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CASE REPORT

Long Term Remission of Capillary Leak Syndrome Associated with Monoclonal Gammopathy with Progression to Multiple Myeloma After Autologous Stem Cell Transplantation: a Case Report and Review of the Literature

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ABSTRACT

Background: Clarkson's disease is a very rare entity characterised by acute episodes of systemic oedema and severe hypotension associated with paraproteinaemia. Its classical treatment relies on methylxanthine combined with terbutaline. Although this prophylactic therapy reduces the mortality rate, relapses are frequent. Eighty percent of patients with Clarkson's disease present with monoclonal gammopathy of unknown significance (MGUS). The risk of progression to multiple myeloma is 1% per year.

Case Description: Here, we present a 49-year-old woman who suffered multiple such episodes requiring treatment in the intensive care unit. Treatment with terbutaline and theophylline was ineffective. She was diagnosed with multiple myeloma (MM) 8 years after the first of these acute episodes. Antimyeloma treatment with bortezomib and dexamethasone was started, followed by autologous haemopoietic transplantation, with no further acute episodes since then.

Conclusion: Our case is, to our knowledge, unique because eradication of MM was followed by complete disappearance of acute episodes of capillary leakage. Our case report is also the first to support the use of bortezomib and dexamethasone in this setting. Furthermore, autologous peripheral blood progenitor cell transplantation consolidated the MM stringent complete remission achieving a very long progression-free survival (> 11 years) of both MM and Clarkson's disease.

Keywords: Capillary leak syndrome (CLS); Monoclonal gammopathy; Multiple mieloma; Autologous stem cell transplantation

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Key Summary Points

Clarkson's disease is a potentially fatal disorder characterised by recurrent acute life-threatening episodes of hypovolemic shock and generalised oedema, and it is frequently associated with monoclonal gammopathy of unknown significance (MGUS).

Our case report is the first to support the use of bortezomib and dexamethasone for capillary leak syndrome (CLS) associated with multiple myeloma.

The combination of bortezomib and dexamethasone plus consolidation with autologous peripheral blood progenitor cell transplantation led us to successfully achieve a stringent complete remission with very prolonged progression-free survival (> 11 years) of both multiple myeloma and Clarkson's disease.

INTRODUCTION

Idiopathic systemic capillary leak syndrome (SCLS), or Clarkson's disease, described in 1960 by Clarkson et al. [1], is one of a large group of rare syndromes now collectively referred to as "clinically significant monoclonal gammopathies" with a common feature: the presence of a monoclonal gammopathy [2]. The clinical manifestation consists of acute recurrent life-threatening episodes of generalised oedema, severe hypotension, haemoconcentration and hypoalbuminaemia [3–5]. Rare manifestations of this syndrome are renal damage and rhabdomyolysis due to increased compartment pressure and ischaemic myonecrosis [6, 7]. Chronic cases of this syndrome have been described [8, 9]. The presence of serum M-protein, mainly IgG kappa, is the only relevant laboratory abnormality during the resting phase between attacks. Pathophysiologically, this syndrome is caused by a sudden and reversible increase in capillary permeability, with a rapid shift of plasma from the intravascular to the extravascular compartment, resulting in hypovolaemic shock. A humoral factor promoting this hyperpermeability has been proposed, including interleukin-6 (IL-6), the chemokine CSCL-10 and angiopoietin-2 [10, 11] acting at the level of vascular endothelial catheterin [12]. The role, if any, of the paraprotein present in most SCLS sera is unknown. The development of multiple myeloma has been described [13].

CASE PRESENTATION

Our patient suffered the first episode in April 2002, at the age of 29 years: hypovolemic shock, haemoconcentration, rhabdomyolysis, massive oedema and acute renal failure requiring treatment in the intensive care unit. She was studied in the internal medicine department. Monoclonal IgG lambda was detected in serum. Bone marrow aspirate showed 3% clonal plasma cells. She was diagnosed with SCLS. She started prophylactic treatment with theophylline and terbutaline. Despite this treatment, she suffered a second acute episode in October 2002. The third acute attack occurred in May 2003, again despite treatment with theophylline and terbutaline. A fourth acute episode occurred in December 2004, following a febrile episode. She was treated with low-dose prednisone for 1 week. A fifth episode occurred in April 2005, and empirical treatment with dexamethasone was started for its anti-myeloma activity (40 mg daily for 4 days every 2 weeks for 3 months, followed by maintenance doses of 40 mg daily for 4 days every month). This treatment was discontinued in November 2007. A sixth acute episode occurred in December 2007. Treatment with verapamil was started. Two new episodes occurred in December 2008 and April 2009. In October 2010, the patient was diagnosed with multiple myeloma [serum lambda monoclonal IgG 3 g/dl, 11% clonal plasma cells with t(4;14) and retinoblastoma (RB), left iliac lytic lesion with negative spine MRI and PET]. After expert clinical advice, treatment was started with intravenous cyclophosphamide 300 mg/m^2 days 1, 8, 15 and 22, bortezomib 1.3 mg/m^2

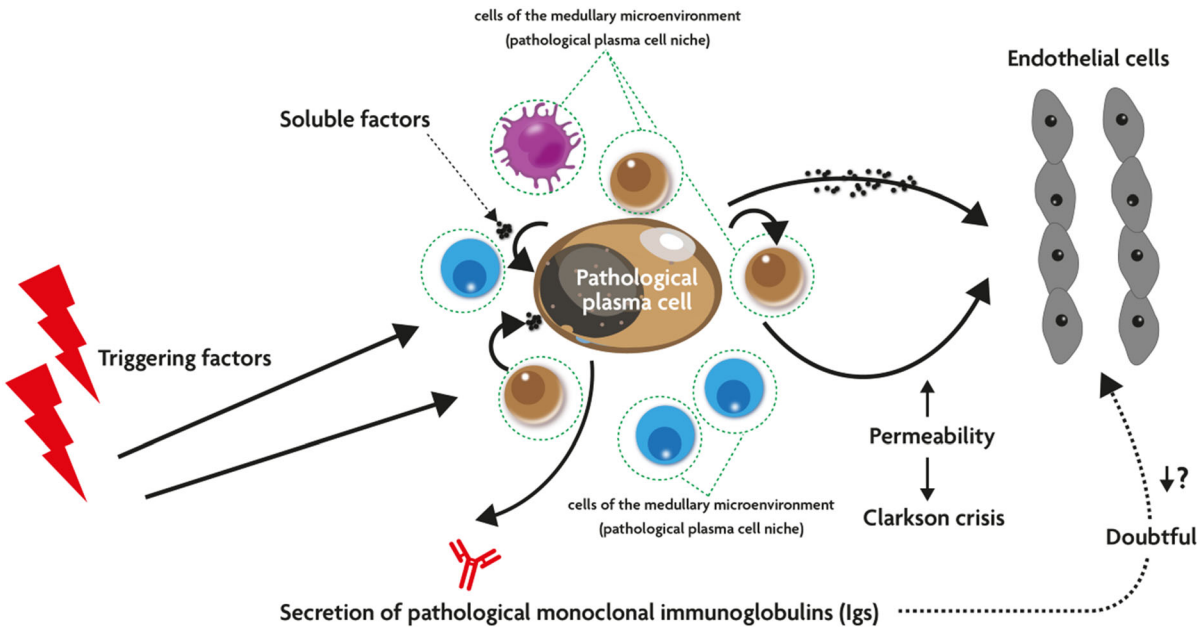

Fig. 1 PPCs themselves, the niche cells or both release soluble factors that act on the endothelium, rapidly increasing its permeability, triggering the crisis. *PPCs* pathogenic plasma cells

days 1, 4, 8 and 11, and oral dexamethasone 40 mg days 1, 4, 8 and 11 in December 2010. After the first cycle, a ninth acute episode occurred in January 2011, controlled in the intensive care unit (as all previous episodes). She has subsequently received five more cycles, with no further episodes.

In July 2011, the patient underwent autologous peripheral blood progenitor cell transplantation (melphalan 200 mg/m^2 as conditioning regimen). At day + 100, re-

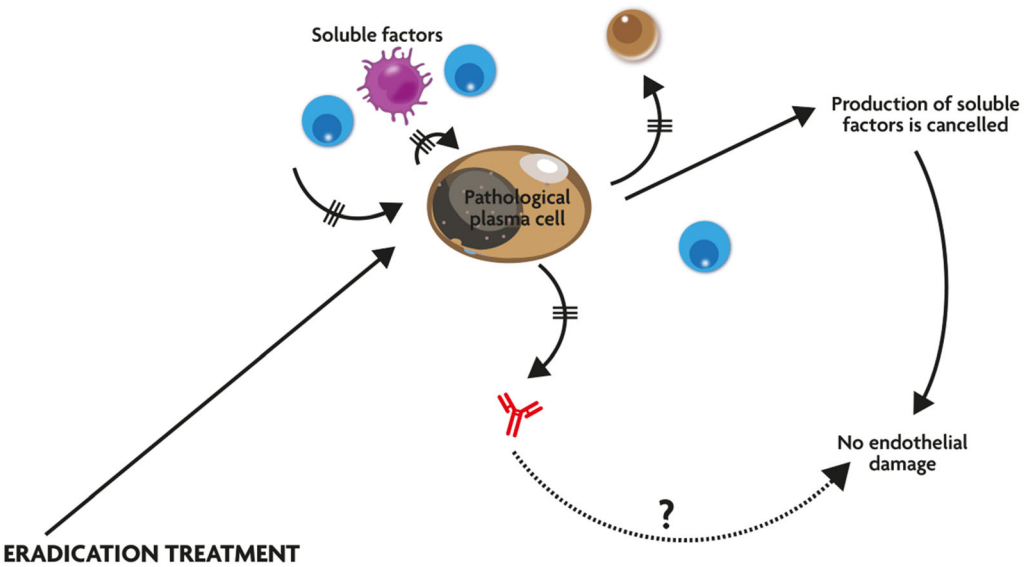

Fig. 2 Abrupt shutdown of the endothelium

evaluation of the myeloma showed a stringent complete remission. Eleven years later, the patient is maintaining this response and has had no new acute attacks of CLL.

DISCUSSION

SCLS is a very rare severe disease with an acute presentation that includes five typical phases, prodromal, haemoconcentration, shock, leak phase and post-leak phase, due to the restoration of the integrity of the vascular wall. Diagnosis is clinical and is based on the presence of hypotension, haemoconcentration and hypoalbuminaemia. A monoclonal paraprotein is found in 75–82% of patients. Initial treatment is based on methylxanthine combined with terbutaline. Although this prophylactic therapy reduced the 5-year mortality rate [14], relapses are frequent [15], as observed in our patient. In recent years, the use of intravenous immunoglobulins (IVIG) as prophylaxis (and in the treatment of acute episodes) has shown great efficacy, improving patient survival [16, 17].

Eighty percent of patients with Clarkson's disease have monoclonal gammopathy of unknown significance (MGUS). The risk of progression to multiple myeloma is 1% per year. In our case, SCLS was associated with MGUS that progressed to symptomatic MM during disease progression [13]. Our case is, to our knowledge, unique because eradication of MM was followed by complete disappearance of acute episodes of capillary leakage. This treatment was proposed by Druey and Greipp in 2010, but without data to support the hypothesis [18]. We now support it.

We hypothesise that normal and pathological plasma cells survive because of their medullary niche in which they interact bidirectionally with surrounding cells [19–21]. They also produce monoclonal immunoglobulins, which are doubtfully pathogenic in Clarkson. Crisis stimuli can stimulate Clarkson's pathogenic plasma cells (PPCs) directly or via niche cells. Subsequently, the PPCs themselves, the niche cells or both release soluble factors that act on the endothelium, rapidly increasing its permeability, triggering the crisis (Fig. 1).

Once the secretion of these substances ceased or was neutralised by homeostatic mechanisms of the vascular wall (or because of anti-myeloma treatments), the endothelium also shut down abruptly (Fig. 2).

SCLS has a high mortality despite the use of IVIg (5- and 10-year overall survival rates of 78% and 69%, respectively). Therefore, we propose the use of anti-myeloma therapy in patients with frequent and severe attacks, especially in those who do not respond to IVIg. A similar strategy has been adopted in some clinically significant cases of MGUS, with good results [2]. Elevated serum levels of Syndecan-1 (CD138) and MYOF mutation could also help in the diagnosis of this entity [22, 23].

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Declarations

Conflict of Interest. Gerardo Hermida, Rodolfo Alvarez-Nuño, Jesús San Miguel-Izquierdo, Santiago González-Quijada and Tomás José González-López have nothing to disclose.

Ethical Approval. A written informed consent was obtained from the patient to have the permission to publish her clinical history.

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