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Systemic autoimmune disorders associated with haemolytic uremic syndrome: a cross-sectional analysis from the French National TMA registry

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Short title: Systemic autoimmune disease-associated HUS

Abstract

Context. Systemic auto-immune diseases (SAID)-associated atypical haemolytic uremic syndrome (HUS) is a rare disorder within the spectrum of thrombotic microangiopathies (TMA) whose management remains debated.

Objectives. To provide a demographic, clinical and therapeutic picture of SAID-HUS.

Methods. A cross-sectional analysis was conducted on adult patients presenting with SAID and HUS from the French National TMA Registry over a 20-year period. Clinical features were extracted and compared to those from a historical cohort of aHUS patients.

Results. Forty-one patients with SAID-HUS were compared to 78 patients with aHUS from a historical cohort. Thirty-nine connective tissue diseases (CTD) were found: systemic lupus erythematosus (n=18), primary Sjögren's syndrome (n=6), systemic sclerosis (n=11), mixed CTD (n=2) and 2 cases of vasculitides, including 7 overlapping forms and 8 cases of primary antiphospholipid syndromes (APLS). Patients with SAID-HUS generally had pre-existing chronic kidney failure (OR= 3.17, 95%CI: 1.204 to 7.923; p= 0.016) compared to aHUS patients, though creatinine levels were significantly lower (216 [IQR, 108-334] $\mu\text{mol/L}$ vs. 368 [IQR, 170-722] $\mu\text{mol/L}$; p= 0.002). Patients were less likely to recover if renal replacement therapy was needed at onset (OR= 0.07; 0.02 to 0.34; p <0.0005). Two patients died. Thirty patients responded to immunosuppressive treatment and complete remission was achieved in 25 cases. By contrast, TPE did not have an early effect on TMA features at Day-7 nor Day-15 (p >0.05).

Conclusion. The management of SAID-HUS implies an early initiation of immunosuppressive drugs for flares of the associated SAID, whereas TPE seem ineffective.

Keywords:

Thrombotic microangiopathy; haemolytic uremic syndrome; autoimmune disease; connective tissue disease; systemic lupus; systemic sclerosis

Key messages:

- Systemic auto-immune diseases (SAID) in atypical haemolytic uremic syndrome (HUS) include mainly systemic lupus erythematosus, systemic sclerosis and primary Sjögren's syndrome.
- SAID-associated HUS improves with the treatment of the underlying SAID
- TPE does not seem have an early effect on TMA features at Day-7 nor Day-15

Introduction

The term thrombotic microangiopathy (TMA) defines a syndrome characterized by the association of a peripheral thrombocytopenia, a mechanical haemolytic anaemia and organ failure [1]. Thrombotic thrombocytopenic purpura (TTP) and the haemolytic uremic syndrome (HUS) (including Shigatoxin-associated HUS and atypical HUS [aHUS]) are the two most common forms of TMA. aHUS can also occur in association with treatments such as antineoplastic agents, recreational drugs, or various other conditions such as transplantation, malignant hypertension or systemic auto-immune diseases (SAID). From a pathophysiological viewpoint, features of TMA reflect vascular damage with arteriolar and capillary thrombosis and endothelial abnormalities occurring in patients with determined risk factors [1]. TTP results from a severe deficiency in the von Willebrand factor-cleaving protease ADAMTS13 (A Disintegrin and Metalloproteinase with Thrombospondin-1 motifs; 13th member), that is either due to antibodies directed against the enzyme (immune-mediated TTP [iTTP]) or to biallelic mutations of the encoding gene. aHUS is, on the other hand, a consequence of a deregulation of the alternative complement pathway that leads to excessive endothelial deposits of C5a and C5b9 [2]. Of note, when TMA is associated with an underlying condition – typically with detectable or normal ADAMTS13 activity, it is usually referred to as “secondary aHUS” [3]. However, whether alterations in the alternative complement pathway play a part in secondary aHUS is still a matter of debate [3].

TMA seem to be overrepresented in patients with SAID [4,5]. A previous study had sought to characterize autoimmune diseases associated with iTTP [6]. Such forms make up less than 15% of all iTTP [5]. Though therapeutic management as well as prognostic factors such as relapse, flare-up or death did not significantly differ from those of iTTP without SAID [6] – on iTTP diagnosis, anti-dsDNA and anti-SSA antibody-positivity were found to be potential risk factors for the development of SAID [6]. In patients with a detectable ADAMTS13 activity, microangiopathic haemolytic anaemia and thrombocytopenia may be primary features of SAID, suggesting that “secondary aHUS” is more common in SAID than previously thought [7]. SAID-associated HUS have been difficult to assess due to knowledge gaps that range from epidemiological features, to clinical presentations and treatment strategies. SAID-HUS may also differ from aHUS whose prognosis has greatly improved during the last decade as comprehension of pathophysiological mechanisms have increased and have led to treatment strategies involving anti-complement agents [8].

SAID-HUS have heterogeneous presentations – with systemic lupus erythematosus (SLE) being its best described aetiology [9–11]. Other forms include (but are not limited to) APLS [12] and scleroderma renal crises (SRC) [13]. In some cases, TMA is purely renal and diagnosis is ultimately histopathological [14]. This begs the role of immunosuppressive treatment to control the underlying SAID in the management of patients with SAID-HUS, and whether TPE and complement blocking strategies should be given in such circumstances, as it is the case for aHUS [15,16].

We chose to focus, through a cross-sectional analysis of data from the French national TMA registry, on this lesser-known group of SAID presenting with TMA in adult subjects. Our objectives are to provide a demographic and clinical picture of SAID-HUS and assess therapeutic approaches.

Materials and Methods

Study population and definitions

Over a period spanning from October 2000 to October 2019, records of adult patients (age > 18 years) included in the registry of the French reference centre for TMAs were extracted (**Supplementary material**). TMA patients who fulfilled criteria for SAID – but with a detectable ADAMTS13 activity ($\geq 20\%$) to exclude patients with TTP – were included in the study (**Figure 1**). To address whether SAID modifies clinical presentation or impacts prognosis, characteristics of these patients were then compared to those of a historical cohort of adult (≥ 18 years) aHUS patients, from our Registry, without SAID, but with detectable ADAMTS13 activity [16]. These aHUS patients did not have confounding factors such as HIV infection, cancer and/or chemotherapy, transplantation, and malignant hypertension. Patients with Shiga-toxin and *Escherichia sp.* associated-infections were also excluded.

Flare-ups and relapses were defined as per the Consensus terminology promoted by the International Working Group for TTP [7]. Durable platelet recovery was defined as a sustained normalisation of the platelet count at Day-15 from the initiation of therapeutic plasma exchange (TPE). Kidney failure was defined by an estimated glomerular filtration rate (eGFR) of less than 60 mL/mn/1.73m² or, when eGFR was unavailable, plasma creatinine levels of more than 100 $\mu\text{mol/L}$.

SLE was mostly defined according to the 2019 European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) classification criteria, but previous international classification criteria were also accepted [17,18]. APLS could also refer to patients presenting with its catastrophic form [19,20], prior to the

knowledge of TMA on renal biopsies. Primary Sjögren's syndrome (pSS) was diagnosed based on the 2016 ACR/EULAR consensus [21] whereas diagnoses of systemic sclerosis (SSc) were reassessed using the 2013 ACR/EULAR criteria [22]. Patients with SAID were required to not have cancer or HIV infection. All cases were reviewed for accuracy by 2 senior authors (NM and PC).

Clinical parameters

Clinical features on admission were systematically extracted. For patients with available data, outcome was assessed at three, six and twelve months. Previously identified prognostic features, such as lactate dehydrogenase (LDH) levels and central nervous system involvement, were similarly described [23]. The *French score* [24] was systematically determined for each subject : a platelet count $< 30.10E9/L$ and serum creatinine $< 200 \mu\text{mol/L}$ being highly suggestive of TTP. We also sought to calculate the *chronic kidney disease (CKD) score* described in [16], in the event that it could be used as a marker for SAID-TMA. ADAMTS13 activity and anti-ADAMTS13 antibodies were assessed as previously described [5].

Renal biopsies

Histopathology reports of patients with SAID-TMA who underwent routine renal biopsies were reclassified according to the following categories: glomerular injury, tubular injury, endocapillary hypercellularity, interstitial fibrosis and vascular lesions. Lupus nephritis class was determined based on the 2003 International Society of Nephrology and Renal Pathology Society (ISN/RPS) classification [25]. Histological evidence of SRC and APLS was also noted based on pathological records.

Treatment

Treatment strategies including hospitalization in intensive care units, transfusion of blood and blood products, TPE, corticosteroids, hydroxychloroquine, immunosuppressors, disease-modifying anti-rheumatic drugs (DMARDs), and biologics (i.e. rituximab and eculizumab) were reported.

Statistical analysis

Continuous variables are expressed as median values with their interquartile range (IQR) and extreme values are specified when appropriate. Differences between groups were analysed using the Mann-Whitney test. The chi-square test was used to study statistical associations between qualitative variables. Odds ratios (OR) and their 95% confidence intervals (95%CI) were calculated accordingly and Fisher's exact test used for P-value calculations. Due to the small study samples, logistic regression was not conducted. P-values of less than 0.05 were considered statistically significant using two-sided tests. Statistical analyses were performed with GraphPad® Prism 6.2 and MS Excel 2010.

Ethics

Informed patient consent was gathered as part of routine clinical practice and data were anonymized at the time they were recorded for the Registry. Due to its retrospective approach, this study did not require specific approval from an institutional review board. Data storage and its use complied with standards of the French Data Protection Authority ([Supplementary material](#)).

Results

Patient characteristics

Sixty-two cases from a total of 2493 patient-files were extracted from the Registry using filters for “autoimmune disease” and “HUS” ([Figure 1](#)). Fourteen records were wrongly classified owing to organ specific autoimmune disease (such as autoimmune thyroiditis, or multiple sclerosis) (n=3), or incomplete classification criteria for the suspected connective tissue disease (CTD) and/or missing data (n=11). Ultimately, 41 cases of SAID-HUS were available for analysis. From the historical cohort of aHUS – after excluding malignant hypertension-related causes – 78 patients were included for the group comparison ([Figure 1](#)). Of these 78 patients, a full complement deficiency workup was performed in 56 cases and mutations were identified in 12 cases (21.4%): CFH (n=5), CFI (n=4), MCP (n=2) and C3 (n=1).

Details on SAID are presented in [Table 1](#). Overlapping forms of CTD are represented in a Venn diagram ([Figure 2a](#)). Ten patients had a positive workup for antiphospholipids of which, 4 were “triple positive” for lupus anticoagulant, anti-β2-glycoprotein I and anti-cardiolipin antibodies. Antiphospholipid antibodies were identified on multiple occasions not less than 12 weeks apart in 8 documented cases. However, none showed signs of

macrovascular thrombosis at the time of aHUS and ALPS was diagnosed concomitantly to TMA features in all but 2 cases. Two patients had systemic vasculitides consisting in *polyarteritis nodosa* with renal involvement and ANCA-positive renal micropolyangiitis (reported in [26]). In 10/41 cases, the diagnosis of SAID was made at the same time as that of aHUS or briefly after. In the 31 remaining cases, the pre-existing SAID was known to the clinician. The median time between the first manifestations of SAID and TMA was of 3.34 years (IQR, 13.5 days-3.45 years). No SAID was reported during the follow-up of patients from the historical aHUS cohort.

Clinical features of SAID-HUS (Table 2)

Patients with SAID-HUS were in their early forties at the time of diagnosis. They were mostly females and unlike aHUS subjects, were more often known to have pre-existing chronic kidney failure (OR= 3.17, 95%CI: 1.204 to 7.923; p= 0.023) than aHUS patients, though creatinine levels at presentation were significantly lower (p=0.002) (Table 2). LDH levels were also lower. There was no difference in *the CKD score* [16] between either group. Neurological involvement and cardiovascular features (i.e. hypertension) had a comparable prevalence between SAID-HUS and aHUS.

Kidney and neurological involvement whether associated or not with TMA defined active SAID. Overall, 23/41 patients were previously following immunosuppressive therapy for their SAID at the time of aHUS diagnosis. Long-term therapy with DMARDs prior to admission was mostly given to SLE patients: methotrexate (n=4), mycophenolate mofetil (n=4) and azathioprine (n=2). Only 2/11 patients with SSc had ongoing steroid therapy prior to their hospitalization, but dosing was not recorded. At the time of the diagnosis of SRC, patients with SSc had a disease progression of less than 4 years and positive anti-centromere (n=1), anti-topoisomerase I (n=3), anti-RNA-polymerase III (n=1) and anti-PM-Scl (n=2) antibodies. These markers overlapped with anti-SSA antibodies on 2 occasions.

Renal biopsies were performed in 26 SAID-HUS patients. Pathological lesions were mostly glomerular (n=24) with an overlap of tubular lesions (Figure 2b). TMA-specific features were described in 25/26 kidney specimens (Figure 2c) with 16 lupus-related glomerulonephritis and 4 SRC. Lupus nephritis presented the following classes: II (n=2), III (n=2), IV (n=7), IV+V (n=1) and V (n=2). Reports also documented endocapillary hypercellularity (11/14) and interstitial fibrosis (11/12). Vascular damage was found in 22/26 specimens. Lympho-plasmocytic

infiltration was identified in pSS irrespectively of signs of cryoglobulinaemic vasculitis. Activity and chronicity indexes were not systematically available for SLE specimens and were therefore not studied.

Three female patients with SAID-HUS (i.e. 2 APLS and 1 SLE) were pregnant at the time of HUS diagnosis and pregnancy outcomes were favourable with deliveries occurring within the 27th and the 34th weeks of gestation.

Treatment and outcomes

More than half of patients with SAID-HUS were hospitalized in an intensive care unit (ICU) and 18/41 required renal replacement therapy. Six patients, who had a *French score of 2*, received TPE with a median of 4.5 (IQR, 1.75-6.5) procedures. For these patients, TPE – but also caplacizumab (n=1) – were discontinued when iTTP was eliminated in patients with SLE, MCTD, SSc and ALPS (**Table 2**). However, 22 patients were treated with TPE despite having features of aHUS (*French score* ≤ 1) and/or ADAMTS13 activity $\geq 20\%$. These patients received between 3 to 53 TPE procedures (median number of procedures of 14 [IQR, 9.75-25]) that were usually followed by immunosuppressive therapy. Both patients with vasculitides received TPE. Treatment combinations associating TPE (n=26) and their outcomes are presented in **table 3**. Of interest, all 26 SAID-HUS patients had received steroids or immunomodulatory/immunosuppressive drugs prior to TMA. **Figure 3** illustrates the trend in platelet counts in 10 patients with SLE with sufficiently available biological data who underwent TPE procedures and suggests that TPE was unable to provide an early improvement of TMA. Conversely, an effect on platelet count, kidney function as well as sustained haematological response resulted from concomitant immunosuppressors. This is highlighted by the remaining 15 patients who did not receive TPE and were treated specifically for their SAID with similar outcomes. Overall, when early platelet-response (i.e. platelet count $\geq 150.10E9/L$) was compared between patients receiving TPE (n=16) and those who did not (n=11): there was no statistically significant differences at Day-7 (p=0.440) and/or Day-15 (p=0.180).

The 3 patients who had been started on second-line eculizumab therapy after receiving steroids and TPE for SSc, SLE and MCTD were respectively taken off the drug after 6, 3 and 2 infusions. The patient with MCTD died shortly after the 2nd infusion. Complete remission was only obtained in the case of SSc but could not be attributed to eculizumab as the diagnosis of SRC led to a change in the therapeutic approach (i.e. discontinuation of steroids). The SLE patient did not receive an immunosuppressor despite having focal and segmental glomerulosclerosis on

kidney biopsy and was lost to follow-up after 104 days. None of the 3 patients had antiphospholipid antibody markers.

TMA was treated as a flare-up of SAID in 30 cases, with an induction therapy of either rituximab (n=5) or cyclophosphamide (n=6), or both (n=3) in the case of SLE, APLS and medium/small vessel vasculitides. DMARDS were usually either mycophenolate mofetil (n=7), azathioprine (n=1), tacrolimus (n=1), or methotrexate (n=1) and used as maintenance therapy. Complete remission was achieved after splenectomy in a setting of refractory TMA due to SLE-associated catastrophic APLS. None of the patients received platelet transfusions. All 30 patients responded to treatment with complete remission being documented in 25 cases. Remission was achieved after a median of 30 days (IQR, 18;62.5). Durable recovery from kidney failure was achieved in 4/22 patients and 3/22 patients required chronic dialysis, which was not significantly different from the 17/78 aHUS patients (p=0.069).

Four patients experienced treatment refractoriness (i.e. patients without a durable platelet recovery in relation to an ongoing HUS): SSc (n=2), SLE (n=1), APLS (n=1). The 2 patients with SSc were on steroids, and patients with the SLE and APLS received immunosuppressive therapy. SAID-HUS flare-ups were described in 2 cases and there were only 2 cases of relapse. Neither flare-up episodes nor relapses were associated with death.

Out of 17 patients with central nervous system features, 14 had a complete recovery of neurological symptoms while the remaining 3 had stroke sequelae.

Hospital stays lasted a median of 28 days (IQR, 18.5-55) (range, 6-353 days). Two patients, one with SSc and the other with MCTD, died during their hospitalization at day-15 and day-26, respectively.

Prognostic markers for SAID-HUS

Patients were less likely to achieve complete remission of SAID-HUS if they needed renal replacement therapy at the onset (OR= 0.07; 0.02 to 0.34; p <0,001). Steroid treatment and anti-hypertensive drugs taken prior to the TMA could not be associated with more complete remission. Neither renal replacement therapy nor intensive care were associated with worse long-term outcomes. None of the clinical nor biological features were significantly associated with remission status. On the other hand, patients achieving remission had lower plasma urea levels (p= 0.002). There was no difference in platelet values or serum creatinine levels between responders and non-responders. Lastly, SRC without the appropriate support treatment including angiotensin-converting enzyme (ACE) inhibitors and the early discontinuation of steroids were less likely to respond than SLE patients.

Long-term follow-up

Relapse of SAID-HUS was noted in one SLE patient who experienced a flare-up. The only other case of HUS relapse was identified in another SLE patient who was previously believed to have Evans syndrome (i.e. positive direct antiglobulin test) and who presented with hypertensive encephalitis. Signs of TMA and lupus nephritis were found on the renal biopsy of this patient but no further signs for a lupus flare were found.

Since discharge from hospital, follow-up ranged from 2 days to 6.34 years.

Discussion

This cross-sectional analysis provides a new insight into SAID-HUS. Small sample sizes in mostly retrospective cohorts and undifferentiation between TTP and other forms of TMA in previously published series have led to few changes to the clinical approach of SAID-HUS. To the best of our knowledge, ours is the first to assess SAID-HUS and evaluate its management.

Unlike SAID associated with iTTP, those occurring in aHUS either precede microangiopathic signs or are found simultaneously [6,27]. Hence, up to a quarter of patients had a known active SAID at the time SAID-HUS was suspected. SLE and pSS are just as frequently observed in SAID-HUS as in iTTP, reflecting the prevalence of these CTD amongst SAID [6]. Moreover, there is no evidence to support that one group presented with more severe forms of SAID.

Few biological markers setting apart SAID-HUS from aHUS are available to clinicians. Kidney failure is often less pronounced even though patients with SAID-HUS present more frequently with chronic kidney disease. Extra-renal and extra-haematological features, especially CNS involvement, can however be suggestive of HUS diagnosis in the context of SAID and highlight the importance of a clinical knowledge of CTD. However, inflammatory rheumatic disorders without overt physical signs – such as pSS – or primary APLS, may be more problematic to identify and to treat. It thus becomes crucial to have immunological markers (i.e. antinuclear antibodies) to provide early diagnoses of CTD since SAID-HUS are to be treated differently from aHUS.

Unsurprisingly, SLE is the most prevalent aetiology of SAID-HUS. It is also the most frequently diagnosed CTD [28]. TMA represents around 10% of cases of lupus nephritis [10,29]. It is known as one of the most severe forms of renal vascular disease in SLE with a high mortality rate, and appears to be an independent risk factor for

renal outcome in lupus nephritis [9]. Generally, these patients present only with pathologically evidence of TMA but they have also been found to have fairly active diseases with increased SLEDAI scores as it was the case in our series [9,27]. TMA is systematically found with lupus nephritis [4]. Diagnosing lupus in such circumstances is rarely challenging since most patients have systemic manifestations (i.e. cutaneous, articular, pleural, respiratory and even neurological features) [4,9]. Echoing findings from previous studies on TMA-associated CTD, antiphospholipid antibodies were not predisposing conditions for TMA [4,6]. On the other hand, very little is known of pSS associated-TMA and only 6 cases (including overlap syndromes) were documented over the 20-year period of the Registry. pSS associated-TMA is uncommon and has been described in the context of iTTP and to a lesser extent in aHUS [6,30,31]. Typical renal features of pSS are tubulo-interstitial and result from lymphoplasmocytic infiltration [32]. Of importance, SRC is associated with mortality, and though it occurs in less than 5% of patients with SSc, identifying adverse prognostic factors – such as the use of high-dose steroids – is crucial for its proper management [33,34].

There is no clear consensus on the therapeutic approach to SAID-HUS. In most cases, treatment of the SAID with immunosuppressive drugs led to the control and even to the remission of the TMA syndrome along with its associated SAID. Accounting for refractory disease, TPE was still liberally used despite the lack of evidence for its efficacy in SLE and other connective tissue disorders [35,36]. Moreover, TPE has not been found to improve mortality or prevent end-stage kidney disease in ANCA-associated vasculitides [37], and evidence is lacking to suggest its efficacy in vasculitides-associated TMA. As the management of SAID-HUS mostly requires controlling the underlying CTD, it is likely that TPE lacks efficacy in SAID-HUS. Our results cannot support the use of TPE for the treatment of SAID-HUS.

We found that despite the heterogeneity of the cohort, mortality is relatively low in SAID-HUS as only 2 deaths associated with refractory disease were reported. One of the 2 patients who died presented with a refractory SRC despite symptomatic measures and the other, suffering from MCTD, did not receive immunosuppressive therapy. Patients with SSc need to be considered as a high-risk group for mortality [33]. This implies that controlling the underlying SAID is the cornerstone of the treatment of SAID-HUS and that a delay in immunosuppressive therapy may negatively impact the overall prognosis.

Eculizumab was used in only 3 cases, including for SRC, with disappointing results. Previous case-series and reviews have also failed to provide solid evidence for the efficacy of eculizumab in SLE-associated TMA [12,38]. In most cases, patients received other immunosuppressive drugs either prior and/or in combination with eculizumab

[38]. There are no controlled trials involving the latter for the treatment of CTD-associated TMA. Other than in refractory (catastrophic) APLS, we believe that eculizumab cannot be promoted in SAID-HUS at this time [12,39].

Our study has limitations. There was no centralized testing of immunological markers and/or their retesting; and parameters for SAID activity (i.e. such as complement fractions) are not reported as these data were often lacking in patient files submitted to our Registry. Furthermore, we do need to acknowledge the selection bias due to improvements made to the management and understanding of SRC that have led to fewer cases and reduced mortality over time [40]. In the same vein, it is likely that SRC and lupus nephritis were managed in expert centres that did not systematically perform ADAMTS13 dosing for TMA, precluding the patient's inclusion in the Registry. Despite these drawbacks, we were able to pretty reliably describe a mostly overlooked group of TMA. Our findings reflect what has previously been described in cancer-associated TMA [41] – in the sense that treating the underlying disease is crucial to managing aHUS, and that TPE is probably ineffective.

In the setting of such infrequent clinical entities, we believe in the implementation of prospective long-term patient registries to gain better knowledge of heterogeneous diseases such as SAID-TMA. The absence of standards of care require a more systematic approach that includes performing timely renal biopsies. Furthermore, the management of SAID-HUS relies on clinical understanding of CTD, as some SAID (i.e. SSc) require a specific therapeutic approach. The latter revolves around treating SAID flares and/or its systemic complications by initiating immunosuppressive therapies.

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Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Tables

Table 1. Diagnoses-associated with SAID-HUS, immunological features, treatment strategies.

	SAID-HUS (N=41)
Clinical aspects	
Connective tissue disease and APLS, n	39
Systemic lupus erythematosus, n	19
Primary Sjögren's syndrome, n	7
Systemic sclerosis, n	11
Mixed connective tissue disease, n	2
Primary APLS, n	8
Overlap forms, n	7
Vasculitides, n	2
Ongoing treatments at baseline	
Anticoagulant treatment, n	5
Antiplatelet drug, n	1
Hydroxychloroquine, n	14
Steroids, n	10
DMARD, n	10
Cyclophosphamide, n	7
Rituximab, n	1
Intravenous immunoglobulins, n	1
Treatment strategies for TMA	
Hospitalization in Intensive care	27
Antithrombotic treatment, n	17
Antihypertension drugs, n	35
Renal replacement therapy, n	18
Plasma exchange therapy, n	26
Number of TPE procedures, median [IQR]	10 [2-17.5]
Steroids, n	30
Hydroxychloroquine, n	15
DMARD, n	9
Cyclophosphamide, n	9
Rituximab, n	11
Caplacizumab, n	1
Packed red blood cell transfusions, n	23
Number of transfused packed red blood cells, median, [IQR]	2 [1-8]
Fresh frozen plasma transfusions, n	13
Eculizumab, n	3

Table 2. Demographics, clinical, biological and radiological features at baseline.

	SAID-HUS N=41	aHUS N=78	<i>p-value</i>
Age, years, median [min-max]	42 [18-78]	41 [18-90]	
Male-to-female ratio, M/F	10/31	23/55	0.67
Time to HUS diagnosis, days, median [min-max]	3 [-32-8]	5 [2-13]	0.155
Pre-existing renal failure, n	12	9	0.023
Pregnancy-related, n	3	NA	
BMI, kg/m², median [IQR]	23.1 [19.7-25.9] (n=19)	24 [22-26.6] (n=38)	
Mean arterial pressure, mmHg, median [IQR]	110 [93-129]	110 [97-120]	
CKD score, median [IQR]	2 [1-4]	3 [2-4]	0.073
Fever, n	3	6	
Neurological involvement, n	21	31	0.250
Headache, n	13	12	
Confusion, n	10	12	
Seizures, n	10	6	
Coma, n	6	4	
Focal deficit, n	7	11	
Chest pain, n	2	NA	
Hypertension, n	35	51	
Pericardial effusion, n	2	NA	
WBC, *10E9/L, median [IQR]	9.26 [6.88-12.90] (n=35)	9.39 [6.41-12.90] (n=78)	
Haemoglobin, g/L, median [IQR]	85 [67.5-10.2] (n=40)	86.5 [6.98-9.65] (n=77)	
Platelets, *10E9/L, median [IQR]	79.5 [38.3-105] (n=38)	67 [31.5-127] (n=76)	0.750
ADAMTS-13 activity ≥20%,	33 (n=33)	78	
Urea, mmol/L, median [IQR]	24.7 [13.5-31.9]	25 [13.5-34.3]	
Creatinine, μmol/L, median [IQR]	216 [108-334]	368 [170-722]	0.002
LDH, *N, median [IQR]	2.5 [1.95-4.42] (n=33)	3.58 [2.08-6.95] (n=73)	0.024
ACT, *N, median [IQR]	1.0 [0.93-1.15] (n=22)	1.09 [0.93-1.15] (n=64)	
PT, %, median [IQR]	94 [94-100] (n=25)	85.5 [72.8-97.5] (n=58)	
Fibrin, median [IQR]	3.9 [3.27-5] (n=19)	3.82 [0.68-4.7] (n=51)	
Proteinuria, n	35 (n=41)	45 (n=46)	
Haematuria, n	23 (n=41)	37 (n=46)	

Table 3. Therapeutic plasma exchange (TPE) and associated therapies for SAID-HUS, and their outcomes, in 26 patients. Abbreviations: SSc= systemic sclerosis, APLS= antiphospholipid syndrome, SLE= systemic lupus erythematosus, pSS = primary Sjögren syndrome, MCTD= mixed connective tissue disease, PAN= periarteritis nodosa, RTX= rituximab, CYC= cyclophosphamide, ECZ= eculizumab, CPL= caplacizumab, Spl. = splenectomy, MMF= mycophenolate mofetil, ATT= antithrombotic treatment, NA= (data) non available, CR= complete remission.

	Age (years)	Number of TPE (n)	Steroids	RTX	CYC	Other	ATT	Flare-up ≤ 30 days	Relapse > 30 days	Outcome at M+6
SSc	41	37	+	0	0		+	0	0	CR
SSc	63	3	+	0	0	ECZ	+	0	0	CR
SSc	44	9	0	0	0		0	0	0	CR
SSc	74	12	+	0	0		0	0	0	NA
SSc	60	28	+	0	0		0	0	0	CR
APLS	53	10	0	0	0		+	0	0	CR
APLS	31	4	+	0	0	CPL	+	0	0	CR
SLE + APLS	26	14	+	0	+	Spl.	+	0	0	NA
SLE + APLS	28	25	+	+	+	AZA	+	0	0	CR
SLE	35	3	+	+	+		+	0	0	NA
SLE	51	6	+	0	0	ECZ	0	0	0	NA
SLE	41	10	+	0	+		+	0	0	CR
SLE	26	20	+	+	0		NA	0	0	NA
SLE	26	1	+	0	+	ECZ, MMF	0	0	0	NA
SLE	34	5	+	0	0		+	0	0	CR
SLE	22	33	+	+	+	MMF	+	0	0	NA
SLE	27	53	+	0	+	MMF	0	+	0	CR
pSS	18	14	+	0	0		+	0	+	NA
pSS	42	15	+	0	0		+	0	0	CR
pSS	32	25	+	0	0		NA	0	0	CR
Overlap SLE / RA	56	14	+	0	0		+	0	0	CR
Overlap SLE/Sjo.	57	13	+	+	0		NA	+	+	CR
Overlap SLE/Sjo.	33	24	+	0	0		NA	0	0	CR
MCTD	68	7	+	0	0	ECZ	0	0	0	Death
ANCA+ vasculitis	69	10	+	+	0		0	0	0	NA
PAN	53	6	+	0	+		0	0	0	CR

Figures

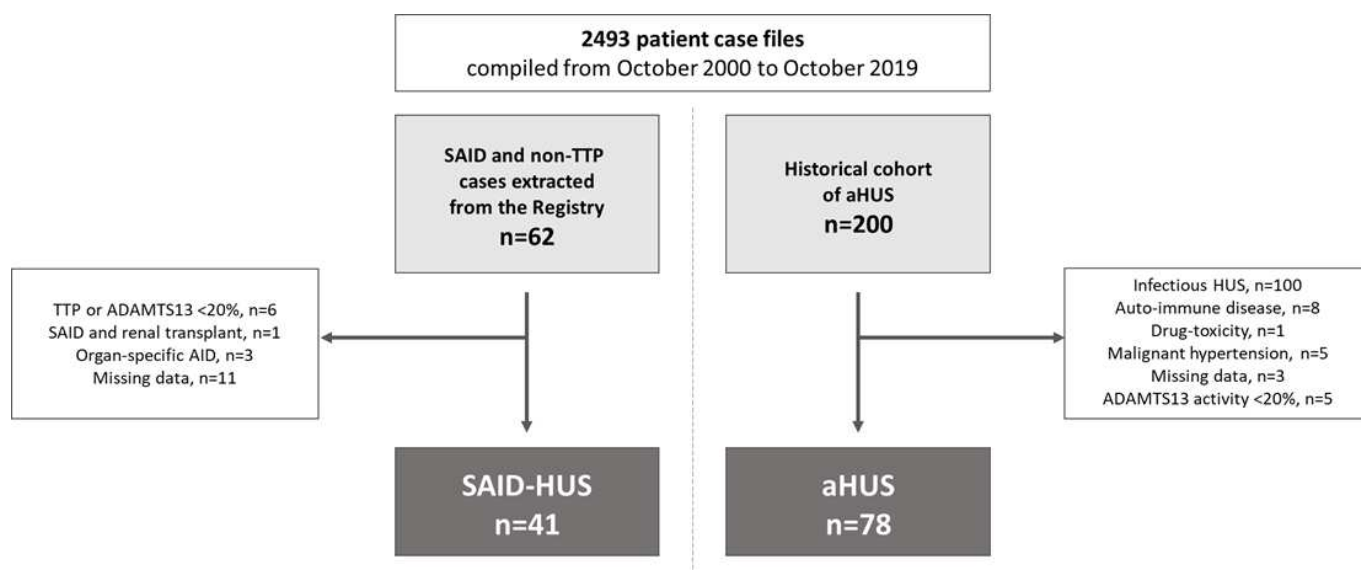


Figure 1. Study flow-chart.

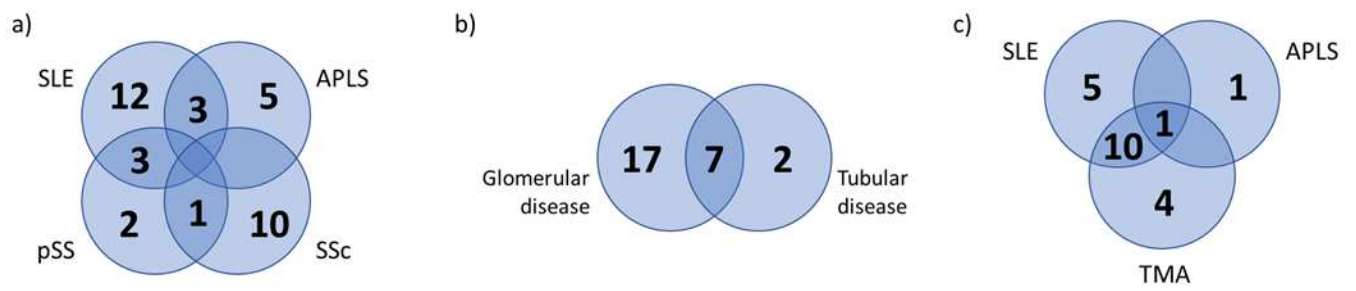


Figure 2. Venn diagrams of a) overlapping connective tissue diseases and APLS, b) the distribution of glomerular and tubular lesions in renal biopsies, and c) histopathological diagnoses. *Abbreviations: SLE= systemic lupus erythematosus, APLS= antiphospholipid syndrome, pSS= primary Sjögren’s syndrome, SSc= systemic sclerosis and TMA= thrombotic microangiopathy.*

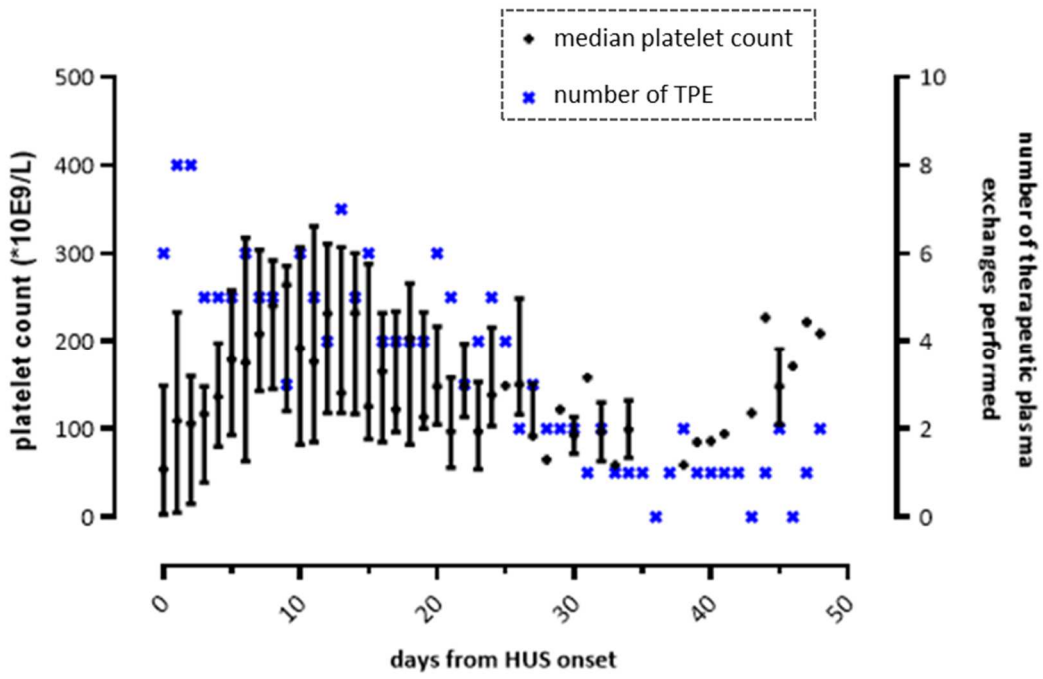


Figure 3. Line-graph showing the modifications in the median platelet count [black cross +] of 10 SLE patients receiving therapeutic plasma exchange (TPE) [blue cross x] over the course of their initial management. Maximal and minimal values of platelet counts are represented as horizontal bars.

Supplementary Material

Study population and definitions

The French National TMA Registry (referred to hereinafter as the Registry) is an initiative of the French Reference Centre for TMA that is supported by the Ministry for Health. Twenty-seven participating centres provide a network of immunology, haematology, nephrology and intensive care departments that regularly update this valuable database of patients presenting with TMA across the country (www.cnr-mat.fr). Patients that are included in the Registry present either with biological criteria for TMA (i.e. microangiopathic anaemia and/or thrombocytopenia, with or without organ failure), or with pathological evidence of TMA.

Ethics

‘Commission Nationale Informatique et Libertés’, CNIL, autorisation n°911539, and ‘Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé’, CCTIRS, autorisation n°11.537, Paris, France.