EXTENDED REPORT

Thrombotic microangiopathic haemolytic anaemia and antiphospholipid antibodies

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Tables W1 and W2 are available at http://www.annrheumdis.com/supplemental

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Objective: To analyse the clinical and laboratory features of patients with thrombotic microangiopathic haemolytic anaemia (TMHA) associated with antiphospholipid antibodies (aPL).
Methods: A computer assisted (PubMed) search of the literature was performed to identify all cases of TMHA associated with aPL from 1983 to December 2002.
Results: 46 patients (36 female) with a mean (SD) age at presentation of TMHA of 34 (15) years were reviewed. Twenty eight (61%) patients had primary antiphospholipid syndrome (APS). TMHA was the first clinical manifestation of APS in 26 (57%) patients. The clinical presentations were haemolytic-uraemic syndrome (26%), catastrophic APS (23%), acute renal failure (15%), malignant hypertension (13%), thrombotic thrombocytopenic purpura (13%), and HELLP (haemolysis, elevated liver enzymes, and low platelet count in association with eclampsia) syndrome (4%). Lupus anticoagulant was detected in 86% of the episodes of TMHA, and positive anticardiolipin antibodies titres in 89%. Steroids were the most common treatment (69% of episodes), followed by plasma exchange (PE) (62%), anticoagulant or antithrombotic agents (48%), immunosuppressive agents (29%), and immunoglobulins (12%). Recovery occurred in only 10/29 (34%) episodes treated with steroids, and in 19/27 (70%) episodes treated with PE. Death occurred in 10/46 (22%) patients.
Conclusions: The results emphasise the need for systematic screening for aPL in all patients with clinical and laboratory features of TMHA. The existence of TMHA in association with an APS forces one to rule out the presence of the catastrophic variant of this syndrome. PE is indicated as a first line of treatment for all patients with TMHA associated with aPL.

The term thrombotic microangiopathic haemolytic anaemia (TMHA) was introduced by Symmers in 1952 to describe clinical disorders related to the presence of localised or diffuse microvascular thrombosis.[1] TMHA is characterised by thrombocytopenia, microangiopathic haemolytic anaemia (as indicated by erythrocyte fragmentation on peripheral blood smears) accompanied by a negative Coombs' test, fever, neurological symptoms, and kidney involvement.[2] The conditions that should be considered in the differential diagnosis of TMHA include thrombotic thrombocytopenic purpura (TTP), haemolytic-uraemic syndrome (HUS), acute postpartum and contraceptive associated renal failure, malignant hypertension, HELLP (haemolysis, elevated liver enzymes, and low platelet count in association with eclampsia) syndrome, cancer, immunosuppressive treatment, systemic sclerosis, undifferentiated connective tissue disorder, and human immunodeficiency virus infection.[3] Typical histological findings in this syndrome include hyaline thrombi composed of fibrin and platelets which occlude the microvasculature.

Recently, several reports have pointed out the relationship of TMHA with the presence of antiphospholipid antibodies (aPL).[4 5] Systemic lupus erythematosus (SLE) was the first autoimmune disease in which the association of TMHA with aPL was recognised.[6–8] In some patients with SLE it was found that renal lesions of TMHA might develop during the course of TTP or HUS or be associated with antiphospholipid syndrome (APS), regardless of the underlying type of lupus glomerulopathy existing.[9 10] In the reports of coexistent SLE and TTP, lupus anticoagulant (LA) was documented in 2 of 12 patients[5 11] and anticardiolipin antibodies (aCL) were recorded in 4 of 5 patients examined.[5 12] Patients with a previously diagnosed APS may also develop TMHA.[4 13 14] One of these reported cases was a patient with a 7 year history of SLE complicated by APS who later developed TTP.[13] Therefore, an association between aPL and the development of TMHA is clearly evident.

In this article we analyse the clinical and laboratory features of 46 patients—45 taken from published reports and one from our clinics—with TMHA associated with aPL, and support the hypothesis that TMHA might be a manifestation of the APS.

METHODS

A computer assisted (PubMed, National Library of Medicine, Bethesda, MD) search of the literature was performed to identify all cases of TMHA associated with aPL published in English, Spanish, and French from 1983 (when APS was first defined)[15] to December 2002 (keywords: microangiopathic haemolytic anaemia, thrombotic microangiopathy, microangiopathic anaemia, thrombotic thrombocytopenic purpura, haemolytic-uraemic syndrome, schistocytes, malignant hypertension, phospholipid, antiphospholipid, antiphospholipid syndrome, antiphospholipid antibodies, anticardiolipin, anticardiolipin antibodies, lupus anticoagulant, coagulation inhibitor, lupus inhibitor), and bibliographies of all articles

Abbreviations: aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; FFP, fresh frozen plasma; HELLP, haemolysis, elevated liver enzymes, and low platelet count in association with eclampsia; HUS, haemolytic-uraemic syndrome; LA, lupus anticoagulant; PE, plasma exchange; SLE, systemic lupus erythematosus; TMHA, thrombotic microangiopathic haemolytic anaemia; TTP, thrombotic thrombocytopenic purpura; vWF, von Willebrand factor

were scanned for references not identified in the initial search. Only cases with well documented clinical summaries and relevant information were included. Data were summarised using a standardised data form, including sex, age, previous abortions or thrombotic events, immunological features, treatment, and evolution (web extra table W1, available at http://www.annrheumdis.com/supplemental).

For practical purposes, patients were included only if they had the following criteria: microangiopathic haemolytic anaemia, as indicated by erythrocyte fragmentation (schistocytes) on peripheral blood smears, with a negative Coombs' test, thrombocytopenia, and presence of LA or positivity for aCL, or both. We categorised patients as having TTP if neurological dysfunction predominated, whereas patients with predominantly glomerular damage were diagnosed as the HUS.

To facilitate synthesis of these data we categorised patients in the following diagnostic categories:

- SLE, if they met four or more criteria of the American College of Rheumatology revised criteria for the classification of SLE[16 17]
- ''Lupus-like'' syndrome if they met only two or three criteria
- ''Primary'' APS if they met criteria of the international consensus statement on preliminary classification criteria for definite APS syndrome,[18] and did not meet any of the above described criteria for SLE or lupus-like syndrome
- ''Catastrophic'' APS if they presented with an acute devastating APS with multiple organ involvement, as previously defined.[19]

RESULTS

A total of 63 patients with TMHA associated with aPL were found in the literature search, but 18 of them (corresponding to six articles)[20–25] were not included because their clinical and immunological characteristics were not described. Because of this, 46 patients—45 from the literature[4 5 13 14 26–51] and one from our clinics (see appendix 1)—with 47 episodes of TMHA (one patient had two episodes of TMHA[40]) were finally reviewed.

General characteristics

Table 1 shows the general clinical features of the complete series of patients. The patients comprised 36 (78%) women and 10 (22%) men with a mean (SD) age of 34 (15) years (range 7–73). Twenty eight (61%) patients had primary APS, 15 (33%) patients were categorised as having APS associated with defined SLE, 2 (4%) with lupus-like syndrome, and 1 (2%) with systemic sclerosis of paraneoplastic origin. During the follow up, the first diagnosis of primary APS was changed in three patients: one patient[32] developed a clinical picture of SLE 3 months later, another patient[14] developed a lupus-like syndrome 9 months later, and another[46] developed SLE 4 years later. In addition, one patient[35] had multicentric Castleman's disease, and the necropsy of another patient disclosed a carcinoma of the uterus with pleural, bone, and hepatic metastasis.[41]

Clinical presentation and precipitating factors

In 26 (57%) patients, TMHA was the first clinical manifestation of APS, whereas a total of seven (15%) patients had a previous history of major vascular occlusions. Deep venous thrombosis was reported as occurring in four (9%) patients, and in one this was accompanied by pulmonary embolism. Arterial occlusions occurred in two (4%) patients, arteriovenous fistula thrombosis in one, and haemodialysis vascular access and renal graft thrombosis in one patient.

Table 1 General characteristics of 46 patients (mean age 34 years)with thrombotic microangiopathic haemolytic anaemia associated with antiphospholipid antibodies

Characteristic	No (%)
Sex	
Female	36 (78)
Male	10 (22)
Autoimmune diseases	
Primary APS	28 (61)
SLE	15 (33)
Lupus-like	2 (4)
Systemic sclerosis of paraneoplastic origin	1 (2)

Spontaneous abortions or fetal death had occurred in 14 (39%) of the 36 female patients.

Table 2 shows the clinical presentation of 47 episodes of TMHA. HUS was the most common clinical presentation (26%), occurring in the postpartum period in three patients, and then catastrophic APS (23%), acute renal failure (15%), malignant hypertension (13%), TTP (13%), HELLP syndrome (4%), amaurosis fugax with microangiopathic haemolytic anaemia (2%), thrombocytopenia (2%), and thrombotic microangiopathy in renal allograft (2%).

In 21/46 (46%) patients, some precipitating factors contributed to the development of TMHA (table 3). This occurred during pregnancy in nine patients (fetal death in one patient) and in the postpartum period in six patients (one with acute enterocolitis). Major surgical procedures were evident as precipitating factors in three patients (one vascular surgery and two after renal transplantation), infection in two, and renal biopsy and oral contraceptive use (one case each).

Histopathological studies

Histopathological studies were performed in 32 patients (kidney biopsy in 27). The major finding was the presence of fibrin thrombi in glomerular capillaries in 18/24 (75%) patients, followed by double contours in glomerular capillary walls in 12/24 (50%), ischaemic glomeruli in 11/24 (46%), fibrin thrombi in arterioles in 11/24 (46%), and interlobular arteries in 8/24 (33%). In three cases the results of renal histopathological examination were reported only as ''consistent with thrombotic microangiopathy''. In all cases, histological examination ruled out the presence of vasculitis.

Table 2 Clinical presentation of 47 episodes of thrombotic microangiopathic haemolytic anaemia associated with antiphospholipid antibodies

Clinical presentation	No (%)
Haemolytic uraemic syndrome	12 (26)
Catastrophic antiphospholipid syndrome	11 (23)
Acute renal failure	7 (15)
In postpartum period	3
Pregnancy related	3
Malignant hypertension	6 (13)
Thrombotic thrombocytopenic purpura	6 (13)
HELLP syndrome	2 (4)
Amaurosis fugax with microangiopathic haemolytic anaemia	1 (2)
Thrombocytopenia	1 (2)
Thrombotic microangiopathy in renal allograft	1 (2)

Table 3 Precipitating factors in 46 patients with thrombotic microangiopathic haemolytic anaemia associated with antiphospholipid antibodies

Precipitating factors	No (%)
Obstetric complications	15 (33)
During pregnancy	9
In the postpartum period	6
Major surgical and invasive procedures	4 (9)
After renal transplantation	2
Vascular surgery	1
Renal biopsy	1
Infections	2 (4)
Oral contraceptives	1 (2)

Laboratory findings

Table 4 shows the laboratory pattern of the patients in this series. LA was detected in 31/36 (86%) episodes of TMHA in which this test was performed. The aCL titre was positive in 39/44 (89%) episodes of TMHA. This comprised all patients who tested positive for the IgG isotype of aCL, 50% of patients who were positive for the IgM isotype, and only one patient who was positive for the IgA isotype. Both LA and aCL positivity were detected in 22/33 (67%) patients. Antinuclear antibodies were positive in 15/29 (52%) patients. Anti-dsDNA antibodies were found in 7/24 (29%) patients, all of them with defined SLE.

Treatment and outcome

Table 5 shows the treatment of the 47 episodes of TMHA. For the statistical analysis, each episode of TMHA was considered separately, including those in the patients who had recurrences. Data on treatment were not available in five patients. Finally, 42 episodes of TMHA were analysed. Steroids (usually in high doses) were the most common treatment, used in 29/42 (69%) episodes. Plasma exchange (PE) was used in the treatment of 62% of episodes. Fresh frozen plasma (FFP) was given as replacement fluid in 13 (50%) episodes, together with normal saline in two, and with albumin in one; 5% albumin in two (8%) episodes; and in 12 episodes this information was not specifically reported. In four (10%) episodes, infusion of FFP without plasma removal was used as treatment. Twenty (48%) episodes of TMHA were treated with some form of anticoagulant or antithrombotic agent (heparin in nine, aspirin in eight, dipyridamole in four, and oral anticoagulant in three). Immunosuppressive agents were used in 12 (29%) cases (cyclophosphamide in 10, vincristine in two, and azathioprine in one). Intravenous immunoglobulins were used in five (12%). Intravenous prostaglandin E1 was used in one case. Most patients, however, received a combination of these treatments (web extra table W2, available at http://www.annrheumdis.com/supplemental).

Table 4 Immunological features in 46 patients with thrombotic microangiopathic haemolytic anaemia associated with antiphospholipid antibodies

Immunological features	No/total number (%)
Lupus anticoagulant	31/36 (86)
aCL	39/44 (89)
IgG aCL	27/27 (100)
IgM aCL	11/22 (50)
ANA	15/29 (52)
Anti-dsDNA	7/24 (29)

aCL, anticardiolipin antibodies; ANA, antinuclear antibodies; anti-dsDNA, anti-double stranded DNA antibodies.

Table 5 Treatment of 42 episodes of thrombotic microangiopathic haemolytic anaemia associated with antiphospholipid antibodies

Treatment	No (%)
Steroids	29 (69)
Plasma exchange	26 (62)
FFP as replacement fluid	13
FFP with normal saline	2
FFP with albumin	1
Albumin	2
Infusion of FFP without plasma removal	4 (10)
Anticoagulant or antithrombotic agent	20 (48)
Heparin	9
Aspirin	8
Dipyridamole	4
Oral anticoagulant	3
Immunosuppressive agents	12 (29)
Cyclophosphamide	10
Vincristine	2
Azathioprine	1
Intravenous immunoglobulins	5 (12)

FFP, fresh frozen plasma.

When the presence or not of a single treatment is considered, recovery occurred in only 10/29 (34%) episodes treated with steroids (in all of them, steroids were used together with other treatments). In the seven cases in which steroids were the unique first treatment used, the clinical status and laboratory abnormalities worsened. Recovery occurred in 19 of the 26 (73%) episodes treated with PE. In nine patients this treatment was not the first treatment used, and its use correlated with a marked improvement of the laboratory abnormalities and patients' clinical status. Specifically, one patient presenting with a clinical picture of TTP was initially treated with steroids.[31] No change in her neurological status was seen and the platelet count decreased. PE was then used, and the patient's neurological status improved and the platelet count rose. The same clinical course was seen in four additional patients,[32 44 51] initially treated with steroids, heparin, and infusions of FFP and intravenous immunoglobulins. Indeed, one patient, presenting with malignant hypertension who had improved with PE, had a recurrence of thrombocytopenia upon withdrawal of PE.[14] Another patient developed thrombocytopenia and worsening of her neurological status 3 weeks after the acute episode of catastrophic APS supervened.[48] Intravenous immunoglobulin was added but her mental status continued to deteriorate. Monthly intravenous cyclophosphamide did not improve the clinical status and, finally, PE was restarted. Significant improvement was noted within 48 hours, and the patient responded to repeated PE over 3 years. Only in one case was heparin use directly related to an improvement in laboratory abnormalities and clinical status.[13] In four cases this improvement appeared when heparin was used together with other treatments (in three of them PE). In the remaining four cases in which heparin use was not followed by a clinical improvement, PE was not used. Considering the four patients treated with infusions of FFP, in two of them no significant response was noted and the remaining two were discharged, but renal function remained impaired.

Of seven patients who presented with vascular occlusions before the development of an acute episode of TMHA, only three were receiving anticoagulant treatment (two of them, prolonged oral anticoagulant treatment, and the third patient, aspirin and heparin subcutaneously during pregnancy and recurrent spontaneous abortions).

Among the 46 patients, 10 (22%) finally died. Specifically, death occurred in three patients with clinical presentation of catastrophic APS, two with TTP, two with HUS, and

thrombocytopenia, malignant hypertension, and acute renal failure (one case each). The causes of death were catastrophic APS (three patients), infection (three patients), and myocardial infarction, massive cerebral haemorrhage, and massive haemorrhage after abdominal surgery (one case each). The remaining patient[37] illustrates the difficulty of establishing the differential diagnosis between TTP and catastrophic APS. This patient presented with a clinical picture of SLE with diffuse proliferative glomerulonephritis and thrombotic microangiopathy. In the post-biopsy course, she developed shortness of breath with bilateral pleural effusions. Renal function continued to deteriorate and then generalised tonic-clonic seizure occurred. At this moment, thrombocytopenia and haemolytic anaemia with an increase in schistocytes was noted, and an LA was detected. Finally, arterial desaturation occurred with a synus bradycardia, which progressed to asystole and was followed by unsuccessful resuscitation. The postmortem examination of this patient showed extensive arteriolar and small arterial hyaline thrombi in multiple organs, including the myocardium, cerebral cortex, pancreas, kidney, and genitourinary tract. In some cases, the differential diagnosis between TTP and catastrophic APS remains difficult, and the patient described is an example of this problem (Appendix 1).

DISCUSSION

The term TMHA was first introduced to describe conditions in which localised or diffuse microvascular thrombosis occurs.[1] TMHA encompasses a spectrum of disorders including TTP, HUS, malignant hypertension, postpartum renal failure, pre-eclampsia, and scleroderma renal crisis. The typical clinical picture may be complicated by thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurological symptoms, and/or renal dysfunction, but not all these manifestations are required. Table 6 shows an attempt to establish a differential diagnosis of disorders that present with TMHA.

An intriguing question is whether aPL may have a role in the development of TMHA in patients with SLE. On the one hand, because aPL are present in up to 50% of patients with SLE,[52] a positive aPL assay could be expected in a similar proportion of patients with SLE who develop TTP without necessarily implying an existing causal relationship. In a review of 28 patients with SLE and TMHA performed by Nesher *et al*,[53] tests for LA or aCL were reported in eight patients and were positive in five. The contribution of aPL to the association of TTP and SLE was also suggested by the review of Musio *et al*.[44] These authors detected aCL in nearly half of the patients tested (8/17) and the LA was seen in 14% (2/14).

The role of aPL in idiopathic TMHA is controversial. Although aPL have not commonly been detected in primary TTP[54 55] or HUS,[20] there are some data favouring a causal relationship. Ardiles *et al* studied 17 patients presenting with diarrhoea associated HUS.[20] The possibility of SLE was excluded clinically and by laboratory tests. IgG aCL were present in eight patients, two patients had IgM aCL, and one had IgA antibodies on the solid phase enzyme linked immunosorbent aCL assays. Von Tempelhoff *et al* studied the incidence of acquired and/or inherited thrombophilia in 32 women with HELLP syndrome.[56] Twenty two of them presented with aPL positivity: 17 with LA and 15 with aCL. They concluded that the aPL were the predominant thrombophilia defect, being present in 69% of patients with HELLP syndrome and thrombophilia defects. Most cases of HELLP syndrome are however aPL negative. Indeed, in our review, 28 (61%) patients were categorised as having a primary APS, and TMHA was the first manifestation of the APS in 26 (93%) of them. In the light of these data, we may conclude that in some patients (with or without SLE), aPL may play a part in the development of TMHA.

The aetiology of TMHA, especially in autoimmune diseases, is unclear. Systemic endothelial cell damage appears to be a central phenomenon in the pathogenesis of all TMHA syndromes. Direct evidence for this is the demonstration of apoptosis of microvascular endothelial cells in spleens removed from patients with TTP[57] and the demonstration that plasma from patients with TTP or adult HUS can cause apoptosis of microvascular endothelial cells.[58] Endothelial damage, regardless of its aetiology, may result in widespread release of unusually large von Willebrand factor (vWF) multimers. A plasma vWF-cleaving protease (a metalloproteinase) has been postulated to decrease the size of large vWF multimers to their normal size in plasma after secretion. Deficiency of this protease has been reported in patients with acute idiopathic TTP,[59] and an IgG autoantibody to the enzyme itself is responsible for its depletion. vWF-cleaving protease deficiency may result in larger plasma vWF multimers that can cause platelet agglutination.[60] However, these abnormalities may not be specific for idiopathic TTP. Other studies have shown that thrombotic episodes, especially arterial thrombosis, were more common in LA positive patients with low vWF-cleaving protease activity.[61] Moreover, Diez-Ewald *et al* found that vWF was significantly higher in patients with LA and thromboses and considered that the increased vWF was derived from endothelial cells damaged by LA.[62] An abnormal vWF multimeric pattern was found in 71% of patients with multiple abortions and in 50% of those with strokes.[63] These results suggest that decreased activity of vWF-cleaving protease may be an additional risk factor for arterial thrombosis in patients with aPL. Trent *et al* described two patients with chronic relapsing TTP and aPL.[25] The first was found to have unusually large vWF multimers in her plasma during TTP remission. Plasma of the second patient has not been analysed for the presence of unusually large vWF multimers. We could not include these two patients in our review because the aPL encountered were antiphosphatidylinositol IgM and antiphosphatidylserine IgM respectively, with aCL and LA negativity. Mukai *et al* described a patient with arterial thromboses in APS

Table 6 Differential diagnosis of thrombotic microangiopathic haemolytic anaemia

	HUS	Catastrophic APS	TTP	Malignant hypertension
Thrombocytopenia	+	++	+++	+
Microangiopathic haemolytic anaemia	+	+	+	+
Fever	+	+/−	++	−
CNS disease	+	++	+++	+
Renal disease	+++	+	+	++
Hypertension	+	+/−	+/−	+++

HUS, haemolytic-uraemic syndrome; APS, antiphospholipid syndrome; TTP, thrombotic thrombocytopenic purpura; CNS, central nervous system.

associated with an excess of a large multimer of vWF.[64] Unfortunately, these authors did not measure the activity of vWF-cleaving protease or the antibodies. Until now, the levels of vWF-cleaving protease have only been investigated in one patient with SLE and aPL who developed TTP or a TTP-like syndrome, similar to catastrophic APS.[65] The authors found a decreased vWF-cleaving protease activity. On the basis of this finding, it is possible that some cases of catastrophic APS had been diagnosed as TTP and/or cases of TTP had been diagnosed as catastrophic APS. As there are no more reports of any relationship between this protease, phospholipids, and TMHA, further evaluation is needed.

As we indicated above, endothelial damage is thought to be another important aetiological factor in some forms of TMHA, resulting in the release of unusually large vWF forms, theoretically overwhelming physiological degradation systems and causing a relative deficiency of vWF-cleaving protease.[66] Patients with malignant hypertension or HELLP syndrome (17% of the patients in our review) showed endothelial injury, indicated by the higher vWF levels and raised serum levels of vascular cell adhesion molecule-1 and E-selectin, respectively.[67 68] There is evidence that endothelial cells do appear to have a role in the induction of the prothrombotic diathesis of the APS. Autoantibodies including aPL, anti-endothelial cell, and anti-dsDNA have all been shown to react with endothelial cells, providing a stimulatory signal, and up regulation of adhesion molecules or tissue factor. Nakamura *et al* demonstrated that LA could induce apoptosis in umbilical vein endothelial cells,[69] and the IgG from patients with aPL can enhance endothelial cell adhesion molecule expression and monocyte adherence.[70]

However, other pathogenic mechanisms cannot be completely ruled out[71] because a decrease in specific vWF-cleaving protease activity has been found in 89% of TTP patients but only in 13% of patients with HUS.[72 73] In addition, Hashimoto *et al* were able to find from lupus prone mice a hybridoma clone producing an antibody able to induce thrombotic microangiopathy with some characteristics of TTP when injected into syngeneic mice.[74]

The clinical picture of TMHA, SLE, and APS may overlap and, if any two of the three conditions coexist in the same patient, the diagnosis may be difficult at the time of initial presentation. In one patient the diagnosis of TTP was based on thrombocytopenia, microangiopathic haemolytic anaemia, motor epileptic fits, and fever without any evidence of infection or disseminated intravascular coagulation. The partial thromboplastin time was prolonged owing to the presence of LA. The authors excluded the diagnosis of catastrophic APS owing to the presence of microangiopathic haemolytic anaemia in the absence of any evidence of disseminated intravascular coagulation, but we consider that this patient might be categorised as having catastrophic APS. In some patients, the diagnosis of TTP does not exclude the diagnosis of catastrophic APS, but TTP specifically and TMHA, in general, may be the clinical presentation of an APS.

Patients treated with PE had a recovery rate of 73%. In fact, PE is the most important component of treatment and is indicated for all patients with suspected TTP and HUS.[75] However, in contrast with TTP, where the infusion of healthy plasma, in addition to the removal of the patient's plasma, is very important for recovery, some published reports (exemplified in the patient reported here) suggest that in the case of catastrophic APS, removal of the plasma containing the damaging substance may be enough to establish remission without the need for the infusion of healthy plasma. Because plasma infusion is generally associated with more severe immediate adverse effects than infusion of 5% albumin,[76] and because FFP may on occasion be associated with severe complications[77] whereas albumin solution is almost free of side effects, it might be advisable to begin treatment of a catastrophic APS with PE using 5% albumin as a replacement fluid and, only when there is a lack of prompt response, consider the use of FFP. The value of additional treatments (especially antiplatelet drugs and steroids) is unknown. An appropriate randomised study to assess the role of steroids has not been carried out. Consequent on this analysis and review, we recommend, in cases of TMHA in association with APS, the use of PE as a first line of treatment. However, steroids should be still used in association with anti-coagulation, in order to limit or treat the massive cytokine release.

In conclusion, TMHA is a rare complication in patients with APS but it may be the first clinical manifestation of this syndrome. Furthermore, it may be part of the multiorgan failure syndrome seen in patients with catastrophic APS. This would support the need for systematic screening for LA and aCL in all patients with clinical and laboratory features of microangiopathic haemolytic anaemia. In addition, the existence of TMHA in an APS mandates the ruling out of the existence of the catastrophic variant of this syndrome. PE, perhaps using albumin as the initial replacement fluid, is the most important component of treatment and is indicated as first line of treatment for all patients with TMHA associated with aPL.

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APPENDIX 1

CASE REPORT

A 32 year old man was admitted with a 2 week history of confusion, headache, vomiting, abdominal pain, and fatigue. His previous medical and surgical history was unremarkable, and no drugs had been taken previously. On admission, the patient appeared confused with a bi-temporal headache. Blood pressure was 155/90 mm Hg and physical examination did not disclose any significant findings, except for a distended, non-tender abdomen. Bowel sounds were sluggish. Initial laboratory data included white blood cell count 9.6×10^9/l with normal differential, haemoglobin 86 g/l, platelet count 48×10^9/l, lactate dehydrogenase 1159 IU/l (normal range 250–450), haptoglobin 0.087 g/l (0.320–1.810), and serum creatinine 140 µmol/l (30–110). Both direct and indirect Coombs' test were negative and peripheral blood smear showed many schistocytes. Urine analysis showed 2+ protein with mild haematuria (10 red blood cells/high power field). The prothrombin time and activated partial thromboplastin time were within the normal ranges, and normal D-dimer levels were found. Magnetic resonance imaging of the brain showed changes consistent with mild microvascular ischaemia in the cerebral white matter.

Soon after his admission, he developed episodes of an acute coronary syndrome (angina), and an electrocardiogram showed T wave inversion and Q waves on the inferior surface.

Creatine kinase and troponine T tests were normal. A myocardial gammagraphy perfusion study showed mild anterolateral and inferior ischaemia. LA (determined following the guidelines of the Subcommittee for the Standardisation of Lupus Anticoagulants of the International Society of Thrombosis and Hemostasis[78]) was present and aCL IgG, measured using standardised enzyme linked immunosorbent assay (ELISA; Chesire Diagnostics, Chester, United Kingdom), was markedly raised at 65.9 IgG phospholipid (GPL) units (normal<15 GPL units). Antinuclear, anti-double stranded DNA antibodies, rheumatoid factor, and cryoglobulin levels were negative. Because of altered mental status, microangiopathic haemolytic anaemia, thrombocytopenia, renal failure, and cardiac involvement, a presumptive diagnosis of catastrophic APS was made.

Treatment was started with PE using 5% albumin as replacement fluid (four sessions), intravenous prednisolone (80 mg daily), and intravenous heparin. After 20 days in hospital, his neurological, renal, and cardiac status stabilised and thrombocytopenia and microangiopathic haemolytic anaemia resolved. During 12 months of follow up, with tapering doses of prednisone and coumadin adjusted to an international normalised ratio of 2.5–3.5, there was no evidence of recurrent thromboembolism, although aCL IgM titres remained high (68 MPL units) and LA was still present.

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Table W1 Demographic and clinical characteristics of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Gender	Age* (years)	Diagnosis	Previous APS manifestations	Precipitating factor	Clinical presentation
1 (37)	F	30	SLE	-	-	Malignant hypertension
2 (37)	F	24	SLE	Spontaneous abortion	-	Malignant hypertension
3 (37)	F	33	SLE	-	-	Acute renal failure
4 (37)	F	29	SLE	Spontaneous abortion, fetal death	Pregnancy	Pregnancy-related renal failure
5 (37)	F	23	PAPS	Fetal death	Puerperium	Postpartum renal failure
6 (37)	F	20	PAPS	Fetal death	Puerperium	Postpartum renal failure
7 (37)	F	35	PAPS	Fetal death	Puerperium	Postpartum renal failure
8 (37)	F	30	PAPS	Fetal death	Pregnancy	Pregnancy-related renal failure
9 (37)	F	23	PAPS	Spontaneous abortion	Oral contraceptive	Malignant hypertension
10 (37)	F	25	PAPS	Fetal death	Pregnancy	Pregnancy-related renal failure
11 (46)	M	73	Systemic sclerosis	-	-	HUS
12 (16)	F	23	PAPS	TIA, fetal death, Livedo reticularis	Plasma exchange	Amaurosis fugax, Microangiopathic hemolytic anemia
13 (38)	F	33	PAPS	Spontaneous abortion	Pregnancy	Postpartum-HUS
14 (29)	F	19	SLE	-	-	TTP
15 (29)	F	32	SLE	-	-	TTP

Abbreviations: F: female; M: male; Age*: age at time of TMHA; APS: antiphospholipid syndrome; PAPS: primary APS; SLE: systemic lupus erythematosus; TIA: transient ischemic attack; DVT: deep vein thrombosis; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic-uremic syndrome; HELLP: hemolysis, elevated liver enzymes, and low platelet count; PS: present series.

Table W1: Demographic and clinical characteristics of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Gender	Age* (years)	Diagnosis	Previous APS manifestations	Precipitating factor	Clinical presentation
16 (33)	F	40	SLE	-	Arterial occlusion with amputation	HUS
17 (33)	M	26	PAPS	-	-	HUS
18 (41)	F	33	PAPS	-	-	Malignant hypertension
19 (72)	F	46	PAPS	Spontanoeus abortion, arterial trhombosis	-	Catastrophic APS
20 (35)	F	37	SLE-like	-	-	TTP
21 (35)	F	56	SLE	-	-	HUS
22 (35)	F	48	SLE	-	-	Thrombocytopenia
23 (59)	F	29	PAPS	Thrombocytopenia	Pregnancy	HELLP
24 (59)	F	33	PAPS	DVT Spontaneous abortions	Pregnancy	HELLP
25 (40)	F	17	PAPS	DVT	Pregnancy	Catastrophic APS
26 (39)	F	27	PAPS	Spontaneous abortions	Puerperium	Postpartum-HUS
27 (42)	M	65	SLE-like	-	-	HUS
28 (66)	M	29	PAPS	-	-	Malignant hypertension
29 (32)	F	25	PAPS	-	Acute enterocolitis in puerperium	Postpartum-HUS

Abbreviations: F: female; M: male; Age*: age at time of TMHA; APS: antiphospholipid syndrome; PAPS: primary APS; SLE: systemic lupus erythematosus; TIA: transient ischemic attack; DVT: deep vein thrombosis; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic-uremic syndrome; HELLP: hemolysis, elevated liver enzymes, and low platelet count; PS: present series.

Table W1: Demographic and clinical characteristics of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Gender	Age* (years)	Diagnosis	Previous APS manifestations	Precipitating factor	Clinical presentation
30 (54)	M	46	SLE	-	Renal biopsy	TTP
31 (60)	F	15	PAPS	-	-	HUS
32 (11)	M	34	SLE	DVT, arteriovenous fistula thrombosis	Renal trasplantation	Thrombotic microangiopathy in renal allograft
33 (9)	F		PAPS	DVT		
1st episode		67			-	Catastrophic APS
2nd episode		71			-	Catastrophic APS
34 (26)	F	33	SLE	-	-	Catastrophic APS
35 (58)	M	38	PAPS	Hemodialysis vascular access and renal graft thromboses	-	Malignant hypertension
36 (4)	M	50	PAPS	-	Renal trasplantation	HUS
37 (23)	F	30	PAPS	-	Pregnancy	HUS
38 (62)	F	18	PAPS	-	-	HUS
39 (53)	F	38	SLE	-	-	TTP
40 (53)	F	23	PAPS	-	-	TTP
41 (6)	F	22	SLE	-	Puerperium	Catastrophic APS
42 (57)	F	65	PAPS	-	Fetal death, HELLP	Catastrophic APS

Abbreviations: F: female; M: male; Age*: age at time of TMHA; APS: antiphospholipid syndrome; PAPS: primary APS; SLE: systemic lupus erythematosus; TIA: transient ischemic attack; DVT: deep vein thrombosis; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic-uremic syndrome; HELLP: hemolysis, elevated liver enzymes, and low platelet count; PS: present series.

Table W1: Demographic and clinical characteristics of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Gender	Age* (years)	Diagnosis	Previous APS manifestations	Precipitating factor	Clinical presentation
43 (3)	F	22	SLE	Fetal death	Infection	Catastrophic APS
44 (76)	F	28	PAPS	-	-	Catastrophic APS
45 (15)	M	7	PAPS	HUS with negative aCL 7 months before	-	Catastrophic APS
PS	M	32	PAPS	-	-	Catastrophic APS

Abbreviations: F: female; M: male; Age*: age at time of TMHA; APS: antiphospholipid syndrome; PAPS: primary APS; SLE: systemic lupus erythematosus; TIA: transient ischemic attack; DVT: deep vein thrombosis; TTP: thrombotic thrombocytopenic purpura; HUS: hemolytic-uremic syndrome; HELLP: hemolysis, elevated liver enzymes, and low platelet count; PS: present series.

Table W2 Treatment and outcome of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Therapy	Outcome
1 (37)	Steroids	Stabilized but died later of infection
2 (37)	-	Bilateral nephrectomy for hypertension control. Dyalisis, transplantation
3 (37)	NR	Died of massive hemorrhage following abdominal surgery
4 (37)	Steroids	Well, but impaired renal function
5 (37)	Heparin+Steroids+Dypiridamol	Well. Renal function improved
6 (37)	PE	Well. Renal function returned promptly to normal
7 (37)	PE	Well. Renal function returned promptly to normal
8 (37)	NR	Well, but impaired renal function
9 (37)	Anticonceptive withdrawal	Spontaneous resolution after ceasing oral contraceptive
10 (37)	NR	Well. Renal function improved
11 (46)	AAS+Infusion of FFP	Well, but impaired renal function
12 (16)	Coumadin+Steroids+PE	Thrombocytopenia unaffected
	Stop PE	Platelet count returned to normal within 5 days after the last plasma exchange.
13 (38)	PE+Dypiridamol+AAS	Well. Renal function improved
14 (29)	Steroids	Platelet count decreased and renal function continued to deteriorate
	PE (FFP)+Cyclo	Her condition dramatically improved
15 (29)	Steroids	Mental status worsened with a right hemiparesis and platelet count decreased
	PE (FFP)+Cyclo	Mental status improved and platelet count began to rise
16 (33)	Steroids	Platelet count decreased
	Heparin	Platelet count increased and creatinine decreased
		Steroids, Azathioprin and warfarin were administered for 2 years without recurrence of thrombotic episodes and normal renal function

Abbreviations: AAS: acetyl-salicylic acid; Cyclo: cyclophosphamide; FFP: fresh-frozen plasma; IVIg: intravenous immunoglobulins; NR: not reported; PS: present series. PE (ALB) or (FFP): plasma exchange using (ALB) albumin or FFP as replacement fluid

Table W2: Treatment and outcome of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	**Therapy**	**Outcome**
17 (33)	Steroids+AAS+PE (FFP and normal saline)	Platelet count increased and creatinine improved and stabilized Discharged on steroids, azathioprin, and AAS. During the next 9 months, hospitalized twice for pulmonary emboli. Over the next 6 months, he had progressive renal insufficiency and finally, he died of *Staphylococcus epidermidis* endocarditis.
18 (41)	PE (FFP)	Increase in hematocrit and platelet count and improvement of the renal function Discharged on AAS, steroids
19 (72)	AAS+Dypiridamol+PE (FFP)+ Steroids+Cyclo	Hematological improvement was not followed by renal improvement. She died 26 days after admission of catheter-related staphylococcal sepsis
20 (35)	Steroids	No changes in neurologic status and platelet count decreased
	PE (FFP)	Improvement in neurologic status and platelet count began to rise
21 (35)	Steroids+Cyclo+AAS	Patient continued to have thrombocytopenia and episodes of stroke.
22 (35)	Steroids+Cyclo+IVIg	Platelet count decreased
	PE (FFP)+Vincristine	Platelet count increased but hemolytic anemia recurred. Died of acute myocardial infarction (over 1 year)
23 (59)	Steroids	Clinical status did not improve, platelet count and transaminitis remained abnormal
	PE (FFP and saline)	Clinical status improved with normalization of platelet count and liver enzymes
24 (59)	Heparin+Steroids	Platelet count decreased with increasing of liver enzymes
	PE (ALB and saline)	Marked drop in liver enzymes. Abdominal continued but less severe
	PE (FFP)	Improvement with plasma exchange, steroids and anticoagulation. Liver enzymes and platelet count returned to normal. Discharged on warfarin and steroids

Abbreviations: AAS: acetyl-salicylic acid; Cyclo: cyclophosphamide; FFP: fresh-frozen plasma; IVIg: intravenous immunoglobulins; NR: not reported; PS: present series. PE (ALB) or (FFP): plasma exchange using (ALB) albumin or FFP as replacement fluid

Table W2: Treatment and outcome of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Therapy	Outcome
25 (40)	PE +Steroids	Clinical status improved markedly. At this point, heparin was initiated. Platelet count increased but creatinine remained elevated. Discharged on steroids and heparin
26 (39)	Infusions of FFP	Thrombocytopenia resolved but renal function remained impaired The patient remained dialysis dependent for 7 months and then there was gradual recovery of renal function
27 (42)	Steroids+Azathioprin	The patient improved progressively over the next 3 weeks
28 (66)	PE (FFP)	Increase in platelet count; upon withdrawal of the PE, thrombocytopenia recurred. When AAS was prescribed (after receiving aCL determination results), the platelet count returned to normal. There was no improvement in renal function, and the patient was discharged on hemodyalisis
29 (32)	Infusion of FFP	No significance response was noted
	PGE1+Heparin	Acute renal failure, hypertension and episodic anemia still persisted. Discharged on peritoneal dialysis
30 (54)	Steroids+Cyclo	Renal function deteriorated over 2-week period
	PE (FFP)	Clinical status worsened and patient died of catastrophic APS
31 (60)	Heparin+Steroids+Cyclo	Thrombocytopenia and renal failure remained unchanged
	IVIg+PE +Steroids	Platelet count increased and serum creatinine decreased. Discharged with maintenance immunosuppresion consisted of steroids, azathioprin and IVIg every 4 weeks
32 (11)	PE (ALB and FFP)	Platelet count normalized.

Abbreviations: AAS: acetyl-salicylic acid; Cyclo: cyclophosphamide; FFP: fresh-frozen plasma; IVIg: intravenous immunoglobulins; NR: not reported; PS: present series. PE (ALB) or (FFP): plasma exchange using (ALB) albumin or FFP as replacement fluid.

Table W2: Treatment and outcome of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Therapy	Outcome
33 (9)		
1st episode	Steroids+Warfarin	Renal function and mental status returned to baseline. Discharged on warfarin
2nd episode	Steroids+Warfarin (INR 3.0-3.5)	Transaminitis and microangiopathic hemolytic anemia resolved gradually.
34 (26)	Steroids+Cyclo+AAS	Died of catastrophic APS
35 (58)	NR	NR
36 (4)	PE	Died (21 d): catastrophic APS
37 (23)	Steroids	Platelet count remained persistently low and creatinine began to rise
	PE	Renal function and thrombocytopenia gradually improved
38 (62)	Steroids	Renal function was deteriorating rapidly and dialysis was begun. Discharge on steroids and dipyridamole
39 (53)	PE +Steroids+ AAS+ Dipyridamol+IVIg+Vincristine	In spite of this continuous escalation of treatment, her condition remained refractory, and she died of massive cerebral hemorrhage
40 (53)	PE +Steroids+AAS	Recovery
41 (6)	NR	Died of catastrophic APS
42 (57)	PE (FFP) +Steroids	Patient remained critically ill
	Heparin+ PE +Steroids	After 40 days clinical status stabilized. Discharged on steroids and warfarin. Three weeks later thrombocytopenia developed and neurologic status worsened. IVIg was added to the treatment and the platelet count rose to normal, but the mental status continued to deteriorate. Monthly intravenous cyclo did not improve the patient, and PE without FFP was restarted. Dramatic improvement was noted within 48 hours. Patient responded to repeated PE over 3 years.

Abbreviations: AAS: acetyl-salicylic acid; Cyclo: cyclophosphamide; FFP: fresh-frozen plasma; IVIg: intravenous immunoglobulins; NR: not reported; PS: present series. PE (ALB) or (FFP): plasma exchange using (ALB) albumin or FFP as replacement fluid.

Table W2: Treatment and outcome of patients with thrombotic microangiopathic hemolytic anemia associated with antiphospholipid antibodies.

Patient No. (reference)	Therapy	Outcome
43 (3)	Cyclo+Steroids+IVIg+Heparin	Blood pressure remained elevated with worsening of neurologic status. Finally, the patient underwent left nephrectomy because of hematomas that led to severe hypertension. Discharged on steroids.
44 (76)	PE +Heparin+ Steroids+Cyclo	After 3 days rapid neurologic and laboratory improvements were noted Discharged on steroids and coumadin (INR 3-3.5), there was no evidence of recurrent thromboembolism
45 (15)	Infusion of FFP+IVIg PE	Patient developed acute renal failure with severe hypertension Improvement in hematological parameters, but never recovered the renal function and patient received peritoneal dialysis. Seven months later, a relapse was observed with a severe dilated cardiomyopathy and painful acrocyanosis (probable catastrophic APS). PE was restarted with improvement in hematological parameters, but no improvement was noted in cutaneous lesions. Iloprost infusion and low molecular weight heparin were initiated, with no apparent effect, and later on vincristine with a complete remission of the acrocyanosis and an improvement on echocardiographic findings.
PS	Steroids+ PE (ALB) +heparin	Recovery Discharged on tapered steroids and warfarin (INR 2.5-3.5). No further thrombotic events after 12 months of follow-up

Abbreviations: AAS: acetyl-salicylic acid; Cyclo: cyclophosphamide; FFP: fresh-frozen plasma; IVIg: intravenous immunoglobulins; NR: not reported; PS: present series; PE (AL) or (FFP): plasma exchange using (AL) albumin or FFP as replacement fluid.