Case report

Capillary leak syndrome in a patient with cancer-associated anti-transcriptional intermediary factor 1γ dermatomyositis treated with rituximab

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ABSTRACT

Capillary leak syndrome (CLS) is a rare condition characterised by increased capillary permeability, with subsequent hypoalbuminaemia and hypotension, leading to an increased risk of shock and death. We present the case of a patient with anti-transcriptional intermediary factor 1γ dermatomyositis that developed CLS one week after starting treatment with rituximab and prophylactic co-trimoxazole. The patient was admitted to the Intensive Care Unit (ICU), recovered after treatment with intravenous immunoglobulin, albumin, and Ringer lactate, but died a month after the discharge due to a poorly differentiated hepatocarcinoma diagnosed in the ICU.

Introduction

Capillary leak syndrome (CLS) is a rare condition characterised by increased capillary permeability, leading to plasma and protein leakage into the interstitial space. The subsequent hypotension may lead to shock and death (1). Anaphylaxis, systemic inflammatory response syndromes (including sepsis), angioedema, venoms, drug-induced adverse events, and autoimmune diseases may lead to CLS (2-4), which is rarely idiopathic (5).

Case report

A 47-year-old man presented to our Unit in September 2020 complaining of muscle weakness, dysphagia, cutaneous rash, arthralgia, and low-grade fever in the previous two months. He had a history of eradicated hepatitis C infection. Heliotrope and malar rash, shawl sign, Gottron's papules and sign were noted. Manual muscle testing (MMT8) score was 135/150, serum muscle enzymes were increased, antinuclear antibodies (1:640, speckled pattern) and anti-transcriptional intermediary factor 1γ (TIF1γ) antibodies were positive. Magnetic resonance (MR) documented bilateral oedema of the iliopsoas and quadriceps femoris muscles, as observed in myositis. Swallowing tests confirmed oropharyngeal muscle dysfunction. Total-body computed tomography (CT), fluorodeoxyglucose positron-emission-tomography (FDG-PET)/CT, oesophagogastroduodenoscopy, colonoscopy, testicular and thyroid gland ultrasonography (US) were negative for occult neoplasms, although FDG-PET detected an abdominal lymph node, interpreted as reactive. A diagnosis of dermatomyositis was made, and three daily methylprednisolone 500 mg intravenous (IV) pulses were administered, followed by oral prednisolone 1 mg/kg/day (60 mg/day), with clinical improvement. After prednisolone tapering to 40 mg/day, the patient worsened, and two cycles of IV immunoglobulin (IVIg) 2 g/kg were administrated (October and November 2020). Due to skin and muscle involvement refractoriness, rituximab treatment (1.000 mg infusion) was started with prophylactic cotrimoxazole. One week later, the patient presented to the Emergency Department (ED) with facial rash and oedema (Fig. 1), interpreted as dermatomyositis-related skin involvement or allergic reaction to rituximab. Chlorphenamine 10 mg (intramuscular and then oral) was started, and prednisolone increased to 50 mg/day.

However, oedema worsened, and dyspnoea ensued. The patient presented again to the ED two days later. At that time, oedema involved the whole face and neck, and the erythema spread to

the superior third of the thorax. Sinus tachycardia was observed. The patient was admitted to our Unit and treated with IV methylprednisolone 40 mg twice daily and IV chlorphenamine 10 mg thrice daily. Blood workup revealed a progressive increase in haematocrit and leukocyte count, high d-dimers, decreased platelet count, fibrinogen and albuminemia (Fig. 2). Serum procalcitonin, blood cultures and SARS-CoV-2 polymerase chain reaction test were negative. Thrombotic thrombocytopenic purpura (TTP) diagnosis was made, based on ADAMTS13 deficiency and schistocytes at the blood smear. Plasma and platelet transfusions were started with good clinical response. Total body CT scan revealed pleural and pericardial effusions, ascites, and a necrotic peripancreatic lymph node (31x30 mm). CLS was assumed. Supportive oxygen therapy was started, as well as IV albumin and Ringer lactate. Twelve days after the admission, the patient was in anasarca, severely hypotensive, tachycardic, tachypnoeic and hypoxemic despite 50 L/min oxygen therapy with a Venturi mask and a thoracentesis. The patient was admitted to the intensive care unit (ICU), where continuous positive airway pressure (CPAP) and IVIg were started (2g/kg). After successful intravascular volume reconstitution, diuretic therapy ensued. Anasarca resolved, and the patient became normotensive and euvolemic. The patient was readmitted to the Rheumatology Unit, and oxygen therapy was successfully reduced until suspension. Forty-five days after admission, a total-body CT documented enlargement of the peripancreatic lymph node (54 x 39 mm) and multiple hypodense hepatic lesions. Liver biopsy revealed poorly differentiated hepatocarcinoma that eventually led to the patient death, in March 2021.

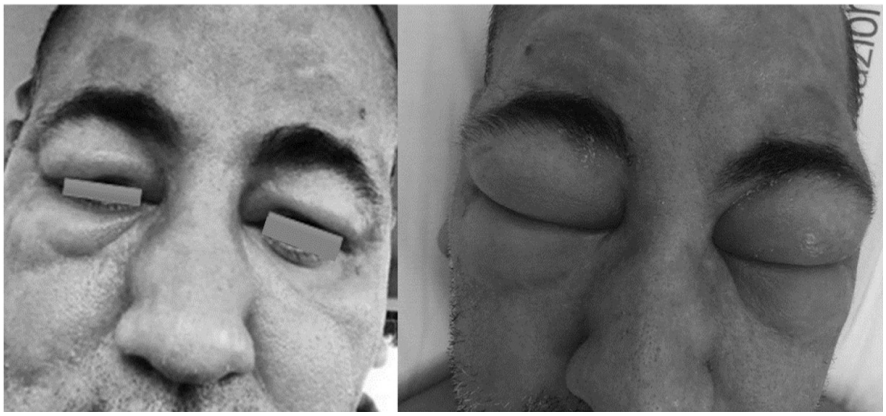

Fig. 1. Facial oedema occurring with erythema before presenting to the Emergency Department (on the left) and during the hospitalisation at the Rheumatology Ward (on the right).

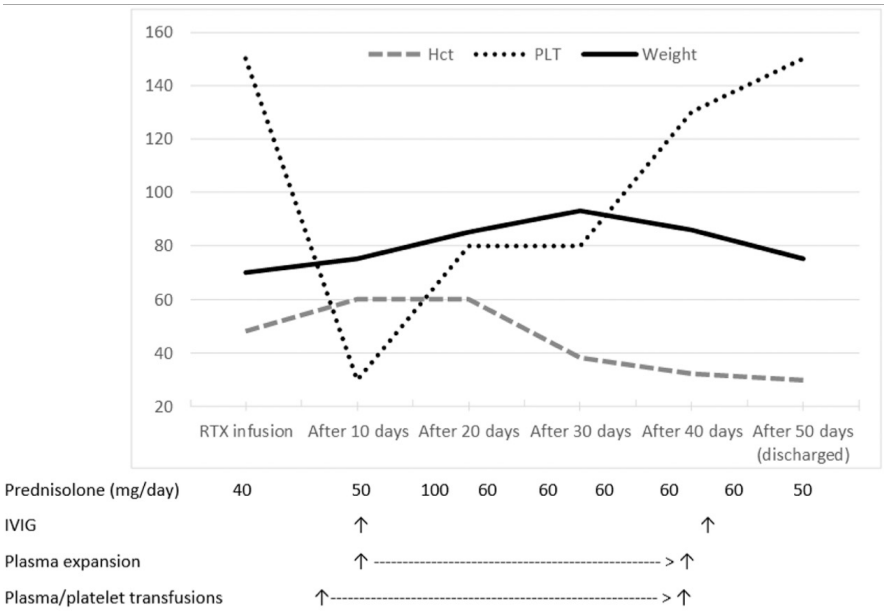

Fig. 2. Evolution of blood workup values and weight (in kilograms) throughout the course of the disease.
Hct: haematocrit; IVIg: intravenous immunoglobulin; PLT: platelet count; RTX: rituximab.

Discussion

CLS has been associated with cancer, including hepatocarcinoma (6), and autoimmune disorders (3, 4). Also, rituximab can induce a cytokine-mediated increase in capillary permeability, manifesting as CLS (7). Although the CLS trigger in our patient is not clear, the temporal association with rituximab seems to support its role as the inciting agent.

Prodromal symptoms/signs such as hypotension, haemoconcentration and peripheral oedema may precede more severe signs by one to two days (8), representing a precious window of opportunity to recognise CLS. The facial rash and oedema were initially ascribed to a dermatomyositis flare or an allergic reaction to rituximab. However, our patient displayed the typical CLS haemoconcentration since ED admission and TTP with severe thrombocytopenia. Acquired TTP has been suggested to be secondary to severe CLS since the loss of ADAMTS13 into the interstitial space could lead to severe serum deficit (9). Therefore, it is possible to hypothesise that, in some cases, the thrombocytopenia commonly observed in patients with CLS and cancer (6) may be due to an undiagnosed secondary TTP.

In conclusion, although we cannot definitively identify the trigger of CLS, clinicians should be aware of this possible complication when refractory and oedematous skin changes appear in patients with dermatomyositis, especially if associated with hypotension, haemoconcentration, and abnormal platelet count.

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