Autoimmunity Reviews 10 (2011) 664–668

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Management of refractory cases of catastrophic antiphospholipid syndrome

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ARTICLE INFO

Available online 1 May 2011

Keywords:
Catastrophic antiphospholipid syndrome
Refractory
Anticardiolipin antobodies
Lupus anticoagulant
Rituximab
Defibrotide
Eculizumab

ABSTRACT

The catastrophic variant of the antiphospholipid syndrome (APS) is the most severe form of APS with acute multiple organ involvement and small vessel thrombosis. Refractory catastrophic APS may be defined as patients who did not respond to first-line therapies (anticoagulation, glucocorticoids and plasma exchange and/or intravenous immunoglobulins) and died in the acute phase of the episode or patients with recurrent episodes of catastrophic APS. The purpose of this review is to focus on the current management of these refractory patients and some of the potential new therapeutic approaches.

Contents

1. Introduction

The catastrophic variant of the antiphospholipid syndrome (APS) is characterized by thrombosis in multiple organs developing over a short period of time in the presence of antiphospholipid antibodies (aPL) [1]. The hallmark of catastrophic APS is the histopathological evidence of small vessel occlusions. In other words, catastrophic APS is a thrombotic microangiopathic condition, characterized by a diffuse thrombotic microvasculopathy [2].

However, the explanation as to why some patients developed classic APS in form of deep venous thrombosis or cerebrovascular accident as the two main venous and arterial clinical manifestations whereas a minority of patients with aPL developed a multiorgan failure syndrome are unknown.

At present, there are no studies on the pathophysiological mechanisms of catastrophic APS. Possibly, some of the features of catastrophic APS may respond to the manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive cytokine release from affected and necrotic tissues (3).

The current treatment of catastrophic APS is based on the following statements. Besides identification and treatment of any precipitating factor, first-line therapies should always include the combination of anticoagulation (AC) against thrombosis plus glucocorticoids (GC) against manifestations of SIRS plus plasma exchange (PE) and/or intravenous immunoglobulins (IVIG) against both directly aPL and SIRS [4]. However, new therapeutic modalities (i.e.,

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doi:10.1016/j.autrev.2011.04.031

biologic therapies) may have a role in the treatment of these patients. Some of them have been used in catastrophic APS although the number of patients treated is too low to draw significant conclusions.

2. Definition of refractory catastrophic APS

It is difficult to define what does the term refractory mean in the context of catastrophic APS. However, we will use this term to refer to patients who died despite the use of first-line therapies or to patients suffering recurrent episodes of catastrophic APS.

2.1. Mortality rate in the catastrophic APS

Data from the "Catastrophic APS Registry", an International registry of patients with catastrophic APS ("CAPS Registry") created in 2000 by the European Forum on Antiphospholipid Antibodies, has enabled us to know the therapeutic regimen with higher survival rate. In this sense, the combination of AC plus GC plus PE (77.8% versus 55.4%, $p = 0.083$), followed by AC plus GC plus PE and/or intravenous immunoglobulins (IVIG) (69% versus 54.4%, $p = 0.089$) has showed the higher recovery rate. More interestingly, the mortality rate decreased from 53% in the patients diagnosed before 2000 to 33.3% in those diagnosed from 2001 to February 2005 ($p = 0.005$; odds ratio [OR] 2.25; 95% confidence interval [CI], 1.27 to 3.99). This reduced mortality was related to the more frequent use of combined treatment with AC plus GC plus PE and/or IVIG in the second period. ($p = 0.025$; OR 2.26; 95% CI 1.10–4.62) [5].

2.2. Relapsing catastrophic APS

Considering refractory catastrophic APS also as patients with recurrent episodes of catastrophic APS ("relapsing" catastrophic APS), our group documented in 2008 three patients with seven episodes [6]. The median time between the episodes of catastrophic APS was 12.5 months (range, 2.5–48). From the clinical point of view, the most significant manifestations were renal involvement (present in 5 episodes), followed by central nervous system and cardiac involvement (4 episodes each), and pulmonary and hepatic involvement (3 episodes each). Interestingly, thrombocytopenia (platelet count less than 50×10^9/L) and red cell fragmentation (schistocytes) were reported in all 7 episodes. Laboratory features of definite microangiopathic hemolytic anemia (MHA) (hemolytic anemia, schistocytes on peripheral-blood smears, and negative Coombs test associated to thrombocytopenia) were present in 5 of 7 episodes of relapsing catastrophic APS. The remaining episodes presented with thrombocytopenia, schistocytes, and anemia but data concerning hemolysis and Combs test were not reported. AC (with unfractioned heparin), CS (as intravenous pulses or in high doses), and PE were the most frequent treatment, used in all of the episodes. IVIG were used in 5 episodes, cyclophosphamide in 3 episodes and rituximab in 2 episodes.

We have also collected 9 additional cases out of 282 (3%) patients from the "CAPS Registry" with 35 episodes of catastrophic APS (6 patients presented 2 recurrences, 2 patients suffered 3, and one patient developed 17) [7]. Unfortunately, the last patient was not included in the descriptive analysis because their clinical and immunological characteristics were not fully reported. A total of 18 episodes were analyzed. In 9 (50%) episodes, a precipitating factor was identified. The most remarkable precipitating factor, found in 5 (28%) episodes, was infection. The other precipitating factor was related with incomplete anticoagulation treatment and was identified in 4 (22%) episodes. Brain, kidney, heart and lung were the most common organs involved. The frequencies of the major demographic, clinical, and immunological features of relapsing catastrophic APS were also comparable to the most recent review of catastrophic APS derived from the "CAPS Registry" [8]. There were no differences in the organ involvement at time of catastrophic APS episode. Interestingly, laboratory features of MHA were present in 13/18 (72%) episodes (definitive in 9, corresponding to 4 patients and probable in 4, corresponding to 2 patients). Three relapses did not present with features of MHA and in the remaining 2, these data were not reported. The prevalence of MHA features in patients with catastrophic APS from the "CAPS Registry" who relapsed was significantly higher than in those who did not relapse (72% vs. 7%; $p < 0.0001$; 95% CI 0.459–0.841). All episodes were treated with AC and CS, PE were used in 11 episodes, IVIG in 7, cyclophosphamide in 4, and rituximab in 2 episodes. Three (38%) patients died.

Taking into account this higher prevalence of MHA laboratory features, a hypothesis of an association between MHA and relapsing catastrophic APS could be established [9]. Besides, thrombotic microangiopathy is the hallmark of thrombotic thrombocytopenic purpura (TTP). A severe deficiency of von Willebrand factor (vWF)-cleaving protease, 1-5ADAMTS13 is found in most patients with TTP, and this deficiency is thought to be responsible for platelet aggregation and microthrombi formation in the circulation, which in turn cause typical thrombotic microangiopathies to develop [10]. In this sense, it is also possible that secondary deficiency of ADAMTS13 may account for the development of microthrombi formation in disease states other than TTP, such as catastrophic APS. Austin et al. [11] evaluated ADAMTS13 and vWF in 68 patients with aPL including 52 with APS. Thirty-three (49%) patients had IgG anti-ADAMTS13 antibodies with 12 of these patients having reduced ADAMTS13 activity. In addition, low ADAMTS13 activity (median 34%) was demonstrated in 33% of them, all with normal ADAMTS13 antigen levels consistent with dysfunctional ADAMTS13. They did not find associations between the ADAMTS13 abnormalities and any aPL profile or thrombotic/obstetric features, although this study was not adequately powered to address clinical associations. These findings highlight that ADAMTS13 autoantibodies and ADAMTS13 dysfunction can occur in APS, although the clinical significance remains undetermined. Until now, there has not been any published case report of relapsing catastrophic APS with ADAMTS13 deficiency.

3. Potential therapeutic modalities

In this section, we refer to treatments used in patients with catastrophic APS in an anecdotally form such as rituximab, defibrotide and eculizumab.

3.1. Rituximab

Rituximab is a chimeric monoclonal antibody against a surface antigen expressed by the B cells named CD20. Rituximab is approved for the treatment of patients with relapsed or refractory low-grade or follicular, CD20+, B-cell non-Hodgkin lymphoma and for the treatment of rheumatoid arthritis. Recently, 188 patients with systemic lupus erythematosus (SLE) treated with rituximab have been described [12]. Overall, more than 90% of them showed a significant improvement in one or more of the systemic SLE manifestations. Specifically, 103 patients with lupus nephritis showed an overall rate of therapeutic response of renal involvement of 91%. A quarter of patients had adverse events, being infections the most frequent (19%).

Erre et al. [13] collected 12 patients with APS treated with rituximab due to recurrent thrombosis or refractory thrombocytopenia. With a follow-up ranging from 10 to 36 months, the majority of patients remained free of thrombosis following rituximab introduction. More interestingly, 8 patients showed normalization or reduction of aPL titers.

At present, 9 patients with catastrophic APS have been treated with rituximab [14–21]. The main clinical and laboratory characteristics are depicted in Table 1. Specifically, they were seven women and