

# Catastrophic Antiphospholipid Syndrome: An Orchestra with Several Musicians

Ignasi Rodríguez-Pintó MD<sup>1,2</sup>, Alessandra. Soriano MD<sup>2</sup>, Gerard Espinosa MD PhD<sup>1</sup>, Yehuda Shoenfeld MD FRCP<sup>2</sup> and Ricard Cervera MD PhD FRCP<sup>1</sup>

<sup>1</sup>Department of Autoimmune Diseases, Hospital Clinic, Catalonia, Spain

<sup>2</sup>Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Since 1992, when Ronald Asherson described the first group of patients who developed a catastrophic form of the classic antiphospholipid syndrome [1], hundreds of patients presenting this devastating clinical variant of APS have been reported.

Currently, the editorial policies of many journals limit the publication of case reports; nonetheless, case reports and case series have an important role and are often the first warning of rare diseases. In fact, the series of cases of *Pneumocystis pneumoniae* reported in Los Angeles in 1981 were the first report of acquired immune deficiency syndrome (AIDS) [2]. In addition, in rare diseases, case series are the only way to pool data in order to achieve a sufficient sample size for epidemiological and clinical research. Catastrophic APS is a rare disease affecting around 1% of patients with APS [3].

Much of the current knowledge on CAPS was provided by the study of cases included in the CAPS Registry. The CAPS Registry was created in 2000 by the European Forum on Antiphospholipid Antibodies, a group of experts dedicated to perform international systematic studies

on antiphospholipid antibodies. This registry is a database in a web-based format that includes all patients with CAPS published or reported directly to the CAPS Registry Project Group. Their results are freely available on the web site: <https://ontocrf.costaisa.com/en/web/caps>.

In the present issue of this journal, De Meis et al. [4] describe the development of CAPS in four patients with malignancies; in all cases the catastrophic episode was triggered by an infection, and in two cases it followed a surgical procedure.

The pathophysiology of CAPS is not yet known. In fact, most patients with circulating aPL do not develop a thrombosis. This is why an exposure to a second hit has been proposed as mandatory to trigger the thrombotic event [5]. In CAPS, the main precipitating factors are infectious agents – found in about 50% of patients – as well as malignancies and surgical procedures responsible for almost 20% of the cases [6]. However, none of them has been found to be sufficient for the development of CAPS. Most likely, different conditions have a role in increasing the chance of a clot developing, by enhancing pro-thrombotic factors or by decreasing the effect of natural coagulation inhibitors.

The increased risk of thrombosis in patients with malignancy was first described in the 19th century by Trousseau [7], who observed the peculiar presence of thrombophlebitis in patients with cancer. Several explanations of this increased risk have been proposed, such as the secretion of pro-coagulant substances by tumor or

endothelial cells, blood flow stasis due to local vascular invasion, as well as immobilization, chemotherapy and central venous devices. Furthermore, malignancies and infections are well-known triggers of disseminated intravascular coagulation and have been linked to the development of circulating aPL [8].

The signaling and activation of the endothelial cells through Toll-like receptor 4, by both lipopolysaccharide and anti-β<sub>2</sub>-glycoprotein-I antibodies, have been proposed as possible mechanisms leading to the upregulation of pro-adhesive and pro-coagulant molecules in the cell surface, such as tissue factor [9]. Noteworthy, gram-negative bacteria have been found to be a leading trigger in CAPS. In this regard, a recent analysis of the CAPS Registry revealed that infections are the main trigger of CAPS in the pediatric age [10], possibly due to their higher incidence in childhood than other potential precipitating factors such as cancer, surgery or medications. One of the cases described by de Meis et al. is a 9 year old boy who developed CAPS in the setting of a *Klebsiella pneumoniae* bacteremia. Moreover, as CAPS in its acute presentation may resemble a severe sepsis, several authors investigated the possible common links between the two conditions, starting from the first years following the description of CAPS [11]. Among the potential common denominators, a plausible mechanistic role of ferritin in the pathogenesis of immune-mediated and autoimmune diseases, including CAPS and severe sepsis, was recently suggested [12].

In recent decades high levels of ferritin were found in the synovial fluid and serum

APS = antiphospholipid syndrome  
CAPS = catastrophic APS

aPL = antiphospholipid antibodies

of patients with rheumatoid arthritis, in patients with systemic lupus erythematosus, multiple sclerosis and different forms of myositis, and were associated with the disease activity in most of the studies [13-15].

In 2012 Agmon-Levin and colleagues [16] investigated ferritin levels in a population of patients with APS and CAPS. Among patients with APS, hyperferritinemia was associated with venous thrombosis, and cardiac, neurological and hematological manifestations. Interestingly, in the subgroup of patients with CAPS, hyperferritinemia was detected in 71% of subjects, whereas ferritin levels in this subgroup were significantly higher compared with APS-non-CAPS patients. Thus, CAPS has recently been included in the definition of the hyperferritinemic syndrome, in which four potentially life-threatening conditions characterized by extremely high levels of ferritin (namely, adult-onset Still disease, macrophage activation syndrome, CAPS, severe sepsis) merge in a single syndromic entity [12].

Undoubtedly, further investigations are needed to clarify the pathogenic mechanisms and the interplay of the cytokine storm, the endothelial damage and the activation of macrophages, that lead to such high levels of ferritin, as well as the exact role of serum ferritin in the inflammatory process in the course of CAPS.

The case series reported by de Meis et al. [4] represents a paradigmatic example

of the complex interplay of malignancies, infections and surgery, which contribute to an extremely rare but life-threatening condition called CAPS. The goal will be to pool samples of whole blood and serum of CAPS patients during the acute episode in order to perform mechanistic studies. This will lead to a better understanding of the role of each molecule, including ferritin, in the pathogenic sequence of the events taking part in this catastrophic condition, as in an orchestra. Furthermore, it might reveal new therapeutic targets for treatment of patients with APS and CAPS.

#### Correspondence

**Dr. I. Rodríguez-Pintó**

Dept. of Autoimmune Diseases, Hospital Clinic, Catalonia 08036, Spain

**email:** ignasirodriguezpinto@gmail.com

#### References

- Asherson RA. The catastrophic antiphospholipid syndrome. *J Rheumatol* 1992; 19 (4): 508-12.
- Centers for Disease Control. Pneumocystis pneumonia – Los Angeles. *MMWR Morb Mortal Wkly Rep* 1981; 30 (21): 250-2.
- Cervera R, Piette J-C, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002; 46 (4): 1019-27.
- de Meis E, Brandão LR, Capella FC, Garcia JAP, Gregory SC. Catastrophic antiphospholipid syndrome in cancer patients: an interaction between clotting, autoimmunity and tumor growth? *IMAJ* 2014; 16: 544-7.
- Ortega-Hernandez O-D, Agmon-Levin N, Blank M, Asherson RA, Shoenfeld Y. The pathophysiology of the catastrophic antiphospholipid (Asherson's) syndrome: compelling evidence. *J Autoimmun* 2009; 32 (1): 1-6.
- Cervera R, Bucciarelli S, Plasín MA, et al. Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the "CAPS Registry". *J Autoimmun* 2009; 32 (3-4): 240-5.
- Trousseau A. *Plegmasia alba dolens*. In: Lectures on Clinical Medicine, delivered at the Hotel Dieu, Paris, 1865: 654-712.
- Cervera R, Asherson RA, Acevedo ML, et al. Antiphospholipid syndrome associated with infections: clinical and microbiological characteristics of 100 patients. *Ann Rheum Dis* 2004; 63 (10): 1312-17.
- Meroni P, Chighizola C. Pathophysiology of the antiphospholipid syndrome (APS) Physiopathologie du syndrome des antiphospholipides. *Le Rev Méd Int* 2012; 33S: 2-4.
- Berman H, Rodríguez-Pintó I, Cervera R, et al. Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the "CAPS registry". *Autoimmun Rev* 2014; 13 (2): 157-62.
- Espinosa G, Cervera R, Asherson RA. Catastrophic antiphospholipid syndrome and sepsis. A common link? *J Rheumatol* 2007; 34 (5): 923-6.
- Rosário C, Zandman-Goddard G, Meyron-Holtz EG, D'Cruz DP, Shoenfeld Y. The hyperferritinemic syndrome: macrophage activation syndrome, Still's disease, septic shock and catastrophic antiphospholipid syndrome. *BMC Med* 2013; 11: 185.
- Zandman-Goddard G, Shoenfeld Y. Hyperferritinemia in autoimmunity. *IMAJ* 2008; 10 (1): 83-4.
- Zandman-Goddard G, Orbach H, Agmon-Levin N, et al. Hyperferritinemia is associated with serologic antiphospholipid syndrome in SLE patients. *Clin Rev Allergy Immunol* 2013; 44 (1): 23-30.
- Da Costa R, Szyper-Kravitz M, Szekanecz Z, et al. Ferritin and prolactin levels in multiple sclerosis. *IMAJ* 2011; 13 (2): 91-5.
- Agmon-Levin N, Rosário C, Katz B-SP, et al. Ferritin in the antiphospholipid syndrome and its catastrophic variant (cAPS). *Lupus* 2013; 22 (13): 1327-35.