The rheumatology/hematology interface: CAPS and MAS diagnosis and management

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Catastrophic antiphospholipid antibody syndrome (CAPS) and macrophage activation syndrome (MAS) are both life-threatening hematologic disorders that infrequently afflict patients with rheumatologic disease. CAPS is characterized by fulminant multiorgan damage related to small vessel thrombosis in the setting of persistent antiphospholipid antibodies. It can occur in patients with rheumatologic diseases such as systemic lupus erythematosus but can also affect patients who do not have rheumatologic disease. By contrast, the term MAS is applied when patients with rheumatologic disease develop hemophagocytic lymphohistiocytosis (HLH); therefore, patients with MAS have an underlying rheumatologic disease by definition. Similar to CAPS, HLH/MAS can have a fulminant presentation, but the pathogenesis and manifestations are different. In both CAPS and MAS, management generally includes but is not limited to immunosuppression with steroids. Fatalities are relatively common and morbidity is often significant. Early recognition of these disorders and initiation of timely treatment are important. More effective therapies for both syndromes are urgently needed.

Learning Objectives

- Recognize the features of catastrophic antiphospholipid antibody syndrome
- Become familiar with treatment options for macrophage activation syndrome

Catastrophic antiphospholipid antibody syndrome (CAPS)

Case 1: CAPS

A 44-year-old woman with antiphospholipid antibody syndrome presented to the emergency room with acute onset abdominal pain and right-sided chest pain after holding her rivaroxaban in anticipation of a sleeve gastrectomy. She was found to have inferior ST elevations and an elevated troponin. Cardiac catheterization showed no significant obstructive disease and no acute thrombosis. A ventriculogram showed a newly reduced ejection fraction of 40% with multiple wall motion abnormalities. There was no evidence of pulmonary embolism by computed tomography (CT) angiography of the chest. A percutaneous TandemHeart left ventricular cardiac assist device was placed. Endomyocardial biopsy showed areas of coagulative necrosis most consistent with ischemic myocardial injury. Within a few days of presentation, acute kidney injury related to acute tubular necrosis developed, possibly from microthrombosis, although a kidney biopsy was not performed. The patient also experienced 2 episodes of transient visual loss in the left eye, each lasting a few hours. Review of her medical records showed that she had tested positive for a lupus anticoagulant several times over a period of years and had had multiple venous thromboembolic events, 3 miscarriages, and 1 stillbirth. She did not have systemic lupus erythematosus.

Diagnosis of CAPS

CAPS is a rare, life-threatening disorder characterized by fulminant multiorgan damage related to small vessel thrombosis in the setting of persistent antiphospholipid antibodies. Diagnostic criteria for classification purposes have been proposed to identify patients with either definite CAPS or probable CAPS (Table 1).[1,2] There is a registry of cases,[3] and the aggregation of data in this registry has significantly advanced our knowledge of the disorder. CAPS usually has a precipitant, most often infection but sometimes surgery, malignancy, pregnancy, or another factor.[3] The organs most often involved include the kidney (eg, renal failure, proteinuria), lung (eg, acute respiratory distress syndrome, pulmonary embolism), brain (eg, stroke, encephalopathy), heart (eg, heart failure, myocardial infarction), skin (eg, livedo reticularis), and liver (eg, elevated liver enzymes).[3] Laboratory features other than the presence of antiphospholipid antibodies include thrombocytopenia in 67% of patients and schistocytes in 22%.[3] In approximately 50% of cases, patients newly diagnosed with CAPS do not have a history of the antiphospholipid antibody syndrome.[3] Because patients can have antiphospholipid antibodies that are not pathogenic, the presence of these antibodies, especially if they are low titer, needs to be interpreted with caution. Indeed, it is important to exclude diagnoses that can potentially mimic CAPS such as thrombotic thrombocytopenic purpura (Table 2).

Case 1 continued. The patient developed worsening heart failure, and a Thoratec extracorporeal percutaneous biventricular assist

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Off-label drug use: The off-label use of anakinra, canakinumab, eculizumab, rituximab, cyclosporine, mycophenolate mofetil, intravenous immunoglobulin, cyclophosphamide, and etoposide in treating CAPS and MAS is described.

Table 1. Preliminary criteria for classification of CAPS

1. Evidence of involvement of 3 or more organs, systems, and/or tissues
2. Development of manifestations simultaneously or in <1 week
3. Confirmation by histopathology of small-vessel occlusion in at least 1 organ or tissue (vasculitis may coexist, but significant thrombosis must be present)
4. Laboratory confirmation of the presence of antiphospholipid antibodies (two positive serologies at least 6 weeks apart)

Definite CAPS

All 4 criteria are present

Probable CAPS

All 4 criteria are present, except only 2 organs, systems, and/or tissues are involved

All 4 criteria are present, except for the absence of laboratory confirmation of antiphospholipid antibodies

Only criteria 1, 2, and 4 are met

Only criteria 1, 3, and 4 are met, with development of a third event more than 1 week from but within 1 month of presentation, despite anticoagulation

device was placed. Pathologic examination of tissue from the left ventricular apex revealed organizing thrombi in small vessels. At this point, a diagnosis of CAPS was felt to be likely, with cardiac, renal, and neurologic manifestations. However, formal classification according to the criteria outlined in Table 1 was challenging because clinical judgment is required, and available information about the case was incomplete. In general, the requirement for thrombosis (criteria 1 in Table 1) is met if there is clinical evidence of vessel occlusion confirmed by imaging techniques when appropriate. However, for the purposes of the classification scheme, renal involvement is defined as a 50% increase in serum creatinine, severe systemic hypertension, and/or proteinuria.[1] In this patient's case, hypotension related to cardiac dysfunction was an alternative explanation for the acute kidney injury and therefore the patient fulfilled criteria for either definite CAPS or probable CAPS, depending on the clinical impression. In patients with preexisting antiphospholipid antibody syndrome who develop CAPS, 60% have primary antiphospholipid antibody syndrome,[3] as seen here.

Pathogenesis of CAPS

The pathogenesis of CAPS remains somewhat obscure, but antiphospholipid antibodies and complement activation are felt to play a central role. In the setting of infection, molecular mimicry may provide the trigger that unleashes the thrombotic storm characteristic of CAPS.[4] Regardless of the trigger, however, antiphospholipid antibodies have been postulated to mediate disease by activating platelets, inhibiting anticoagulants, inhibiting fibrinolysis, and activating the classical complement pathway; in addition, the alternative complement pathway can be activated.[5,6] Complement activation is expected to contribute to a prothrombotic state through endothelial activation and apoptosis mediated by the release of tissue factor and other prothrombotic substances. In 1 patient with CAPS, substantial intravascular complement activation was measured, with sC5b-9 levels of nearly 1500 ng/mL.[5]

Management of CAPS

Recently, a retrospective review of triple therapy involving therapeutic anticoagulation, corticosteroids, and plasma exchange and/or intravenous immunoglobulin (IVIG) suggested that triple therapy resulted in a higher chance of survival compared with no treatment or treatment with other combinations of drugs included in this triple therapy.[3] Antiplatelet agents such as cyclophosphamide, rituximab, and eculizumab have also been used.[3,7,8] In terms of the latter 2 drugs, the number of patients being treated with them is small (Table 3), and there may be a publication bias, given that the majority of reports are single clinical case reports. Treatment of CAPS should not be delayed when the diagnosis is strongly suspected but the but patient does not meet the criteria proposed for classification purposes. In some cases, it may not be possible to obtain a biopsy to evaluate for small vessel occlusion, for example, because of clinical instability. The relative merits of various therapeutic anticoagulants have not been studied in CAPS, but intravenous unfractionated heparin has frequently been used in the acute setting. Data regarding the use of direct oral anticoagulants are insufficient.[9] In all cases, a patient's bleeding risk should be considered when initiating therapeutic anticoagulation, especially if an antiplatelet adjunct such as aspirin is being considered. If there is uncertainty regarding whether to initiate plasma exchange or IVIG infusion, the presence of microangiopathic hemolytic anemia should generally prompt initiation of plasma exchange. By contrast, the presence of immune thrombocytopenia would lend more strength to administration of IVIG. Physicians should consider reporting cases of CAPS to the CAPS Registry (https://ontocrf.costaisa.com/en/web/caps) to help increase our knowledge of this rare disorder.

Case 1 continued. The patient was treated initially with intravenous unfractionated heparin and was monitored by using anti-Xa levels because of a baseline prolonged partial thromboplastin time. This baseline prolongation is commonly seen with lupus anticoagulants, which are present in about 80% of patients with CAPS.[3] Once biopsy results showed organizing thrombosis in small vessels and CAPS was felt to be the likely diagnosis, plasma exchange and a course of rituximab (dosed at 325 mg/m^2 after plasma exchange) were added to the regimen. Steroids were recommended but withheld by the primary team because of concern for infection in the setting of low-grade temperatures and multiple trips to the operating room. Initiation of plasma exchange is consistent with guidelines from the American Society for Apheresis.[10] In general, clinical response determines the duration of plasma exchange; antibody titers are sometimes monitored. There are some data to support the use of rituximab in CAPS,[11] and the rationale for its use seems sound. One issue that arose during management of the patient was that the surgical team wanted to hold anticoagulation for 24 hours after implantation of her biventricular assist device. To minimize the thrombotic risk associated with this plan, daily plasma exchange (including intraoperative plasma exchange) was performed. The patient did reasonably well, and once she was clinically stabilized, she was transitioned to warfarin. One year later, she received an orthotopic heart transplant and while she was hospitalized, she developed what was felt to be recurrent CAPS; 5 years later, she was being evaluated for kidney transplantation.

Table 2. Conditions that can mimic CAPS

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome
Disseminated intravascular coagulation
Sepsis
Hemolysis, increased liver enzymes, and low platelets
Heparin-induced thrombocytopenia
Infective endocarditis
Vasculitis
Cryoglobulinemia
Cholesterol emboli

Table 3. Select clinical reports and outcomes of rituximab and eculizumab in CAPS

	No. of patients	Outcome
Rituximab		
Berman et al[11]	20	75% recovered
Single case reports[7,8,48-59]	14	57% recovered
Eculizumab		
Single case reports[5,11,48,49,57,60-62]	8	88% recovered

Macrophage activation syndrome (MAS)

Case 2: MAS

A 27-year-old woman presented to the emergency room complaining of fever, rash, hair loss, and weakness. She had recently suffered an upper respiratory infection. Laboratory tests showed pancytopenia and a transaminitis. An antinuclear antibody, anti-double stranded DNA antibody, and rheumatoid factor were positive. Complement levels were low. Ferritin was 7705 μg/L. Triglycerides were elevated. Urinalysis showed hematuria and proteinuria (suggestive of nearly 2 g/d). The liver and spleen were normal based on abdominal CT.

Diagnosis of MAS

MAS is a form of hemophagocytic lymphohistiocytosis (HLH) that occurs in the setting of rheumatologic disease, classically systemic juvenile idiopathic arthritis (SJIA), systemic lupus erythematosus (SLE), or adult-onset Still's disease. The diagnosis of MAS is a clinical one, and a few diagnostic criteria have been used, including the HLH-2004 criteria and a more recent set of criteria developed specifically for situations in which MAS complicates SJIA (Table 4).[12-14] It is important to recognize that both the HLH-2004 and the MAS/SJIA criteria are based on observations in pediatric patients and therefore may be more difficult to apply to adults. If there is concern for malignancy, obtaining a soluble interleukin-2 receptor alpha (sIL-2Rα) level can be helpful because the sIL-2Rα: ferritin ratio is generally higher in malignancy-associated HLH than in other forms of HLH such as MAS.[15,16]

Case 2 continued. The patient was seen by a rheumatologist and diagnosed with SLE. A biopsy of the skin rash showed leukocytoclastic vasculitis consistent with SLE. A bone marrow biopsy showed hemophagocytosis. Based on the presence of fever, pancytopenia, an elevated ferritin, elevated triglycerides, and hemophagocytosis, a diagnosis of HLH/MAS complicating SLE was made using the HLH-2004 criteria (Table 4).[12] Initially, there was concern for infection but a careful evaluation for infectious agents was unremarkable. In 1 series of patients with MAS related to SLE, coexisting infection was present 38% of the time.[17] At a minimum, Epstein-Barr virus viral loads should be obtained in patients suspected of having MAS. Of note, a ferritin level >10 000 μg/L is sensitive and specific for HLH in the pediatric population[18] but not in adults.[19] In 1 study, the median ferritin in adult patients with HLH on presentation to 2 hospitals was 5823 μg/L.[19] An assessment for an underlying genetic predisposition to HLH should be performed in children and considered in adults. Of note, the case presented here was atypical in that a diagnosis of rheumatologic disease is usually established before the onset of MAS. In more typical cases, there is the danger that MAS is unrecognized, because clinical manifestations can be interpreted as a simple flare of the underlying systemic rheumatologic disease.

Pathogenesis of MAS

MAS results from life-threatening immune hyperactivation in which dysregulation of macrophages and lymphocytes leads to excessive cytokine production. These cytokines include but are not limited to interleukin-18 (IL-18) and its downstream effector interferon-γ (IFN-γ).[20-23] The central role of IFN-γ in the pathogenesis of MAS is supported by data showing that IFN-γ neutralization improves survival in mouse models of HLH and MAS[24-26]; neutralization of other cytokines such as tumor necrosis factor α did not prolong survival in 1 of these models.[26] Furthermore, elevated levels of IFN-γ and its downstream effectors are well documented in patients with HLH and MAS.[20,27-29] Recently, chronic IL-18 elevation, potentially mediated by an epithelial inflammasome source, has been shown to play an important role in the pathogenesis of MAS.[21] A total IL-18 level >24 000 pg/mL was shown to distinguish MAS from familial HLH with 83% sensitivity and 94% specificity.[21] The immune dysregulation and severe inflammation that characterize MAS result in tissue infiltration by lymphocytes and histiocytes, leading to organ failure and potentially death.

Table 4. Comparison of 2 sets of diagnostic criteria that can be applied to patients with suspected MAS

	HLH-2004[12] (5 of 8 needed)	EULAR/ACR/PRINTOMAS/SJIA (5 of 7 needed; must include the elements in italics)
Clinical		*Known or suspected SJIA*
Constitutional findings	Fever	*Fever*
Physical examination and imaging findings	Splenomegaly	
Peripheral blood counts	Cytopenias affecting 2 or 3 lineages: Hemoglobin <9 g/dL Platelets <100 × 10^9/L Neutrophils <1.0 × 10^9/L	Platelet count ≤181 × 10^9/L
Other laboratory values	Ferritin ≥500 ng/mL	*Ferritin >684 ng/mL*
	Fasting triglycerides ≥265 mg/dL and/or fibrinogen ≤1.5 g/L	Triglycerides >156 mg/dL Fibrinogen ≤360 mg/dL
	Soluble CD25 ≥2400 U/mL	Aspartate aminotransferase >48 U/L
	Low or absent natural killer cell activity	
Pathology results	Hemophagocytosis in the bone marrow, spleen, or lymph nodes	

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism. PRINTO, Paediatric Rheumatology International Trials Organisation.

Management of MAS

Although patients with MAS fit the criteria for HLH, they are viewed as a separate group because the implications for therapy are very different. The management of MAS has predominantly focused on treating the underlying rheumatologic disease and modulating immune hyperactivity. High-dose steroids are typically used, and cyclosporine is frequently added.[17,30-35] IVIG is sometimes used.[17,31-33] Limited data suggest that the IL-1 receptor antagonist anakinra is effective in treating MAS[36-39] and a phase 1 clinical trial of this biological agent in MAS is underway (NCT02780583). Of note, patients without MAS who are treated with anakinra or the interleukin-1β–neutralizing antibody canakinumab can still develop MAS.[40-42] Anakinra is approved by the US Food and Drug Administration for the treatment of SJIA and has been used in SJIA-related MAS more often than in other forms of MAS. If patients have SLE-related MAS, then cyclophosphamide and mycophenolate mofetil are reasonable considerations for therapy.[32] Many other treatments for MAS have been attempted, but the chemotherapeutic agent etoposide (used in other forms of HLH) is almost always avoided in the first-line setting. Hematopoietic stem cell transplantation is typically not a consideration for many reasons, including that overall survival in MAS is generally better relative to that in other forms of HLH.[17,43-47]

Case 2 continued. Upon initial admission, the patient was treated empirically for fever of unclear etiology with antibiotics. After 2 days of high-dose steroids, there was no improvement in her condition, and cyclosporine and IVIG (dosed over 5 days) were added with good effect. The patient was discharged, only to return with changes in her mental status. Findings from brain magnetic resonance imaging were characteristic of lupus cerebritis at which point cyclosporine was stopped and monthly cyclophosphamide was initiated at a dose of 500 mg/m^2. Steroids were tapered very slowly and MAS did not recur. Throughout the case, there was close collaboration between the patient's internal medicine team and consultants in rheumatology, infectious disease, and hematology. Such collaboration is beneficial for patients with MAS, given that multiorgan damage and diagnostic conundrums frequently arise.

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