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Catastrophic antiphospholipid syndrome: a clinical review

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ABSTRACT

Context: Catastrophic antiphospholipid syndrome (CAPS) is a rare life-threatening autoimmune disease characterized by disseminated intravascular thrombosis resulting in multiorgan failure.

Evidence Acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, PubMed (NLM), LISTA (EBSCO) and Web of Science have been searched.

Results: CAPS is due to antiphospholipid antibodies directed against a heterogeneous group of proteins that are associated with phospholipids. These autoantibodies activate endothelial cells, platelets, and immune cells, thereby promoting a proinflammatory and prothrombotic phenotype. Furthermore, antiphospholipid antibodies inhibit anticoagulants, impair fibrinolysis, and activate complements. Although CAPS can affect a variety of organs and tissues, the kidneys, lungs, central nervous system, heart, skin, liver, and gastrointestinal tract are most commonly affected. The systemic inflammatory response syndrome, likely to extensive tissue damage, accompanies CAPS. The most frequent renal manifestations are hypertension, proteinuria, hematuria, and acute renal failure. In the majority of patients with CAPS, a precipitating factor such as infection, surgery, or medication can be identified. Antiphospholipid antibodies such as lupus anticoagulant and antibodies against cardiolipin, β2-glycoprotein I, and prothrombin are serological hallmark of CAPS. Laboratory tests often reveal antinuclear antibodies, thrombocytopenia, and anemia. Despite widespread intravascular coagulation, blood films reveal only a small number of schistocytes. In addition, severe thrombocytopenia is uncommon.

Conclusions: Histologically, CAPS is characterized by acute thrombotic microangiopathy. CAPS must be distinguished from other forms of thrombotic microangiopathies such as hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and heparin-induced thrombocytopenia. CAPS is associated with high morbidity and mortality. Therefore, an aggressive multidisciplinary treatment strategy is indicated. Anticoagulation, immunosuppression, plasma exchange, intravenous immunoglobulins, and anti-platelet agents, used in various combinations, have resulted in improved patient outcome.

Implication for health policy/practice/research/medical education:
Catastrophic antiphospholipid syndrome (CAPS) is a rare life-threatening autoimmune disease characterized by disseminated intravascular thrombosis resulting in multi-organ failure.

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Review Article

1. Context

Antiphospholipid antibodies are pathogenic antibodies directed against a heterogeneous group of phospholipid-binding proteins such as cardiolipin, β_2-glycoprotein I (B2GPI), and prothrombin (1,2). Lupus anticoagulant is an antiphospholipid antibody that prolongs clotting times in vitro.

2. Evidence Acquisition

Directory of Open Access Journals (DOAJ) Google Scholar, PubMed (NLM), LISTA (EBSCO) and Web of Science were searched with key words relevant to catastrophic antiphospholipid syndrome, antiphospholipid antibodies, and thrombotic microangiopathy.

3. Results

Twenty research and review articles relevant to this topic directly or indirectly have been found. From the information given in these papers, the following aspects were drawn out.

3.1. Definition

The antiphospholipid syndrome (APS) is an autoimmune disease characterized by arterial and venous thrombosis due to antiphospholipid antibodies. The disorder is referred to as primary when it occurs in the absence of another autoimmune disease. Secondary APS occurs in the context of an autoimmune disorder such as systemic lupus erythematosus. The catastrophic APS (CAPS) is a rare life-threatening form of APS in which widespread intravascular thrombosis results in multiorgan ischemia and failure (3-6). CAPS is the initial presentation of APS in nearly half of patients, while the remaining half has a history of APS.

3.2. Diagnosis

Diagnostic criteria for CAPS are: 1) involvement of three or more organs/tissues; 2) development of manifestations in less than a week; 3) histological evidence of intravascular thrombosis; and 4) presence of antiphospholipid antibodies on two occasions six weeks apart (Table 1) (4). A definite diagnosis of CAPS is made when all four diagnostic criteria are present. The diagnosis of CAPS is probable when a combination of these criteria is present.

Table 1. Diagnostic Criteria for CAPS

1) Involvement of three or more organs/tissues
2) Development of manifestations in less than a week
3) Histological evidence of intravascular thrombosis
4) Presence of antiphospholipid antibodies on two occasions six weeks apart
A definite diagnosis of CAPS requires all four criteria to be met.
A diagnosis of CAPS is probable, if any of the following set of criteria are met:
• 1, 2, and 4
• 1, 3, and 4; however, a third event occurs between a week and a month, despite anticoagulation
• 1-4; however, only two organs/tissues are involved
• 1-4; however, antiphospholipid antibodies could not be assayed six weeks apart due to death of a patient who was never tested before
Modified from reference 3.

3.3. Pathogenesis

The putative pathogenic mechanisms of antiphospholipid antibodies can be arbitrarily divided into four interrelated groups: 1) cellular activation, 2) inhibition of anticoagulants, 3) inhibition of fibrinolysis, and 4) complement activation (Table 2) (1,2).

Antiphospholipid antibodies can stimulate endothelial cells, immune cells, and platelets. Binding of anti-B2GPI/B2GPI complex to various receptors on the surface of endothelial cells promotes a proinflammatory and prothrombotic phenotype mediated in part by p38 mitogen-activated protein kinase and nuclear factor kappa-B. Antiphospholipid antibodies can reduce the activity of endothelial nitric oxide synthase resulting in

Table 2. Putative Pathogenic Mechanisms in CAPS

Cellular activation
Endothelial cell activation
Immune cell activation
Platelet activation
Inhibition of anticoagulants
Inhibition of the protein C pathway
Disruption of annexin A5 shield
Inhibition of fibrinolysis
Inhibition of plasminogen activator inhibitor-1
Blocking of β_2-glycoprotein I
Blocking of annexin A2
Complement activation
Endothelial cell activation by C5a and MAC
Immune cell activation by C5a
Platelet activation by C3a and MAC
Inhibition of fibrinolysis by C5a

MAC, membrane attack complex. Modified from reference 1.

diminished nitric oxide production. Nitric oxide deficiency causes impaired vasodilation and promotes platelet adhesion to the endothelium. Antiphospholipid antibodies cause oxidative stress and stimulate expression of tissue factor on the surface of endothelial cells and monocytes. A membrane-bound lipoprotein, tissue factor is the cell surface receptor and cofactor for coagulation factor VII. Anti-B2GPI/B2GPI complex can induce platelet activation and aggregation via apolipoprotein E receptor 2'.

Antiphospholipid antibodies can inhibit anticoagulants. Endogenous anticoagulants include protein C, protein S, antithrombin, and annexin A5. An endothelial cell surface receptor, thrombomodulin binds thrombin and protein C, thereby facilitating protein C activation. A multifunctional serine protease, activated protein C inactivates coagulation factors Va and VIIIa with the aid of protein S. Antiphospholipid antibodies can inhibit the protein C pathway by: 1) inhibiting the assembly of protein C complex; 2) reducing protein C activation via thrombomodulin-thrombin complex; 3) suppressing protein C activity; 4) binding to and protecting coagulation factors Va and VIIIa from protein C-mediated proteolysis; and 5) enhancing clearance of protein C. Antiphospholipid antibodies disrupt annexin A5, a potent anticoagulant with high affinity for negatively charged prothrombotic phospholipids such as phosphatidylserine.

Antiphospholipid antibodies can impair fibrinolysis. The coordinated actions of the activators, inhibitors, cofactors, and receptors of the fibrinolytic system provide protection from the excessive activity of the coagulation system. Tissue plasminogen activator (tPA) and urokinase (uPA) convert plasminogen to plasmin, which degrades fibrin to its soluble degradation products. B2GPI serves as a cofactor for tPA. A cell surface receptor for tPA and plasminogen, annexin A2 facilitates tPA-mediated plasminogen proteolysis and plasmin generation. Plasminogen activator inhibitor-1 (PAI-1) inhibits the activity of both tPA and uPA. Antiphospholipid antibodies can interfere with fibrinolysis by: 1) inhibiting tPA; 2) blocking B2GPI; and 3) interfering with annexin A2.

Antiphospholipid antibodies can activate complements. Complements are activated through the classical, lectin, or alternative pathways (7). The classical pathway is strongly activated by immune complexes, which are recognized by the versatile pattern recognition molecule C1q. Complement activation results in C3 cleavage into C3a and C3b by the C3 convertases. Binding of C3a to its receptor on the surface of platelets causes activation, adhesion, and aggregation of platelets. C3b facilitates phagocytosis and participates in the assembly of the C5 convertases that cleaves C5 into C5a and C5b. C5a stimulates expression of tissue factor (monocytes, neutrophils, endothelial cells) and PAI-1 (mast cells, basophils). C5b participates in the assembly of membrane attack complex (C5b-9) on the surface of platelets and

endothelial cells resulting in generation of negatively charged prothrombotic phospholipids. Membrane attack complex also triggers release of storage granules and tissue factor-bearing microparticles from platelets.

3.4. Pathology

Intravascular thrombosis affecting predominantly microcirculation characterizes CAPS. In addition, thrombosis of arteries, veins, or both can occur. Detailed descriptions of histopathological alterations in CAPS are sparse (8-10).

Examination of renal biopsy specimens demonstrates an acute thrombotic microangiopathy characterized by the presence of thrombi in glomeruli, arterioles, or both (Figure 1A,B). An inflammatory cell infiltrate is reported in the interstitium in one third of patients. Interstitial hemorrhage rarely accompanies microvascular thrombosis. Immunofluorescence microscopy reveals strong immunoreactivity with antiserum to fibrin in the glomerular capillaries, arterioles, and interstitium (Figure 1C). Immune complex deposition is rarely observed. On ultrastructural examination, glomerular capillaries frequently contain fibrin tactoids (Figure 1D). Interstitial fibrosis, tubular atrophy, and concentric laminations in the fibrotic intima of arterioles and arteries (onion skin pattern) indicate chronic damage.

3.5. Clinical Manifestations

Approximately 72% of patients with CAPS were women (5). The age of patients ranged from 11 to 60 years with a mean of 37 years. A precipitating factor such as infection (22%), surgery (10%), discontinuation of anticoagulation (8%), medication (7%), obstetric complication (7%), or a neoplastic process (5%) can often be identified. A concomitant autoimmune disorder such as systemic lupus erythematosus (40%), lupus-like syndrome (5%), or another autoimmune disease (9%) is frequently present.

CAPS can affect a variety of organs and tissues (Table 3) (5). The kidneys, lungs, central nervous system, heart, skin, liver, and gastrointestinal tract are most commonly affected. Although renal disease is the presenting feature in only 18% of patients, kidneys are eventually involved in 71% of patients during the course of the disease. Renal involvement is defined by a ≥50% rise in serum creatinine concentration, proteinuria (>0.5 g/day), severe hypertension (blood pressure >180/100 mm Hg), or a combination thereof (4). The most frequent renal manifestations are hypertension, proteinuria, hematuria, and acute renal failure (3,5,8,9). Proteinuria ranged between 0.6 g/day and 6.1 g/day with a mean of 2.8 g/day (8). Hypertension is often severe. Renal infarction develops on a rare occasion.

The lungs are involved in 24% of patients upon presentation (5). However, the lungs are eventually involved in 64% of patients during the course of the disease. Acute respiratory distress syndrome and pulmonary embolism are the most common pulmonary manifestations. Thrombosis of pulmonary arteries and arterioles sometimes occurs. Alveolar hemorrhage occurs in 6% of patients (3,9). The pathogenesis of alveolar hemorrhage in CAPS is poorly understood. The histological examination of lung biopsy specimens from patients with APS and alveolar hemorrhage revealed microvascular thrombosis with or without capillaritis (11). Pulmonary capillaritis is characterized by the presence of inflammatory cells, particularly neutrophils, in and around capillaries in the alveolar walls.

The central nervous system is involved in 62% of patients (6). Hypertensive encephalopathy, ischemic encephalopathy, stroke, and cerebral venous thrombosis are some of the more common manifestations. Altered mental status ranging from drowsiness to come, headache, focal neurological

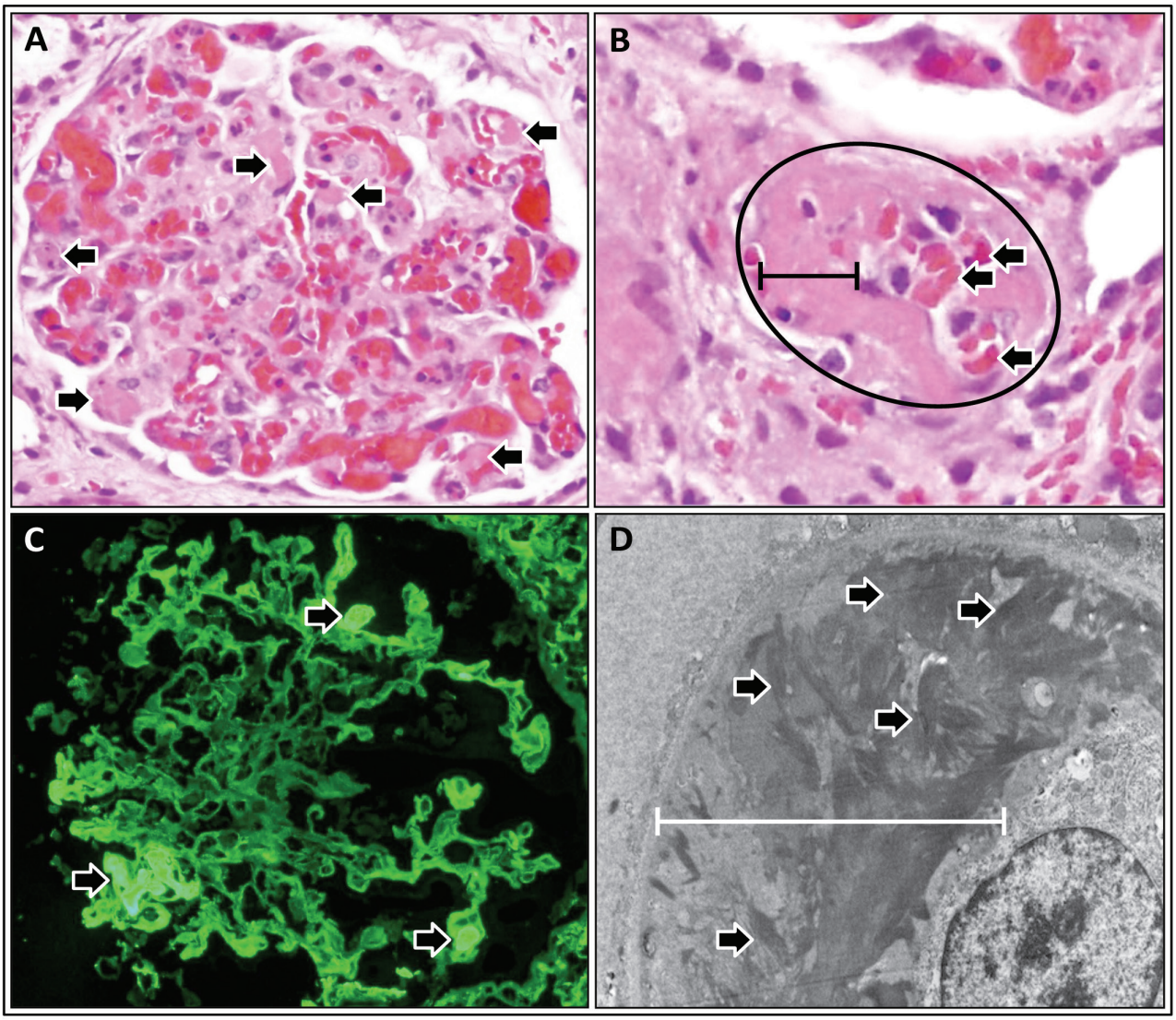

Figure 1. Renal histopathologic features of CAPS. A glomerulus showing congestion and microthrombi (arrows) in the capillarie s (A). An arteriole demonstrating mural thrombi (arrows) partially occluding the lumen, which contains several red blood cells (B). Immunostaining for fibrin demonstrating several fibrin thrombi (arrows) in a glomerulus (C). Ultrastructural examination demonstrating fibrin tactoids (arrows) in the expanded subendothelial space of a glomerular capillary (D). Tissue sections in panels A and B were stained with hematoxylin and eosin. Courtesy of Laura Barisoni, MD, Renal Pathology Laboratory, University of Miami, and Xu Zeng, MD, PhD, Nephrocor Bostwick Laboratory.

deficits, and seizure may occur. The heart is involved in nearly half of patients (6). Thrombosis of coronary arteries can give rise to unstable angina and myocardial infarction. Valvular disease can cause regurgitation. Thrombotic heart valve lesions with sterile vegetations are occasionally encountered. At times, intracardiac thrombi are found. Cutaneous manifestations are observed in nearly half of patients and include livedo reticularis, acrocyanosis, purpura, ecchymosis, splinter hemorrhages, and necrosis resulting in ulcerations (6).

The systemic inflammatory response syndrome (SIRS), likely due to extensive tissue damage, accompanies CAPS (9,12). The manifestations of SIRS include: 1) fever (a body temperature >38°C) or hypothermia (a body temperature <36°C); 2) tachycardia (a heart rate >90 beats/minute); 3) tachypnea (a respiratory rate >20 breaths/minute) or hyperventilation (a PaCO2

Table 3. Organ Involvement in CAPS

Kidney	71%
Lung	64%
Central Nervous System	62%
Heart	51%
Skin	50%
Liver	33%
Gastrointestinal tract	25%
Venous thrombosis	23%
Spleen	19%
Adrenal glands	13%
Arterial thrombosis	11%
Pancreas	8%
Retina	7%
Peripheral Nervous System	5%
Bone marrow	4%

Modified from references 4.

of <32 mm Hg); and 4) leukocytosis (a leukocyte count >12,000/mm^3), leukopenia (a leukocyte count <4,000/mm^3), or a left shift (the presence of >10% immature neutrophils) (13).

3.6. Laboratory findings

Laboratory findings are summarized in Table 4 (5). Anticardiolipin antibodies and lupus anticoagulant are detected in the majority of patients. Antinuclear antibodies are detected in two thirds of patients with CAPS and in 45% of patients with primary APS. The titer of antinuclear antibodies in CAPS is usually <1:320. Thrombocytopenia is present in nearly half of patients. Severe thrombocytponeia is uncommon. A platelet count >100,000/mm^3 was present in 32% of patients (3). Despite widespread intravascular thrombosis, microangiopathic hemolytic anemia is present in only one third of patients. Blood films demonstrate only small numbers of schistocytes (6). In an earlier description of the laboratory features of CAPS, schistocytes were observed in only 14% of

Table 4. Laboratory Findings in CAPS

Anticardiolipin IgG	83%
Lupus anticoagulant	82%
Antinuclear antibodies	66%
Thrombocytopenia	46%
Anticardiolipin IgM	38%
Hemolytic anemia	35%
Schistocytes on blood film	16%
Acute-phase proteins	?

Modified from references 4, 21.

cases (2). A low prevalence of schistocytes (16% of cases) was also reported in a later study (5). An explanation for the paucity of schistocytes in CAPS is not readily available. It can be postulated that the rapidity of onset and completeness of microvascular occlusion prevented enough blood flowing through thrombotic vessels to cause fragmentation of erythrocytes.

In line with SIRS, alterations in the concentrations of acute-phase proteins are noted (9). Positive acute-phase proteins are those whose plasma concentration increases by at least 25% during inflammation (14). They include C-reactive protein, serum amyloid A, ferritin, several components of the complement, coagulation, and fibrinolysis systems. Negative acute-phase proteins of clinical significance are albumin and transferrin. The erythrocyte sedimentation rate can be markedly elevated (9).

3.7. Differential diagnosis

The clinical manifestations of CAPS are usually a consequence of an acute thrombotic microangiopathy. Therefore, the differential diagnosis is broad and includes hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and heparin-induced thrombocytopenia.

Hemolytic-uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are char-

acterized by microangiopathic hemolytic anemia, thrombocytopenia, and ischemic injury to organs (6,15). While fever and neurologic manifestations frequently dominate the clinical picture in TTP, most patients with HUS suffer from renal disease. The differentiation between HUS/TTP and CAPS is sometimes difficult. As a general rule, thrombocytopenia and schistocytosis are marked in HUS/TTP and mild, or even absent, in CAPS. Activated partial thromboplastin time is usually normal in HUS/TTS, but it may be elevated in CAPS in the presence of lupus anticoagulant. Whereas the presence of antiphospholipid antibodies is the serological hallmark of CAPS, plasma activity of ADAMTS-13 (a disintegrin and metalloprotease, with thrombospondin-1–like domains) is <5% of normal in most patients with TTP. HUS occurs in two distinct clinical settings (16). In the majority of patients with HUS, an infection with toxicogenic bacteria such as verotoxin-producing E. coli precedes the onset of the disease. In approximately 10% of cases, a preceding bacterial infection is not identified (so-called atypical HUS). Some patients with atypical HUS demonstrate reduced complement C3 levels in blood, a reflection of complement activation. In fact, genetic mutations involving complement regulatory proteins resulting in complement activation through the alternative pathway can be found in nearly half of patients with atypical HUS.

Disseminated intravascular coagulation (DIC) is characterized by disseminated microvascular thrombosis, consumptive coagulopathy, and a hemorrhagic diathesis (17). DIC is not a primary disorder and can be a complication of a variety of disorders that lead to activation of coagulation. Laboratory features of DIC include absolute or relative thrombocytopenia, prolonged clotting times, reduced plasma fibrinogen concentration, and elevated plasma concentrations of fibrin degradation products. DIC can mimic CAPS (6). Although CAPS is primarily due to vascular thrombosis, DIC usually manifests signs of thrombosis and bleeding at the same time. Nonetheless, DIC may complicate CAPS in one third of patients.

Autoantibodies against platelet factor 4-heparin complex can give rise to a life-threatening prothrombotic disorder known as heparin-induced thrombocytopenia (HIT) (18). As the name implies, HIT follows administration of unfractionated or, less commonly, low-molecular-weight heparin. HIT is characterized by absolute (<150,000/mm^3) or relative (decrease from baseline) thrombocytopenia and vascular thrombosis. However, circulating antibodies against PF4-heparin complex have also been reported in patients without preceding heparin therapy (19). It is postulated that presence of antibodies against PF4-heparin complex could also be a manifestation of autoimmunity such as that leading to the formation of antiphospholipid antibodies.

3.8. Treatment

A life-threatening systemic disease, CAPS requires an aggressive multidisciplinary collaborative treatment strategy. The following treatments, often in combination, have been used for CAPS: anticoagulation (87%), glucocorticoids (86%), plasma exchange (39%), cyclophosphamide (36%), intravenous immunoglobulins (22%), and anti-platelet agents (10%) (5). A recent decline in the mortality rate in CAPS from 53% to 33% has been attributed to the use of aforementioned treatment strategies in combination) (20).

4. Conclusions

Histologically, CAPS is characterized by acute thrombotic microangiopathy. CAPS must be distinguished from other forms of thrombotic microangiopathies such as hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura,

disseminated intravascular coagulation, and heparin-induced thrombocytopenia. CAPS is associated with high morbidity and mortality. Therefore, an aggressive multidisciplinary treatment strategy is indicated. Anticoagulation, immunosuppression, plasma exchange, intravenous immunoglobulins, and anti-platelet agents, used in various combinations, have resulted in improved patient outcome.

Authors' contributions

AN wrote the manuscript. LMO made substantial contributions to conception and design of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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