytosis, ESR, CRP, and D-dimers), which are not usually observed in SCLS. Therefore, the diagnosis of SCL-like syndrome was made.

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CONSENT
Written informed consent was obtained from the patient before and after all procedures, and for the publication of this report.

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