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# Catastrophic antiphospholipid syndrome associated with systemic lupus erythematosus treated with rituximab: case report and a review of the literature

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## ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS) is a rare, acute, life-threatening form of antiphospholipid syndrome. In the last several decades there has been a significant improvement in the treatment of patients with CAPS, but the overall mortality is still very significant. The use of rituximab has been reported in the treatment of refractory cases of CAPS but the data are still scarce and inconclusive. We report a case of 47-year-old male patient with long standing SLE and secondary APS who presented with acute thromboembolic incident (partial thrombosis of superior mesenteric artery). During the first week of his hospitalization he met the criteria for probable CAPS. He was treated with anticoagulants, glucocorticoids, intravenous immunoglobulins and systemic antibiotics. Finally he was treated with rituximab. There was no response to the implemented treatment and he eventually died. Autopsy showed evidence of small vessel thrombosis in the lung microvasculature. With this the criteria for definitive CAPS were fulfilled. To our knowledge, at present time, this is the first ever reported case of definitive CAPS associated with SLE treated with rituximab. There is a great need for further investigation to evaluate the effectiveness of rituximab in treatment of CAPS.

**Keywords:** Systemic Lupus Erythematosus; Rituximab; Antiphospholipid Syndrome

## INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by arterial, venous and small vessel thrombosis and/or pregnancy morbidity occurring in patients with persistently positive antiphospholipid antibodies (aPL).

Catastrophic antiphospholipid syndrome (CAPS) is the most severe, life-threatening variant of APS<sup>1</sup>. It is characterized by small vessel thrombosis developing over a short period of time in multiple organs, resulting in multiorgan dysfunction and often failure, with very high mortality rates. In 2002 the proposed preliminary classification criteria for CAPS were accepted (Table I)<sup>2</sup>.

Etiology and the pathogenesis of CAPS are unknown at present. It has been hypothesized that a specific trigger or multiple triggers, like infection, anticoagulation withdrawal followed by surgery or biopsy, tissue necrosis or thrombosis in patients with positive aPL can lead to cytokine overproduction with development of systemic inflammatory response syndrome and diffuse small vessel thrombosis resulting in CAPS<sup>3</sup>.

Early and correct diagnosis and improvement in therapy has led to decrease in mortality rates from 53% in patients diagnosed before 2001 to 33% in those diagnosed between 2001 and 2005<sup>4</sup>. Improvement in therapy is the consequence of using combined therapy comprised of anticoagulation, glucocorticoids, plasma exchange and/or intravenous immunoglobulins with identification and treatment of any precipitating factor as a first line of therapy<sup>5</sup>. The use of cyclophosphamide is associated with increased survival rates in patients with systemic lupus erythematosus associated CAPS (SLE-CAPS) and has a worsening effect on the survival of patients with primary CAPS (P-CAPS). Generally patients with SLE-CAPS have a higher mortality risk than patients with P-CAPS<sup>6</sup>. Despite the use of first line therapy there is still a significant proportion of patients who will suffer from recurrent episodes of CAPS or who will

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**TABLE I. PRELIMINARY CLASSIFICATION CRITERIA FOR CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME\*****Preliminary classification criteria for catastrophic antiphospholipid syndrome**

Criteria:

1. Evidence of involvement of three or more organs, systems and/or tissues.
2. Development of manifestations simultaneously or in less than a week.
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies and/or anti-Beta2-glycoprotein I antibodies)

**Definite catastrophic APS**

All four criteria

**Probable catastrophic APS**

All four criteria, except for only two organs, systems and/or tissues involvement

All four criteria, except for the absence of laboratory conformation at least six weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS

- 1, 2 and 4
- 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation

APS, antiphospholipid syndrome; aPL, antiphospholipid antibodies  
\*adapted from Asherson<sup>2</sup>

die from it being defined as having refractory CAPS<sup>7</sup>. New biologic drugs such as rituximab, defibrotide and eculizumab have been used in treatment of patients with CAPS and refractory CAPS but there are no studies or guidelines for the usage of these agents.

Rituximab is a chimeric murine/human monoclonal antibody directed against the B-lymphocyte surface antigen CD20. There are no available studies about the use of rituximab in the treatment of CAPS. There are only a few case reports and one systematic review so it is still not possible to determine the influence of rituximab on the mortality rate of patients with CAPS. Nevertheless there is a general agreement that it could have a role in its treatment<sup>8</sup>. We present a case of CAPS treated with rituximab in patient with SLE. To our knowledge, our patient is the first ever to be reported with definite CAPS associated with SLE and treated with rituximab.

**CASE REPORT**

We are presenting a 47-year-old male patient with a 13 year history of systemic lupus erythematosus and secondary antiphospholipid syndrome. He initially presented with deep venous thrombosis of right leg,

non-erosive arthritis, discoid rash, lymphopenia, positive titers of anti-nuclear antibodies (ANA) and anti-dsDNA, anticardiolipin IgG and IgM antibodies and positive lupus anticoagulant (LAC). Despite combined immunosuppressive drugs (chloroquine, moderate to high dose of prednisone and cyclophosphamide during one period for suspected central nervous system lupus) and adequate anticoagulant therapy he experienced several arterial and venous thrombotic events over the time. Given the refractory course of APS combination of *oral* anticoagulant (warfarin) and antiplatelet (acetylsalicylic acid) therapy was implemented.

Three months before his last hospitalization, he developed acute pain and lividness of his second left toe. Angiography was performed and occlusion of distal part of left anterior tibial artery was found. Amputation of ischemic toe was eventually performed. Taking into account the extremely high titers of antiphospholipid antibodies (positive LAC; anticardiolipin IgG antibodies - highly positive; anticardiolipin antibodies IgM - weakly positive; anti-beta2-glycoprotein-I IgG antibodies - highly positive) and refractory course of the disease with limited further therapeutic options, two plasmapheresis were performed with the goal of lowering the titers of aPLs. Patient recovered well and was



**FIGURE 1.** Multi-slice computer tomography (MSCT) angiography of the abdomen and pelvis (with i.v. contrast agent): A) Normal diameter and flow through superior mesenteric, splenic and portal veins. Normal size and structure of the kidneys, spleen, pancreas and biliary tract. B) Partial thrombosis, with narrowing of the lumen (from approx. 6.6 to approx. 1.7 cm), of the superior mesenteric artery approx. 2 cm from the starting point.

dismissed with the recommendation for oral methylprednisolone (0.75 mg per kg/day with slow tapering of the dose to 0.5 mg per kg/day), cyclophosphamide (2 mg per kg/day), acetylsalicylic acid (100 mg per day) and warfarin (targeted INR 2-3).

One month later he was admitted due to very strong acute abdominal pain. On first examination in the emergency department he was cardiorespiratory stable, afebrile and his abdomen was distended, painful but there were no clinical signs of acute peritonitis. Laboratory results showed anemia (Hb 70 g/L, normal range 138-175 g/L), thrombocytopenia (T  $78 \times 10^9/L$ , normal range  $158-424 \times 10^9/L$ ), prolonged activated partial thromboplastin time (aPTT 55.1 s, normal range 24-33 s), prothrombin time in therapeutic range (INR 2.2) with normal creatinine and urea with mildly elevated aminotransferases (AST 49 U/L, normal range 11-38 U/L and ALT 82 U/L, normal range 12-48 U/L) and  $\gamma$ -GT (56 U/L, normal range <177 U/L) and normal alkaline phosphatase and total bilirubin with elevated C-reactive protein (67,7 mg/L, normal range 0-5 mg/L). Additional tests were performed and mesenteric CT angiography showed a partial thrombosis of superior mesenteric artery with 75% lumen occlusion (Figure 1).

At that time the decision was made that the urgent surgical or percutaneous endovascular intervention would not be carried out. The option of thrombolysis was also discussed but was rejected. He was treated with wide spectrum antibiotics, pulses of methylprednisolone and periodic transfusions of packed red blood cells. Warfarin was replaced with low molecular weight heparin. During the next few days pain in the abdomen persisted but there was no signs of acute peritonitis or intestinal necrosis. There was a gradual decline in acute phase reactants accompanied with an significant elevation in liver enzymes and creatinine with mild proteinuria. There was a severe decline in the platelets count (min.  $6 \times 10^9/L$  requiring transfusion) and hemoglobin (min. 75 g/L when transfusion was conducted) with prolongation of aPTT. LAC and IgG anticardiolipine and anti-beta2-glycoprotein I antibodies were again positive in high titer. Analysis of the bone marrow was performed and showed a regular trilineage hematopoiesis. Autoimmune hemolytic anemia and heparine induced thrombocytopenia were excluded. Initial blood smear showed no schistocytes but regarding the above, mentioned and elevated levels of lactate dehydrogenase, microangiopathic anemia was suspected. There were no clinical or laborato-

**TABLE II. CRITERIA FOR DIAGNOSIS OF DEFINITIVE CAPS IN OUR PATIENT**

Involvement of three or more organs, systems and/or tissues (criteria 1) simultaneously or in less than a week (criteria 2)				Laboratory confirmation of the presence of aPLs (LAC and/or aCLs) – criteria 3	Confirmation by histopathology of small vessel occlusion in at least one organ or tissue – criteria 4
Kidney	Reference	Admission	Relevant change in first week	Positive LAC, aCL-IgG (65 GPL-U/ml) and aβ2-GPI (112 RU/ml)	aβ2- GPI small vessel occlusion in lung sample from autopsy
	creatinine (79-125 μmol/L)	96	160		
	urea (2.8-8.3 mmol/L7,6)	13,2			
proteinuria (negative++)	(0,75 g/L)				
Hepatic	AST (11-38 U/L)	49	184		
	ALT (12-48 U/L)	82	243		
	γ-GT (< 177 U/L)	56	84		
	T. bilirubine (3-20 μmol/L)	9	26		
Partial thrombosis of superior mesenteric artery	Confirmed with MSCT angiography at admission (Figure 1)				
Other findings supporting the diagnosis of CAPS	prolonged activated partial thromboplastin time microangiopathic anemia and thrombocytopenia				
FULFILLMENT OF 1st AND 2nd CRITERIA				FULFILLMENT OF 3rd CRITERIA	FULFILLMENT OF 4th CRITERIA
DIAGNOSIS OF PROBABLE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME					
DIAGNOSIS OF DEFINITIVE CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME					

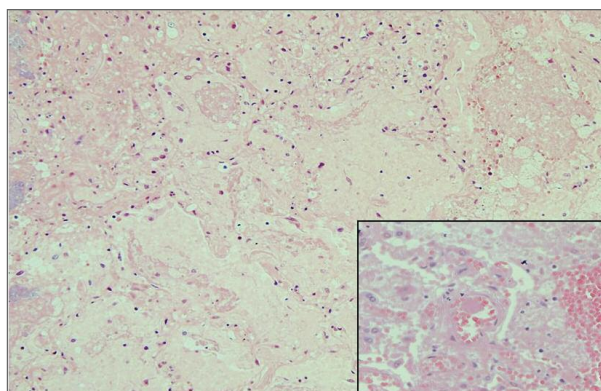
CAPS, catastrophic antiphospholipid syndrome; aPL, antiphospholipid antibodies; aCL, anticardiolipin antibodies; LAC, lupus anticoagulant; aβ2-GPI, antiβ2 glycoprotein 1; AST, aspartate aminotransferase; ALT, alanin aminotransferase; γ-GT, gamma-glutamyl transferase; MSCT, multislice computed tomography

ry sings of SLE activity. The diagnosis of CAPS was made (Table II) and intravenous immunoglobulines in dose of 0.4 g/kg/day for five days were added to the therapy.

With combined therapy for CAPS the patient was stable but the permanent deterioration in renal function was recorded with permanent refractory thrombocytopenia. Three weeks after IVIGs were introduced to the therapy two doses of rituximab (500 mg i.v.) were administered within a 7-day interval. There was no therapeutic response on administered therapy and further deterioration of renal function with persisting thrombocytopenia and anemia were recorded. Six day after the administration of the second dose of rituximab

patient become acutely dyspneic developing partial respiratory insufficiency with the rise in serum acute phase reactants so he had to be moved to the intensive care unit. Computed tomography of the lungs was made and bilateral ground-glass infiltrates with zones of dense consolidation were verified. Bronchoscopy was also made and *Candida albicans* and *Streptococcus* species were isolated from lavage fluid. Cytomegalovirus DNA ( $1.78 \times 10^3$  copies/ml) was detected in plasma using quantitative polymerase chain reaction (PCR) test. Therapy with piperacillin plus tazobactam, teicoplanin and fluconazole was initiated. Because of the possibility of CMV pneumonia therapy with gan-





**FIGURE 2.** Hematoxylin and eosin stain, objective 10x, inset objective 40x. Presentation of infarcted (necrotic) area of the lung where parenchymal architecture can hardly be recognized, some alveolar spaces in the upper parts are filled with abundant fibrin, interalveolar septa completely necrotic, somewhere even completely missing. Small blood vessel with the remnant of fibrinous thrombus in the middle of inset figure, favoring thrombosis as the most probable cause of pulmonary hemorrhagic infarction in our patient.

cyclovir was also applied. Partial clinical improvement with gradual decline in acute phase reactants was achieved but with persisting prolongation of aPTT, severe thrombocytopenia and anemia demanding periodic transfusions of blood products. Few days later significant decline in renal function with hyperkalemia, demanding the start of hemodialysis, with severe pancytopenia (L 0.5, Hb 76, T 10) and raise in acute phase reactants were recorded. Transfusions of blood products were given together with granulocyte colony-stimulating factor (G-CSF) filgrastim. Quantitative CMV PCR plasma test was repeated and came back negative so gancyclovir was excluded from therapy. Despite all measures taken, the patient was permanently pancytopenic, in poor general condition. Soon he became hemodynamically unstable and despite supportive measures eventually died.

The autopsy was performed and evidence of small vessel thrombosis was found in the lung microvasculature (Figure 2). The criteria for the definite CAPS were fulfilled.

## DISCUSSION

At the present time, there are no formal recommendations and guidelines and no studies on the use of rituximab in the treatment of CAPS. In the current literature

11 reports of 13 patients with CAPS treated with rituximab can be found<sup>8-19</sup>. Berman *et al.* in their systematic review included 9 more patients whose clinical cases were never published<sup>8</sup>. Only 2 of the published patients had CAPS associated with known or suspected systemic lupus erythematosus<sup>12,15</sup>. None of them met the criteria for definite CAPS. Our patient is the first ever to be reported with definite CAPS associated with SLE and treated with rituximab. Reported patient did not respond to the first line therapy for CAPS (glucocorticoides, anticoagulation and IVIGs). Treatment with rituximab was also ineffective (Table III) and the patient eventually died from refractory CAPS and complications.

It is important to emphasize a number of factors which probably contributed to the ineffectiveness of the used therapeutic protocol. As already mentioned, patients with CAPS associated with SLE have higher mortality rates than patients with primary CAPS. Treatment with cyclophosphamide has a favourable effect in the treatment of this subgroup of patients. In the described patient, cyclophosphamide and plasmapheresis were not used in the first line of therapy. Considering triple positive aPLs in high titers, not using the plasmapheresis could be an important contributing factor to the ineffectiveness of therapy. In addition it is important to say that the initially verified partial thrombosis of superior mesenteric artery was not resolved during the course of disease. This could be a very important factor in the sustaining of pathogenetical mechanisms responsible for development of CAPS consequently leading to ineffectiveness of used therapy. Furthermore, time between the first line of the therapy and the introduction of rituximab was relatively long. Prolonged course of the disease has led to the development of infectious complications that probably also contributed to sustaining pathogenetical mechanisms responsible for development of CAPS.

Whether more “aggressive” approach in dealing with sustaining factors and simultaneous use of all currently available therapeutic options as first line therapy would have led to a greater effect or would have resulted in earlier death is not possible to conclude at this time.

## CONCLUSION

We presented the first ever reported case of definitive CAPS associated with SLE treated with rituximab. In re-

**TABLE III. RELEVANT LABORATORY RESULTS BEFORE AND AFTER THE APPLICATION OF INTRAVENOUS IMMUNOGLOBULINS AND RITUXIMAB SUGGESTING THE FAILURE OF THERAPY**

	Hb	Platelets	Leucocytes	aPTT	creatinine	urea
Reference	138-175 g/L	158-424 x10 <sup>9</sup> /L	3.4-9.7 x10 <sup>9</sup> /L	24-33 s μmol/L	79-125 mmol/L	2.8mg/dl-8.3
<b>Time point</b>						
Diagnosis of CAPS	75 (packed RBC transfusion)	11 (platelets transfusion)	3.2	55.1	160	13.2
1st day of IVIg administration	90	11 (platelets transfusion)	6.7	32.6	170	14.1
Seven days after IVIg	93	61	8.3	35.1	196	18.2
1st day of RTX administration	91	29	6.5	–	362	–
Seven days after 1st RTX	91	18	9	–	496	25
Seven days after 2nd RTX	79	22	10.9	37	690	38.8

Hb, hemoglobin; aPTT, activated partial thromboplastin time; CAPS, catastrophic antiphospholipid syndrome; IVIg, intravenous immunoglobulin

ported patient combined therapeutic protocol (systemic antibiotics, glucocorticoids, anticoagulation, IVIGs) with rituximab was ineffective. We listed a number of factors that could have influenced the final result. The right timing for the introduction of rituximab is still uncertain. Whether the course of the disease would have been changed if the rituximab was started earlier is also unknown. There is a great need for further investigation to evaluate the effectiveness of rituximab in treatment of CAPS and to define the optimal regime and timing of implementation. It is also necessary to determine possible differences in effectiveness on patients with primary CAPS and CAPS associated with SLE and to determine possible other prognostic factors that could influence therapeutic decisions and results.

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