

Risk Factors for Autoimmune Diseases Development After Thrombotic Thrombocytopenic Purpura

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Abstract: Autoimmune thrombotic thrombocytopenic purpura (TTP) can be associated with other autoimmune disorders, but their prevalence following autoimmune TTP remains unknown. To assess the prevalence of autoimmune disorders associated with TTP and to determine risk factors for and the time course of the development of an autoimmune disorder after a TTP episode, we performed a cross sectional study. Two-hundred

sixty-one cases of autoimmune TTP were included in the French Reference Center registry between October, 2000 and May, 2009. Clinical and laboratory data available at time of TTP diagnosis were recovered. Each center was contacted to collect the more recent data and diagnosis criteria for autoimmunity. Fifty-six patients presented an autoimmune disorder in association with TTP, 9 years before TTP (median; min: 2 yr, max: 32 yr) (26 cases), at the time of TTP diagnosis (17 cases) or during follow-up (17 cases), up to 12 years after TTP diagnosis (mean, 22 mo). The most frequent autoimmune disorder reported was systemic lupus erythematosus (SLE) (26 cases) and Sjögren syndrome (8 cases). The presence of additional autoimmune disorders had no impact on outcomes of an acute TTP or the occurrence of relapse. Two factors evaluated at TTP diagnosis were significantly associated with the development of an autoimmune disorder during follow-up: the presence of antidualstranded (ds)DNA antibodies (hazard ratio (HR): 4.98; 95% confidence interval (CI) [1.64–15.14]) and anti-SSA antibodies (HR: 9.98; 95% CI [3.59–27.76]). A follow-up across many years is necessary after an acute TTP, especially when anti-SSA or anti-dsDNA antibodies are present on TTP diagnosis, to detect autoimmune disorders early before immunologic events spread to prevent disabling complications.

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Abbreviations: (ds) DNA = double stranded deoxyribonucleic acid, ACR = American College of Rheumatology, ADAMTS13 = a disintegrin and metalloprotease with thrombospondin type 1 repeats, AECG = American and European Consensus Group Sjögren syndrome criteria, AI = autoimmune, ANA = antinuclear antibodies, ANCA = antineutrophil cytoplasmic antibody, Anti-SSA = anti-Sjögren-syndrome-related-antigen A, APL = antiphospholipid, APS = antiphospholipid syndrome, CBA = collagen binding activity, CI = confidence interval, eGFR = estimated glomerular filtration rate, ELISA = enzyme-linked immunosorbent assay, GAD = glutamate decarboxylase, HIV = human immunodeficiency virus, HR = hazard ratio, HUS = hemolytic and uremic syndrome, LDH = lactate dehydrogenase, MDRD = modification of diet in renal disease, RNP = ribonucleic protein, SLE = systemic erythematosus lupus, TMA = thrombotic microangiopathy, TPE = therapeutic plasma exchange, TTP = thrombotic thrombocytopenic purpura, USS = Upshaw–Shulman syndrome.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a rare disease with an incidence of less than 4 cases/million people/

year.¹ This thrombotic microangiopathy (TMA) is characterized by the formation of platelet thrombi in the microcirculation of various organs, due to the accumulation of unfolded high-molecular weight Von Willebrand factor multimers. Patients with TTP present typically a microangiopathic hemolytic anemia, a thrombocytopenia, and organ failure of variable severity.² TTP results from a severe deficiency in ADAMTS13 (a disintegrin and metalloprotease with Thrombospondin type 1 repeats; 13th member),³ the protein that cleaves Von Willebrand factor multimers into less adhesive forms, thereby limiting platelet aggregation. A severe deficiency (<10% of normal activity) in ADAMTS13 is specifically observed in TTP, which allows differentiating this condition from other forms of TMA, including the hemolytic and uremic syndrome (HUS), in which the predominant feature is renal failure.^{4,5} Various clinical subtypes of TTP exist, including autoimmune and hereditary (Upshaw–Shulman syndrome) forms. TTP may be idiopathic or associated with a specific condition: antiplatelet agents, pregnancy, and autoimmune disorders.⁶ In most cases, a severe ADAMTS13 deficiency results from autoantibodies directed against ADAMTS13,⁷ which pathophysiological role was demonstrated in a nonhuman primate model.⁸ From these observations, TTP is considered an autoimmune disease.

A number of autoimmune disorders have been reported in association with TTP: systemic lupus erythematosus (SLE), the antiphospholipid syndrome,^{9–11} antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis,^{12–14} Sjögren syndrome,^{15,16} mixed connective tissue disorders,¹⁷ and other systemic diseases, such as Still disease,¹⁸ scleroderma,¹⁹ and ankylosing spondylitis.²⁰ SLE is the most studied of these entities, with reports of cases occurring before, at the same time or after the diagnosis of TTP.^{21–25}

The prevalence of the total spectrum of autoimmune disorders following TTP still remains incompletely unknown and clinicians are currently unsure whether TTP patients require specific monitoring. Our aim here was to assess the prevalence of autoimmune disorders associated with TTP and to determine the risk factors for and the time course of the development of an autoimmune disorder after an episode of autoimmune TTP.

METHODS

The French Thrombotic Microangiopathies (TMA) Reference Center

The present study was designed in June, 2012. We considered that patients had to have a minimum follow-up period of 3 years. Therefore, we included patients from the French Reference Center enrolled between October, 2000 and May, 2009. Patients were managed in 42 different French centers.

This study was approved by our institutional review board and review boards of all participating hospitals in accordance with the Declaration of Helsinki, and the French Data Protection Authority (“Commission Nationale Informatique et Libertés” (CNIL), authorization no. 2012-158, Paris, France).

DEFINITIONS

We included all patients with a diagnosis of autoimmune TTP, either idiopathic or associated with a history autoimmune disorder. Patients with a context of cancer, pregnancy, human immunodeficiency virus infection, organ, or bone marrow transplantation were excluded. TTP was diagnosed on the basis of the presence of a Coombs-negative microangiopathic hemolytic anemia or a microangiopathic haemolysis and acute

thrombocytopenia with the absence of any other identifiable cause of thrombocytopenia and microangiopathic haemolytic anaemia, such as severe disseminated intravascular coagulopathy or malignant hypertension, associated with a severe ADAMTS13 deficiency (<10% activity) and serum anti-ADAMTS13 antibodies. Patients with a severe ADAMTS13 deficiency and no detectable anti-ADAMTS13 antibodies who recovered ADAMTS13 activity during remission were also considered as having an acquired disease.

Definitions of remission, relapse, exacerbation, and refractory TTP were based on previous studies.^{26,27} Treatment was performed according to a written protocol based on a previous study and in accordance with international guidelines.^{28–30} Briefly, therapeutic plasma exchange (TPE) was carried out daily immediately after TTP diagnosis until complete response. TPE sessions were then reduced over 3 weeks and finally stopped. Patients without features of active infection received steroids (1 mg/kg/d for 3 wk). In case of disease exacerbation before achieving a durable remission or disease relapse, daily TPE was resumed, in association with rituximab (Mabthera, Roche) as a second-line treatment.³¹

SLE was defined according to the American College of Rheumatology (ACR) criteria,³² Sjögren syndrome was diagnosed according to the ACR criteria³³ and the American and European Consensus Group Sjögren syndrome criteria (AECG, 2002),³⁴ and APS according to international classification criteria.³⁵ The concomitant Coombs-negative microangiopathic hemolytic anemia and the peripheral thrombocytopenia were related to acute TTP and were not considered diagnosis criteria for SLE.

Clinical and Laboratory Parameters

All clinical and laboratory data available at time of TTP diagnosis were recovered. Assays for antinuclear antibodies (ANA) were performed by indirect immunofluorescence and detection superior to 1:160 dilution was considered positive result. Anti-SSA and other antibodies were also assessed when available: anti-dsDNA antibodies, anticardiolipin antibodies, and anti-β₂ glycoprotein-1 antibodies. Each center was contacted by telephone, to recover the more recent clinical (number of episodes of TTP, development of autoimmune diseases) and biological data (tests for ANA and other autoantibodies). For all patients diagnosed with an autoimmune disorder during follow-up, data were verified to ascertain that the features of autoimmune or systemic disorder identified during follow-up were not present on TTP diagnosis. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) by the MDRD study equation (modification of diet in renal disease).

Detection of ADAMTS13 Activity and Anti-ADAMTS13 Antibodies

ADAMTS13 activity was assessed in laboratories approved by the French Reference Center for TMA, by evaluating collagen binding activity (CBA), or carrying out FRETSS-VWF73 or FRETSS-VWF86 analysis, always before TPE. Anti-ADAMTS13 IgG antibodies were detected by enzyme-linked immunosorbent assay (ELISA).³⁶

Statistical Analysis

Continuous variables are presented as means (standard deviation) or as median (minimal and maximal values), and categorical variables are presented as numbers (percentages).

Kaplan–Meier curves were generated and groups were compared in log-rank tests. Univariate and multivariate analyses were performed using Cox models to identify factors associated with the development of autoimmune disorders after acute TTP. Only variables with a *P*-value <0.05 in univariate analysis were included into the multivariate models. A *P*-value <0.05 was considered significant.

RESULTS

Clinical and Biological Features at TTP Diagnosis

In total, 261 cases of autoimmune TTP, either associated (26 cases) or not with a past-history of autoimmune disorder, were identified among the 962 cases of TMA listed in the French Reference Center registry between October, 2000 and May, 2009 (Figure 1). The main characteristics at diagnosis are shown in Table 1. The population was mostly Caucasian women, and the median age was 37 years. Neurological manifestations were reported in 155 patients (59.3%), and fever in 78 (29.8%). Median serum creatinine concentration was 92 μmol/L (42–1015) and only 22 patients (8.4%) presented severe renal failure (eGFR < 30 mL/min). Two of these patients had a past history of autoimmune disorder (a multiple sclerosis and a mixed connective tissue disease), with a normal renal function before TTP diagnosis in both cases, providing evidence that renal failure was related to TTP.

Anti-ADAMTS13 antibodies were detected in 231 patients (88.5%). ANA were assessed in 248 patients with titers greater than 1/80 in 134 patients (54%) and greater than 1/160 in 94 cases (38%). Anti-SSA antibodies tested positive in 33 patients (13.3%), and anti-dsDNA antibodies in 23 patients (9.3%). In 5 patients negative for ANA, anti-SSA antibodies were positive. All patients received TPE, associated with steroids for TTP treatment in 81.6% of cases and with the monoclonal anti-CD20 antibody rituximab in 25% of cases. Overall, 10.3% of patients died, despite admission to an intensive care unit and daily TPE.

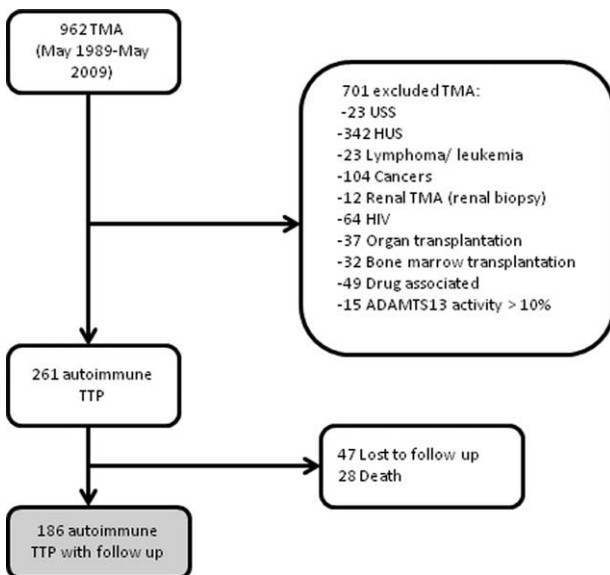


FIGURE 1. Study flow chart. HIV indicates human immunodeficiency virus; HUS=hemolytic and uremic syndrome; USS=Upshaw–Shulman syndrome.

TABLE 1. Clinical and Biological Parameters at Thrombotic Thrombocytopenic Purpura Diagnosis

Demographic Data (N = 261)	
Age (y) (median; min–max)	37 (14–93)
Female	175 (67%)
Ethnic group	
Caucasian	226 (86.6%)
Afro-Caribbean	28 (10.7%)
Asian	7 (2.7%)
Clinical data	
Fever	78 (29.8%)
Neurologic signs	155 (59.3%)
Severe renal failure*	22 (8.4%)
Previous TTP episode	33 (12.6%)
Biological features (median; min–max)	
Hemoglobin (g/dL)	7.7 (3.2–16.5)
Reticulocytes (G/L)	169 (24.6–1200)
Platelets (G/L)	14 (1–124)
Urea (mmol/L)	7.8 (0.4–48)
Creatinine (μmol/L)†	92 (42–1015)
LDH (xN)	4.9 (1.1–47)
Immunological features	
Anti-ADAMTS13 antibody-positive	231 (88.5%)
Antinuclear antibody titer >1/160‡	94 (37.9%)
Anti-SSA antibody-positive‡	33 (13.3%)
Anti-dsDNA antibody-positive‡	23 (9.3%)
Positive for another antibody†,§	58 (22.3%)
Treatment during acute episode	
Plasma exchanges	261 (100%)
Total plasma volume (mL/kg)	585 (22.6–3800)
Corticosteroids	213 (81.6%)
Rituximab	67 (25.6%)
Vincristine	45 (17.2%)
Cyclophosphamide	14 (5.3%)
Splenectomy	11 (4.2%)
Outcome	
Death during acute TTP	28 (10.7%)
Time to platelet normalization (d)	17 (2–162)
Exacerbation	133 (51%)
Relapse	71 (38.1%)
Follow-up data available (>1 yr)	186 (71.2%)
Medical history	
Autoimmune or systemic diseases	26 (9.9%)

dsDNA = double-stranded deoxyribonucleic acid, LDH = lactate dehydrogenase, max = maximal value, min = minimal value, TTP = thrombotic thrombocytopenic purpura. Values reported as percentage unless otherwise indicated. Continuous variables are expressed as medians (with minimum and maximum).

* Creatinine clearance <30 mL/min (by the MDRDs equation).

† Data available for 235 patients.

‡ Data available for 248 patients.

§ Other miscellaneous antibodies: anti-SSB antibodies (n = 7), anti-RNP (ribonucleoprotein) antibodies (n = 11), anti-cardiolipid antibodies (n = 16), anti-Sm antibodies (N = 5), anti-beta2Gp (glycoprotein)-1 antibodies (n = 3), anti-GAD (glutamate acid decarboxylase) antibodies (n = 3), anti-thyroglobulin antibodies (n = 1), anti-thyroperoxidase antibodies (n = 10), anti-smooth muscle antibodies (n = 1), anti-mitochondrial antibodies (n = 1), anti-TRAK (thyreostimulin hormon receptor antibodies) (n = 1), or ANCA (anti-neutrophil cytoplasm antibodies) (n = 1).

|| Data available for 186 patients.

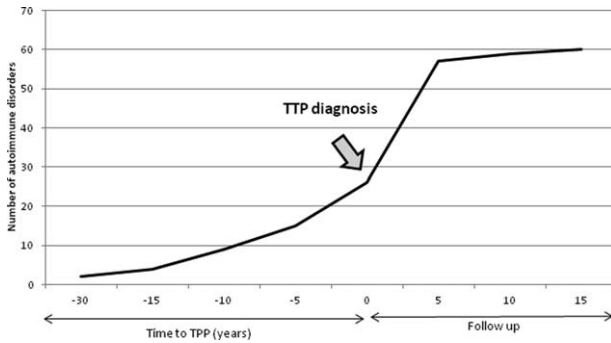


FIGURE 2. Number of autoimmune diseases cases according to date of TTP diagnosis.

Death was tentatively attributed to heart failure (n = 2), multiple organ failure (n = 7), cardiac arrest (n = 6), cerebral bleeding (n = 5), acute respiratory distress syndrome (n = 3), status epilepticus (n = 3), pulmonary embolism (n = 1), or myocardial infarction (n = 1). The prevalence of autoimmune disorders (either before TTP diagnosis or at TTP diagnosis) was comparable between survivors and nonsurvivors (17.4% vs. 5.4%, respectively, *P* = 0.085). During hospitalization, 51% of patients presented an exacerbation, and 38.1% presented a relapse. Again, the prevalence of autoimmune disorders was comparable between groups (16.4% in patients who experienced an exacerbation vs. 14.8% in those who did not, *P* = 0.73 and 14.08% for patients who relapsed vs. 16.3% in those who did not, *P* = 0.7).

Autoimmune Disorders Associated With TTP

In total, 56 patients presented 60 cases of an autoimmune disorder in association with TTP, 9 years before TTP diagnosis (median; min: 2 yr, max: 32 yr) (26 cases), at the time of TTP diagnosis (17 cases) or during follow-up (17 cases) (Figure 2). Clinical and biological data were available for 186 patients during follow-up, because 47 patients were lost to follow-up and 28 died from TTP during the first month. Seventeen patients developed an autoimmune disorder, up to 12 years after TTP diagnosis, with a mean of 22 months (Table 2) and 10 (58.8%)

of them had positive antinuclear antibodies test at presentation of TTP. Four patients who had a history of autoimmune disorder before TTP diagnosis developed another autoimmune disorder after TTP. In total, 21.5% of patients developed 1 or more autoimmune disorders.

The most frequent autoimmune disorder in our series was SLE with 26 cases reported, associated with antiphospholipid syndrome in 2 cases. All patients presented cutaneous, articular, and vascular signs or Raynaud phenomenon, and 8 patients presented with severe features, such as glomerulonephritis, neurological symptoms, pleuritis, or pericarditis, requiring immunosuppressive drugs. All patients with a history of SLE had a treatment with hydroxychloroquine at the time of TTP diagnosis. ANA were positive in all patients at SLE diagnosis, and anti-dsDNA antibody tests were negative in only 9 patients. Anti-SSA antibodies were present in 12 patients. SLE relapsed after TTP diagnosis in 4 patients. The second main autoimmune disorder associated with TTP was Sjogren syndrome, with 8 cases. In 1 case, Sjogren syndrome was secondary (ie, associated with SLE). No extraglandular signs (particularly monoclonal gammopathy, cryoglobulinemia, or lymphoma) were reported.

We analyzed the cumulative incidence of autoimmune disorders after TTP diagnosis: 9.94% of patients developed another autoimmune disease 5 years after TTP diagnosis, 13.5% after 10 years, and 25.9% after 12 years (with a median age of 37 yr at TTP diagnosis).

Parameters Associated With the Occurrence of Autoimmune Disorders During Follow-Up

The mean follow-up for the 186 survivors with available data was 5.85 years (min: 1 yr- max: 15 yr). We carried out survival analysis with a Cox model to investigate the risk factors for the development of an autoimmune disorder over time, excluding patients who had been diagnosed with an autoimmune disease before (N = 20) or at the time point of acute TTP (N = 17). In univariate analysis, 4 factors evaluated at TTP diagnosis were found to be associated with the development of another autoimmune disorder: ANA, ANA titer >1000, anti-dsDNA antibodies, and anti-SSA antibodies. Of note, the use of rituximab at the acute phase of TTP did not significantly reduce the prevalence of autoimmune diseases during follow-up

TABLE 2. Autoimmune and Systemic Diseases Associated With Thrombotic Thrombocytopenic Purpura

Autoimmunity Before TTP (N = 26)	Autoimmunity Concomitantly to TTP (N = 17)	Autoimmunity After TTP (N = 17)
SLE	SLE	SLE
Sjögren syndrome	Sjögren syndrome	Sjögren syndrome
Autoimmune thyroiditis	Mixed connective tissue disorder	SLE with Sjögren syndrome
Mixed connective tissue disorder		Autoimmune thyroiditis
Type 1 diabetes mellitus		Type 1 diabetes mellitus
Inflammatory bowel disease		Inflammatory bowel disease
Raynaud syndrome		Antiphospholipid syndrome
Ankylosing spondylitis		Primary biliary cirrhosis
Sarcoidosis		Cryoglobulinemia
Psoriasis		
Multiple sclerosis		
Autoimmune hemolytic anemia		

SLE = systemic lupus erythematosus, TTP = thrombotic thrombocytopenic purpura.

TABLE 3. Predictors of the Development of Autoimmune Disorders During Follow-Up in 149 Thrombotic Thrombocytopenic Purpura Patients in Univariate Analysis

Factor	Hazard Ratio	95% CI	P Value
Sex	0.86	0.32–2.32	0.76
Age >37 yr	2.48	0.87–7.03	0.08
Fever	1.28	0.45–3.63	0.64
Neurologic signs	1.34	0.51–3.53	0.56
Serum creatinine	1	0.99–1.01	0.64
Serum creatinine level >92 μmol/L	1.06	0.41–2.76	0.89
Hemoglobin (g/dL)	0.82	0.63–1.07	0.15
Platelets (G/L)	0.99	0.95–1.03	0.53
LDH (10 ³ /UI)	0.85	0.82–1.12	0.55
ANA positive	8.07	1.83–35.56	<0.01
ANA titer >1/1000	4.77	1.32–16.91	0.015
Anti-dsDNA antibodies positive	6.47	2.19–19.1	<0.01
Anti-SSA antibodies positive	11.61	4.25–31.71	<0.01
Rituximab	0.91	0.35–2.38	0.84
Cyclophosphamide	1.45	0.33–6.34	0.62
Exacerbation	0.76	0.29–1.99	0.58
Relapse	0.85	0.31–2.32	0.75
AI disease in medical past history	1.84	0.53–6.81	0.91

AI = autoimmune, ANA = antinuclear antibodies, CI = confidence interval, dsDNA = double-stranded deoxyribonucleic acid.

(Table 3). Finally, in multivariate analysis, the presence of anti-dsDNA antibodies and anti-SSA antibodies at TTP diagnosis was found to be significantly associated with the diagnosis of autoimmunity during follow-up (Table 4). The highest 10-year risk of developing an autoimmune disorder was observed in case of anti-SSA antibodies detection (73.7% vs. 7.65%, $P < 0.001$). The presence of either anti-SSA antibodies or anti-dsDNA antibodies at the time of TTP diagnosis (vs. absence of antibodies) was associated with a marked risk of subsequent autoimmune disorder during follow-up (HR: 8.68; 95% CI [3.13–24.1], $P < 0.001$) (Figure 3).

DISCUSSION

In our cross sectional study, autoimmune TTP was associated with the development of other autoimmune diseases,

TABLE 4. Predictors of the Development of Autoimmune Disorders During Follow-Up in 149 Thrombotic Thrombocytopenic Purpura Patients in Multivariate Analysis

Factor	Hazard Ratio	95% CI	P Value
Anti-dsDNA antibodies	4.98	1.64–15.14	<0.01
Anti-SSA antibodies	9.98	3.59–27.76	<0.01
ANA antibodies	2.27	0.59–8.83	0.23
ANA titer >1/1000	3.51	0.7–17.71	0.12

ANA = antinuclear antibodies, CI = confidence interval, dsDNA = double-stranded deoxyribonucleic acid.

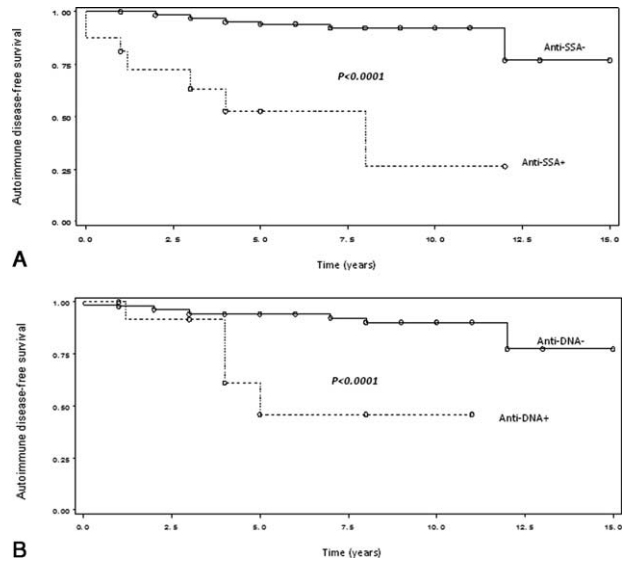


FIGURE 3. Kaplan–Meier survival estimates of autoimmune disease-free survival after autoimmune TTP. Autoimmune disease-free survival as a function of (A) anti-SSA and (B) anti-dsDNA antibody detection at TTP diagnosis.

concomitantly or during follow-up. The incidence of autoimmunity was higher after than before a TTP episode, with an increase in the incidence of autoimmunity throughout time, suggesting a role for age as well as duration of follow-up in the occurrence of an associated autoimmune disorder. We found that anti-SSA and anti-dsDNA antibodies at TTP diagnosis were significant risk factors for the development of autoimmune disorders. In total, 60 cases of autoimmune disorder were diagnosed in 56 of our patients; the calculated frequency (21.5%) is greater than the 10% frequency of autoimmune disorder diagnosis in the general population.³⁷ SLE and Sjögren syndrome were the 2 most frequently diagnosed autoimmune diseases in association with TTP, and their features were apparently otherwise typical in terms of demographic data, clinical presentation, and prognosis (not shown). Our results are clinically relevant, since the identification of anti-SSA and anti-dsDNA antibodies at TTP diagnosis defines a subset of patients at high risk of developing further autoimmune disorders during follow-up. In these patients, the early identification of an associated autoimmune disease before immunologic events spread and multiply until they are manifested as a potentially devastating clinical disease should allow an earlier adapted management and thus prevent the occurrence of disabling complications.

It should be emphasized that autoimmune manifestations may be masked by therapeutical interventions for TTP. Indeed, TPE, steroids, or other immunomodulators may attenuate clinical features of autoimmunity and decrease the serum levels of autoantibodies. Therefore, as for ADAMTS13 activity and anti-ADAMTS13 antibodies, clinical and biological features of autoimmunity should be assessed before treatment is started. Of note, hydroxychloroquine treatment in SLE patients did not prevent the onset of TTP. Moreover, patients with APL antibodies (with or without APS) were not overrepresented in our SLE group of patients, which argues against a predisposing role for antiphospholipid antibodies in the occurrence of TTP.⁹

Only 1 previous study evaluated the risk of autoimmune disorders after TTP,²⁵ in which a standardized questionnaire was used to obtain information about the occurrence of autoimmune disorders in 76 German patients with TTP. The prevalence of such disorders in this group of patients was then compared with that in the general population. The authors reported a high prevalence for Hashimoto's thyroiditis (23%), SLE (6.5%), immune thrombocytopenic purpura (6.3%), psoriasis (9.4%), and celiac disease (3.1%).²⁵ In this study, diagnoses were declared by patients only and no clinical or biological criteria for diagnosis were reported. Some of the cases of SLE or other autoimmune diseases may, therefore, have been incorrectly or not declared; this may account for the lower prevalence of SLE in this study (6.5%) when compared to ours (11.1%). Furthermore, neither the grounds for TTP diagnosis nor the time to autoimmune disease development were provided, as authors defined TTP as a TMA with an ADAMTS13 deficiency, without providing information about levels of ADAMTS13 activity and detection of anti-ADAMTS13 antibodies.²⁵ By contrast, the listing of patients in the French TMA Reference Center registry in our study provides a reliable support for the diagnosis of TTP. In a previous study, Deford et al.³⁸ described the follow-up of 70 patients suffering from TTP from 1995 to 2011, with a median follow-up of 7.8 years. They reported 8 cases (12%) of SLE in these patients, in accordance with the frequency reported here. Musio et al.²³ reported that TTP occurs between 2 weeks and 9 years after SLE diagnosis, with a median time to TTP diagnosis of 2 years after SLE diagnosis. This group studied 40 patients suffering from TTP and SLE, using renal biopsy to diagnose TMA.²³ In 1998, however, ADAMTS13 activity was not widely measured for the diagnosis of TTP, so some of the patients reported in this study may have presented renal signs of SLE rather than typical TTP, as well as other forms of TMA distinct from TTP, such as HUS, which limits the conclusions of this work. By contrast with these studies, we considered a homogeneous group of patients with a diagnosis of autoimmune TTP on the basis of acknowledged accurate diagnosis criteria. With a follow-up period of 1 to 15 years and an accurate collection of data for most patients, our study is therefore the first to provide unique specific information about diagnostic criteria and the time between acute TTP and autoimmunity development.

In our study, SLE and Sjögren syndrome were the most frequent autoimmune diseases occurring after idiopathic TTP; the presence of these autoimmune diseases was not associated with a different risk of relapse, exacerbation, or death due to acute TTP. Previous studies reported, however, that patients with SLE and TTP had a worse prognosis than those with TTP alone.^{21,22,39} A recent literature review of 105 cases of SLE-associated TTP observed between 1999 and 2011²¹ showed that SLE preceded the TTP episode in 50.5% of cases, occurred after TTP in 3.8% of cases, and occurred at the same time as TTP in 45.7% of cases. Moreover, a high mortality rate due to acute TTP (12.5%) was reported in this population, particularly for patients with neurologic and renal impairment.²¹ However, here again, this study did not systematically include ADAMTS13 activity in the definition of TTP, and among patients studied for ADAMTS13 activity, not all had values consistent with the diagnosis of TTP. Last, patients with SLE associated with only renal lesions of TMA (but without other features of TTP) were included.²¹ Therefore, it is likely that these patients presented various forms of TMA and therefore differ from those of the present work, which may account for the discrepant results between both studies. Kwok et al.²⁴ presented a retrospective

study of 1203 cases of SLE, among whom 26 developed TTP. They identified a SLEDAI score upper than 10 and coexisting nephritis as risk factors for TTP development after SLE, but here again TTP was defined on the basis of TMA criteria, with no assessment of ADAMTS13 activity; therefore, this incomplete definition of TTP may have led to an overestimation of mortality, due to the confounding of TTP and TMA features linked directly to SLE.

Rituximab is commonly used to treat lymphoma and various autoimmune diseases.⁴⁰ One could have hypothesized that rituximab may have been efficient in preventing or delaying the appearance of autoimmune disorders. However, our results do not support such hypothesis since rituximab did not reduce the incidence nor apparently modified the type of autoimmune disorders that occurred after an acute TTP.

Our group⁴¹ previously reported a high prevalence of autoantibodies in a population of patients with TTP, with frequencies of 71% for ANA (for a positivity threshold of 1/80), 9.8% for anti-dsDNA antibodies, and 3.2% for other antibodies, in 46 patients with TTP. In the present work, the value of anti-SSA antibodies in predicting the occurrence of an autoimmune disorder supports the view that these antibodies should be systematically assessed on TTP diagnostic irrespective of ANA positivity, since they may be positive in some patients with negative ANA (present work and).⁴² Anti-SSA antibodies, anti-dsDNA antibodies, and ANA are known to be present many years before the diagnosis of SLE,⁴³ but this is the first report of such an association in a population of patients with TTP.

Nonetheless, our study has some limitations. First, there was no central laboratory determination for ANA and no retesting of initially ANA-negative serum specimens. However, because French health authorities require standardization of laboratory tests, our data correspond to the objectives set. Second, our study was not prospective. Rather, it was a cross sectional study; in this regard, data from follow-up are missing for 28% of patients. However, we believe that the cross sectional design of our study is relevant to analyze the outcome of rare diseases, such as TTP, SLE, and Sjögren syndrome. From a perspective point of view, it would be of interest to confirm our results on prospective large-scale studies.

In conclusion, our results are in line with previous works^{37,44} that support the fact that TTP must be considered a chronic autoimmune disease requiring a systematic long-term follow-up. The positivity of anti-SSA and anti-dsDNA antibodies at TTP diagnosis represents good sensitive predictive markers of this association. A follow-up across many years is necessary after acute TTP to detect autoimmune disorders early before immunologic events spread, in an order to prevent disabling complications.

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