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**Venous thrombo-embolism during immune-mediated thrombotic
thrombocytopenic purpura is prevalent in patients with a prolonged
treatment with therapeutic plasma exchange**

**La maladie thrombo-embolique veineuse au cours du purpura
thrombotique thrombocytopenique autoimmun s'associe à un traitement
prolongé par échanges plasmatiques**

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Running title: Venous thrombo-embolism in TTP

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Abstract

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a devastating disease characterized by disseminated microvascular thrombosis. Despite pro-thrombotic predisposing conditions, the prevalence of macrovascular venous thrombosis event (VTE) in immune-mediated TTP (iTTP) has rarely been assessed.

Methods: We reviewed data of all iTTP patients of the French reference Center for thrombotic microangiopathies registry prospectively enrolled through a 10-year period, between 2008 and 2018. Venous thrombosis included either thrombosis of central venous catheter, symptomatic deep venous thrombosis of the limbs or pulmonary embolism.

Results: Forty-eight (12.6%) VTE were diagnosed. VTE was diagnosed after a median time of 7 [IQR, 3-16] days following the first therapeutic plasma exchange (TPE) and consisted mainly in catheter-related thrombosis (73%), and to a lesser extent symptomatic deep venous thrombosis (16%), proximal pulmonary embolism (8%) and splanchnic vein thrombosis (2%). Cases with VTE (VTE+ cases), required more TPE to achieve remission ($P<0.01$), and the total volume of plasma required to achieve remission was larger ($P<0.01$) than for VTE- cases. There was also a trend for more rituximab use in the VTE+ cases as compared to the VTE- cases (47% vs 33%; respectively; $P=0.07$). Curative anticoagulation was started in 38 cases (79%), while 6 VTE cases did not receive any antithrombotic agents, and catheter was systematically removed when catheter-related thrombosis was diagnosed. VTE+ cases had a higher number of inserted central venous catheters than VTE- cases ($P<0.05$).

Conclusion: VTE is a frequent condition occurring during iTTP management and is observed when patients require a prolonged treatment with daily TPE and multiple catheter insertions. Therapeutic strategies aimed at reducing the duration of TPE treatment in iTTP should substantially reduce this complication.

Résumé

Introduction : Malgré le contexte de thrombophilie qui caractérise le purpura thrombotique thrombocytopénique (PTT), la prévalence des macrothromboses veineuses reste mal connue.

Méthodes : Nous avons examiné les données de tous les patients atteints de PTT au sein du registre du Centre français de référence pour les microangiopathies thrombotiques, entre 2008 et 2018. Les cas de thromboses de cathéter veineux central, de thromboses veineuses profondes symptomatiques des membres et d'embolies pulmonaires ont été inclus.

Résultats : Nous avons étudié de manière prospective 314 patients atteints de PTT autoimmun (PTTi), ce qui représente 378 épisodes, sur une période de 10 ans. Quarante-huit cas de MTEV (12,6%) ont été identifiés. La MTEV a été diagnostiquée après un délai médian de 7 [écart interquartile, 3-16] jours suivant le premier échange plasmatique (EP). Il s'agissait le plus souvent de thromboses au niveau du cathéter (73%), et dans une moindre mesure d'une thrombose veineuse profonde (16%), d'une embolie pulmonaire proximale (8%) ou d'une thrombose d'une veine splanchnique (2%). Les cas de MTEV (cas MTEV+) ont nécessité davantage d'EP pour obtenir une rémission durable ($P < 0,01$), et le volume total de plasma requis pour obtenir cette rémission était plus important ($P < 0,01$) que pour les cas MTEV-. Le rituximab a été utilisé davantage chez les patients MTEV+ que chez les patients MTEV- (47% vs 33%; respectivement; $P = 0,07$). Une anticoagulation curative a été débutée chez 38 cas (79%), alors que dans 6 cas de MTEV, aucun anticoagulant n'a été introduit. Le cathéter a été systématiquement retiré en cas de thrombose sur cathéter. Les cas MTEV+ VTE+ ont eu un nombre d'insertions de cathéter plus important que les cas MTEV- ($P < 0,05$).

Conclusion : La MTEV est une complication fréquente au cours de la prise en charge du PTTi. Elle s'observe plus souvent chez les patients nécessitant un traitement prolongé par EP et de multiples insertions de cathéter. Les stratégies thérapeutiques visant à réduire la durée de traitement par EP devraient réduire la prévalence de cette complication.

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a devastating disease characterized by disseminated platelet-rich microthrombi, severe thrombocytopenia, microangiopathic hemolytic anemia, and ultimately organ dysfunction and death in the absence of treatment. The systemic platelet clumping in organs is due to a severe deficiency of the von Willebrand factor (VWF)-cleaving protease ADAMTS13 (A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs, 13th member). In the absence of ADAMTS13, unusually large (UL)-VWF strings are retained on endothelial cells surface, promoting platelet adhesion and finally microvascular thrombosis. In a large majority of cases, TTP is immune-mediated (iTTP) due to specific autoantibodies to ADAMTS13. Also, iTTP is still an acute life-threatening disease with an overall mortality rate of 10%-15%. Death is usually related to microvascular thrombotic events commonly responsible for multiorgan impairment including the brain, the kidney and the heart. The treatment of iTTP consists in daily therapeutic plasma exchange (TPE) and immunosuppression with corticosteroids and B-cell depleting therapies (mostly rituximab) until remission [1]. This historical treatment is increasingly completed by the use of the anti-VWF nanobody caplacizumab, allowing hastening platelet count recovery and preventing exacerbations [2]. Although survival of iTTP is progressively improving with these new compounds, TPE treatment is responsible for acute complications, especially infections and venous thrombotic events (VTE), impacting the burden of care [3]. To date, available data on VTE are mainly issued from small cohort studies with various forms of thrombotic microangiopathies. These studies report mostly catheter-related thrombosis, and rarely limbs deep venous thrombosis, with a VTE prevalence ranging from 9% to 38% [3,4]. Therefore, the prevalence of VTE specifically in iTTP is still imperfectly described while TPE and vascular access for TPE are two additional risk factors for thrombosis. In addition, due to a marked hypercoagulable state and endothelial activation, patients with acute iTTP are

at high risk of venous thrombosis, leading to a dilemma in TTP to use anticoagulant when profound thrombocytopenia is present. The aim of the current study was to assess the prevalence and the impact of VTE in iTTP.

Material and methods

We reviewed data of all iTTP patients of the French reference Center for thrombotic microangiopathies (CNR-MAT, www.cnr-mat.fr) registry prospectively enrolled through a 10-year period, between 2008 and 2018. iTTP diagnostic criteria and management were based on previous studies. Patients with a suboptimal response to standard TPE-based treatment received a salvage therapy with rituximab [5]. Informed consent was obtained from all patients. This study was approved by our institutional review board in accordance with the Declaration of Helsinki, and the French Data Protection Authority (“Commission Nationale Informatique et Libertés”, authorization n°911539, and “Comité consultatif sur le traitement de l’information en matière de recherche dans le domaine de la santé”, authorization n°11.537, Paris).

For each patient epidemiologic, clinical and biological data were collected by a research study nurse, as previously reported [5]. Data were collected retrospectively with particular attention to any thrombophilia risk factors (obesity, oral contraceptive use, presence of antiphospholipid antibodies [anticardiolipin and anti- β 2GP1 antibodies]) and a pre-existing history of VTE. Supplemental data were collected to define other conditions during iTTP potentially increasing the risk of VTE: the time to platelet count recovery from the first TPE, the total volume of plasma required to achieve a durable complete remission, the number and the sites of inserted central venous catheter. Venous thrombosis included either thrombosis of central venous catheter, suspected on the basis of clinical symptoms, *i.e.*, in the presence of a catheter dysfunction, homolateral edema or pain, or every symptomatic deep

venous thrombosis of the limbs or pulmonary embolism. All VTE were confirmed by a Doppler ultrasonography or a computerized tomodensitometry examination.

Median with interquartile range ([IQR] 25%-75%) was determined for continuous variables. Differences between patients with VTE (VTE+) and without VTE (VTE-) were assessed by the Chi-Square test or Fisher's exact test for categorical variables and by the Mann-Whitney U test for continuous variables. Statistical analyses were performed using STATVIEW (Version 5.0 de SAS Institute Inc.) program. Two-sided $P < 0.05$ was considered statistically significant.

Results

During the 10-year period running from 2008 to 2018, among 2912 patients with a diagnosis of TMA included in the national registry, 380 had a diagnosis of iTTP. Among them, 66 had no available data on venous risk factors or on a VTE, leaving 314 patients for the study. Because of recurrent episodes, 378 iTTP episodes (including 287 inaugural episodes) corresponding to the study criteria were analyzed (**Figure 1**). Two hundred and eighty seven patients among the 314 (91%) had a first episode of acute iTTP. Data on central venous catheter insertion sites were available for 123 TTP episodes (32%). Insertion sites were primarily in a femoral vein (n=68) or a sub-clavian/jugular vein (n=55). The mean number of inserted venous catheters per episode was 1.6 ± 0.6 .

Forty-eight VTE (12.7%) occurred during the management of the 378 iTTP episodes. VTE was diagnosed after a median time of 7 [IQR, 3-16] days following the first TPE. VTE consisted in a catheter-related thrombosis (35 cases, 73%), a symptomatic deep venous thrombosis of limbs (8 cases, 16%), an isolated proximal pulmonary embolism (4 cases, 8%), and a splanchnic vein thrombosis (1 case, 2%). Platelet count corresponding to the day of thrombosis diagnosis was 114 [IQR, 32-207] $\times 10^9/L$. In the VTE+ group, exacerbations and

refractoriness were observed in 18 (38%) and 13 (27%) cases, respectively; moreover, a catheter dysfunction was noted in 10 (21%) cases. Curative anticoagulation was started in 38 cases (79%), while 6 VTE cases did not receive any antithrombotic agents, 3 received aspirin and 1 only elastic compression. Catheter removal was systematically performed when catheter-related thrombosis was diagnosed.

Clinical characteristics on admission of VTE+ cases were comparable to those of VTE- cases. Especially, the prevalence of oral contraceptive intake, body mass index and the prevalence of antiphospholipid antibodies were comparable between groups from available data (**Table 1**). A past history of VTE was comparable between VTE+ and VTE- patients (9.7% vs 5.5%, respectively, $P=0.28$). When compared to VTE- cases, VTE+ cases required more TPE to achieve durable remission ($P<0.01$); as a result, the total volume of plasma required to achieve remission was larger ($P<0.01$) (**Table 1**). There was no difference in the use of corticosteroids (84% vs 89%; $P=0.5$) or other immunomodulatory drugs between VTE+ and VTE- cases (46% vs 30%, respectively; $P=0.15$). There was a trend for more rituximab use in the VTE+ cases as compared to the VTE- cases (47% vs 33%; respectively; $P=0.07$), reflecting a longer treatment duration in this group with an increased need of TPE and more salvage therapies to reach complete remission. In addition, the use of anti-platelet agents (mostly aspirin) was comparable between cases with and without VTE (42% vs 46%; $P=0.50$). VTE+ cases had a higher number of inserted central venous catheters than VTE- cases ($P<0.05$). Death rate was comparable between groups (**Table 1**).

Discussion

VTE events are frequent in iTTP at the acute phase (12.7% of patients) and are mostly related to catheter insertion (73% of cases). A prolonged duration of daily TPE, reflecting more refractoriness and exacerbations, was clearly associated with more VTE events. The

insertion of a central venous catheter results in an increased risk of venous thrombosis, ranging from 10% to 35% from series in which a VTE event was systematically screened [6], whereas this prevalence is only of 5-7% [7] when thrombosis is searched only on the basis of clinical symptoms. The prevalence of catheter-related thrombosis reported in our cohort is greater than this observed usually, suggesting a specific role for iTTP and its treatment in the occurrence of VTE. The increased risk of VTE in iTTP may be explained by different ways. First, because of severe thrombocytopenia, most of central venous catheters were initially inserted in the femoral vein (55%), which is associated with a greater risk of thrombosis than jugular or subclavian vein [8,9]. Second, patients who experience a rapid and early platelet count recovery could have a pro-thrombotic rebound while TPE sessions are progressively tapered and some UL-VWF strings as well as various cell-derived microparticles are still present. Third, the addition of pro-thrombotic factors in the management of iTTP, *i.e.*, repetitive vascular parietal strain due to central venous catheter insertion, administration of high volume of plasma and infections generally reported as a precipitating trigger of TTP, are potent medical conditions leading to a high risk of thrombosis in this context.

The treatment of VTE during iTTP management is not consensual. The removal of central venous catheter is required when catheter is the site of thrombosis. In patients experiencing deep venous thrombosis, curative anticoagulation is usually mandatory. As reported here, patients are usually diagnosed with VTE when platelet count has improved, which suggests that a standard anticoagulation could be offered in most cases. Importantly, the increasing use of rituximab frontline, and more recently caplacizumab [1,2,10], should substantially decrease the burden of care and thereby prevent the prevalence of VTE.

In conclusion, we here report that VTE is a frequent condition occurring during iTTP management and is observed when patients require a prolonged treatment with daily TPE and multiple catheter insertions. Consequently, therapeutic strategies aimed at reducing the

duration of intensive TPE treatment in iTTP, like rituximab and caplacizumab should substantially reduce this complication.

Figure legends.

Figure 1. Study flow chart.

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Disclosure of Conflict of Interests

G. Sauvêtre has no conflict of interest to declare. P. Coppo is member of the Clinical Advisory Board for Alexion, Ablynx now part of Sanofi, Takeda and Octapharma. A. Veyradier and Y. Benhamou are members of the Clinical Advisory Board for Ablynx now part of Sanofi. S. Grangé is member of the Clinical Advisory Board for Alexion.

Appendix

The members of the Reference Center for Thrombotic Microangiopathies (CNR-MAT) are: Augusto Jean-François (Service de Néphrologie, dialyse et transplantation ; CHU Larrey, Angers); Azoulay Elie (Service de Réanimation Médicale, Hôpital Saint-Louis, Paris); Barbay Virginie (Laboratoire d'Hématologie, CHU Charles Nicolle, Rouen); Benhamou Ygal (Service de Médecine Interne, CHU Charles Nicolle, Rouen); Bordessoule Dominique (Service d'Hématologie, Hôpital Dupuytren, Limoges); Charasse Christophe (Service de Néphrologie, Centre Hospitalier de Saint-Brieuc); Charvet-Rumpler Anne (Service d'Hématologie, CHU de Dijon); Chauveau Dominique (Service de Néphrologie et Immunologie Clinique, CHU Rangueil, Toulouse); Choukroun Gabriel (Service de Néphrologie, Hôpital Sud, Amiens); Coindre Jean-Philippe (Service de Néphrologie, CH Le Mans); Coppo Paul (Service d'Hématologie, Hôpital Saint-Antoine, Paris); Corre Elise (Service d'Hématologie, Hôpital Saint-Antoine, Paris); Delmas Yahsou (Service de Néphrologie, CHU de Bordeaux, Bordeaux); Deschenes Georges (Service de Néphrologie Pédiatrique, Hôpital Robert Debré, Paris); Devidas Alain (Service d'Hématologie, Hôpital Sud-Francilien, Corbeil-Essonnes); Dossier Antoine (Service de Néphrologie, Hôpital Bichat, Paris); Fain Olivier (Service de Médecine Interne, Hôpital Saint-Antoine, Paris); Fakhouri Fadi (Service de Néphrologie, CHU Hôtel-Dieu, Nantes); Frémeaux-Bacchi Véronique (Laboratoire d'Immunologie, Hôpital Européen Georges Pompidou, Paris); Galicier Lionel (Service d'Immunopathologie, Hôpital Saint-Louis, Paris); Grangé Steven (Service de Réanimation Médicale, CHU Charles Nicolle, Rouen); Guidet Bertrand (Service de Réanimation Médicale, Hôpital Saint-Antoine, Paris); Halimi Jean-Michel (Service de Néphrologie Pédiatrique, Hôpital Bretonneau, Tours); Hamidou Mohamed (Service de

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Table 1. Clinical characteristics of patients according to VTE status

	VTE+ episodes (N=48)	VTE- episodes (N=330)	P- value
Age (y)	45 [27-52]	37 [26-47]	0.09
Female	36 (75%)	216 (65%)	0.17
Oral contraceptive intake	14/42	94/234	0.40
BMI (kg·m ⁻²) (N=172)	27.4 [25-32]	25.3 [22-30.5]	0.15
Neurologic involvement	28 (58%)	201 (61%)	0.73
Hemoglobin level (g/dL)	7.7 [6.6-9.1]	8 [6.5-10.1]	0.32
LDH level (x N)	5.3 [3.7-6.5]	4.6 [3.2-6.6]	0.23
Platelet count (x10 ⁹ /L)	12.5 [9-18.3]	15 [9-20]	0.21
Antiphospholipid antibodies (N=201)	6 (18%)	23 (6.9%)	0.51
Renal impairment (MDRD < 60 mL/min /1,73 m ²)	14/44 (31%)	97/298 (33%)	0.98
Anti-ADAMTS13 Abs (U/mL) (N=213)	87 [40-109]	82 [39-110]	0.47
Number of TPE to achieve remission	13 [IQR, 7.75-20]	8 [IQR, 5-14]	<0.01
Plasma volume (ml/kg) until remission	583 [402-1156]	377 [220-784]	<0.01
Number of catheter insertions until remission	2 [1-2]	1 [1-2]	<0.05
Time to remission (days)	18.5 [9.2-25]	15 [7-25]	0.19
Death	2 (4.2%)	34 (10%)	0.29

BMI: body mass index. MDRD: Modification of the Diet in Renal Disease. LDH: lactate dehydrogenase.

Antiphospholipid antibodies included anticardiolipin antibodies and/or anti-β2GPI antibodies. ADAMTS13: A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs-13. Anti-ADAMTS13 Abs: IgG Anti-ADAMTS13 antibodies. TPE: therapeutic plasma exchange. NS: non-significant. Quantitative values are expressed in median ± Inter Quartile Range (IQR) [25%-75%]. Qualitative values are expressed as % (total number). In case of missing values, the number of patients tested is specified in parentheses in the left column (N). $P < 0.05$ was considered statistically significant.

Figure 1

