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Analysis of Clinical Factors in First Diagnosis of Immune Thrombotic Thrombocytopenic Purpura with Report of 6 Cases

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Keywords:

Thrombotic thrombocytopenic purpura; Treatment; Clinical analysis; Plasma exchange; Rituximab

1. Abstract

1.1. Objective

This study aims to investigate the clinical characteristics, timing of intervention, diagnostic and treatment options, and prognostic factors in patients with iTTP.

1.2. Methods

We conducted a retrospective analysis of iTTP patients who visited the Second Hospital of Jilin University from January 2020 to April 2023, encompassing individuals with complete clinical data.

1.3. Results

The study cohort consisted of 4 male and 2 female patients, with a median age of 58 years (range: 29 - 84 years). All patients underwent plasmapheresis, All six patients underwent treatment with TPE with a median of 7 sessions (range: 5 - 11 sessions). Three of them also receiving rituximab (3/6), with a median start time of 9 days (range: 9 - 18 days) after onset. Of the six cases, three patients survived and achieved complete recovery. The median platelet recovery time was 24 days (range: 23 - 40 days). And the other three patients died with death occurring at a median of 12 days (range: 5 - 19 days) after the onset of symptoms.

1.2. Conclusion

TTP diagnosis is often delayed due to its nonspecific clinical presentation. Accurate clinical diagnosis of TTP relies on assessing ADAMTS13 activity levels and genetic testing. Following PLASMIC-S guidelines, immediate TPE and glucocorticoid therapy are recommended once diagnosis is suspected. Additionally, an increasing number of patients benefiting from a combination of anti-CD20 monoclonal antibodies and other novel drugs. The expanding treatment options enhances the comprehensive diagnostic and therapeutic strategy for iTTP.

2. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare and serious hematologic disorder, typically occurring at an incidence of approximately 2-6 cases per million people [1]. The classical clinical manifestations of TTP encompass microangiopathic hemolysis, thrombocytopenia, neurologic symptoms, fever, and renal damage, collectively forming the Pentalogy. Some patients may exhibit only the initial three symptoms, recognized as trichotillomania. Based on the updated guidelines, the dual syndrome of thrombocytopenia and MAHA was defined. There was no other obvious explanation for thrombocytopenia and anemia, yet only 10% of the patients presented with the pentad syndrome [2]. Hereditary TTP, also known as congenital thrombotic thrombocytopenic purpura (cTTP), results from a severe deficiency of plasma ADAMTS13 activity due to mutations in ADAMTS13. In contrast, iTTP (immune-mediated thrombotic thrombocytopenic purpura) triggered by immune-mediated autoantibodies inhibiting plasma ADAMTS13 activity. In this report, we present clinical data from six iTTP patients treated at the Second Hospital of Jilin University between January 2020 and April 2023. Our analysis, in conjunction with existing literature, explores their clinical manifestations,

laboratory and imaging characteristics, pathological features, diagnosis, and treatment. By discussing clinicopathological features and prognostic factors, we aim to enhance the understanding of iTTP.

3. Information and Methods

3.1. General Information

The retrospective analysis involved the clinical data of six patients diagnosed with TTP who sought medical care at the Second Hospital of Jilin University between January 2020 and April 2023. The cohort comprised 5 males (83.33%) and 1 female (16.67%), with ages ranging from 29 to 84 years and a median age of 58 years. Descriptive analysis was applied to all cases, and confirmation of diagnosis was based on laboratory examination, peripheral blood smear, and ADAMTS13 testing. Retrospective analysis encompassed gender, age, clinical manifestations, accompanying symptoms, laboratory and imaging test results, treatment modalities, and prognosis for each patient.

3.2. Clinical Manifestations

All six patients exhibited common features, including thrombocytopenia, microangiopathic hemolytic anemia, and neuropsychiatric symptoms. Specifically, 4 cases (66.67%) manifested renal function impairment, while 2 cases (33.33%) presented with fever. Among the cases, 2 showed the typical “pentad” manifestations, 2 displayed “quadruple” manifestations, and 2 presented with “triple” manifestations. The most common initial symptoms were thrombocytopenia (median platelet count: 6.5×109/L) accompanied by fatigue, jaundice, dark-colored urine, and in some cases, fever, neurological abnormalities, and petechiae. A few patients had impaired kidney function. The median time from onset to suspected diagnosis was 7.5 days, and the median time to confirmed diagnosis was 12 days.Further details can be found in Table 1.

Table 1: Clinical information of TTP patients.

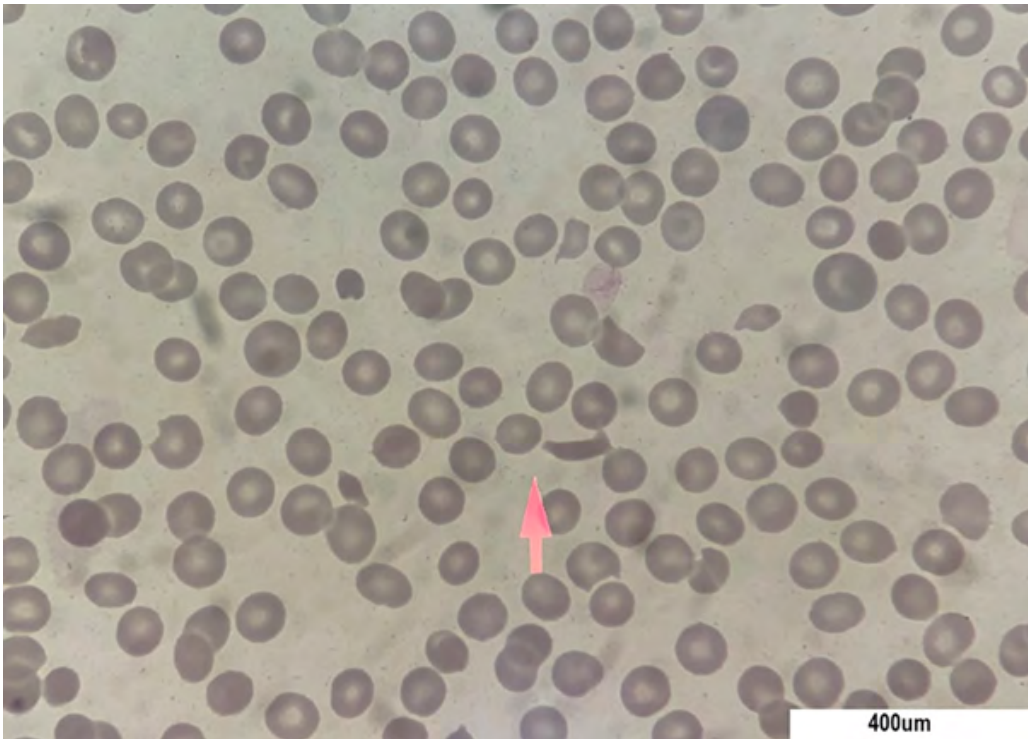
No	1	2	3	4	5		6	Med
Gender	M	F	M	M	M		M	
Age	84	56	29	72	60		47	58
Past medical history	HTN	N	N	MM,DM	HTN		N	
Time of onset	24-03-2021	25-02-2023	05-06-2022	12-07-2022	03-02-2023		20-06-2021	
Platelet count（$\times 10^9$/L）	6	17	5	5	13		7	6.5
Glasgow Coma Scale Score	9	3	14	12	13		14	12.5
MAHA								
Pallor	D3	D5	D5	D1	D13		D18	D5
Fatigue	D-2	D0	D0	D0	D7		D0	D0
Jaundice	D4	D9	D4	D2	D12		D19	D6.5
Dark colored urine	D0	D9	D3	D2	D14		D18	D6
Neurological abnormalities	D4	D9	D3	D0	D16		D12	6.5
Fever(℃)	38.9	37.7	N	N	40		37.9	37.8
Petechiae	N	N	D0	N	D12		N	
Impaired kidney function(μmoI/L)	114	333	N	N	128		101	121
Complication	ACS,ACI	ACS,ACI,	N	ACI,MASA	ACI		ACI	
		MODS						
History of vaccine	N	N	COVID-19	N	COVID-19		N	
Time of suspected diagnose	D4	D10	D5	D2	D14		D19	D7.5
Time of diagnosed	D10	D14	D9	D7	D18		D24	D12
Treatment	PLEX,DX	PLEX,	PLEX,R,	PLEX,m-PSLR,	PLEX,m-PSL		PLEX, m-PSL	
	m-PSL	IVIG	IVIG	,R				
Start time of PLEX	D5-D7	D11-D12	D5-D21 2000ml	D3-D5 3000ml	D14-D19		D19-D21	D8
	3000ml	3000ml QD	QOD	QD,D7 3000ml	2000ml BID		3000ml QD	
	QOD							
Start time of steroid	D5 DX	D10-D13	D3-D4, 80mg	D3	D14-D15	D19-D22	80mg	D7.5
	10mg	80mg BID,	QD,D5-D18	40mg,D4-D11	40mg QD,	QD,		
			120mg QD,	80mg QD	D16-D19	D23-D24	40mg	

		D19-D25 80mg			80mg	BID	QD	
		QD,D26-D32			D20-D23			
		60mg			60mg	QD		
		QD,D33-D39						
		50mg QD						
Start time of R	N	N	D18,D25,D32,D	D9 700mg	D6,D13,D20,	N	D9	
			D39 700mg		D27 700mg			
Platelet recovery time	N	N	D40	N	D24	D23	D24	
Outcome	D5 death	D12 death	Recovery	D11 death	Recovery	Recovery		

Impaired kidney function :Assess creatinine value（Reference:57-111umol/L）; MAHA, Microangiopathic Hemolytic Anemia; HTN, hypertension; D, the number of days from the onset of the disease; cm: centimeter; ℃:degree Celsius; R, rituximab; TPE: Therapeutic Plasma Exchange; DX, Dexamethasone ;MP, methylprednisolone; PLEX: plasmapheresis; IVIG, Intravenous Immunoglobulin; MM, Multiple Myeloma; DM, diabetes, ACS, Acute coronary syndrome; ACI, acute cerebral infarction; MASA, Methicillin-resistant Staphylococcus aureus; MODS, Multiple organ dysfunction; Med, Median; QOD, quaque altera die; QD, quaque die; BID, bis in die.

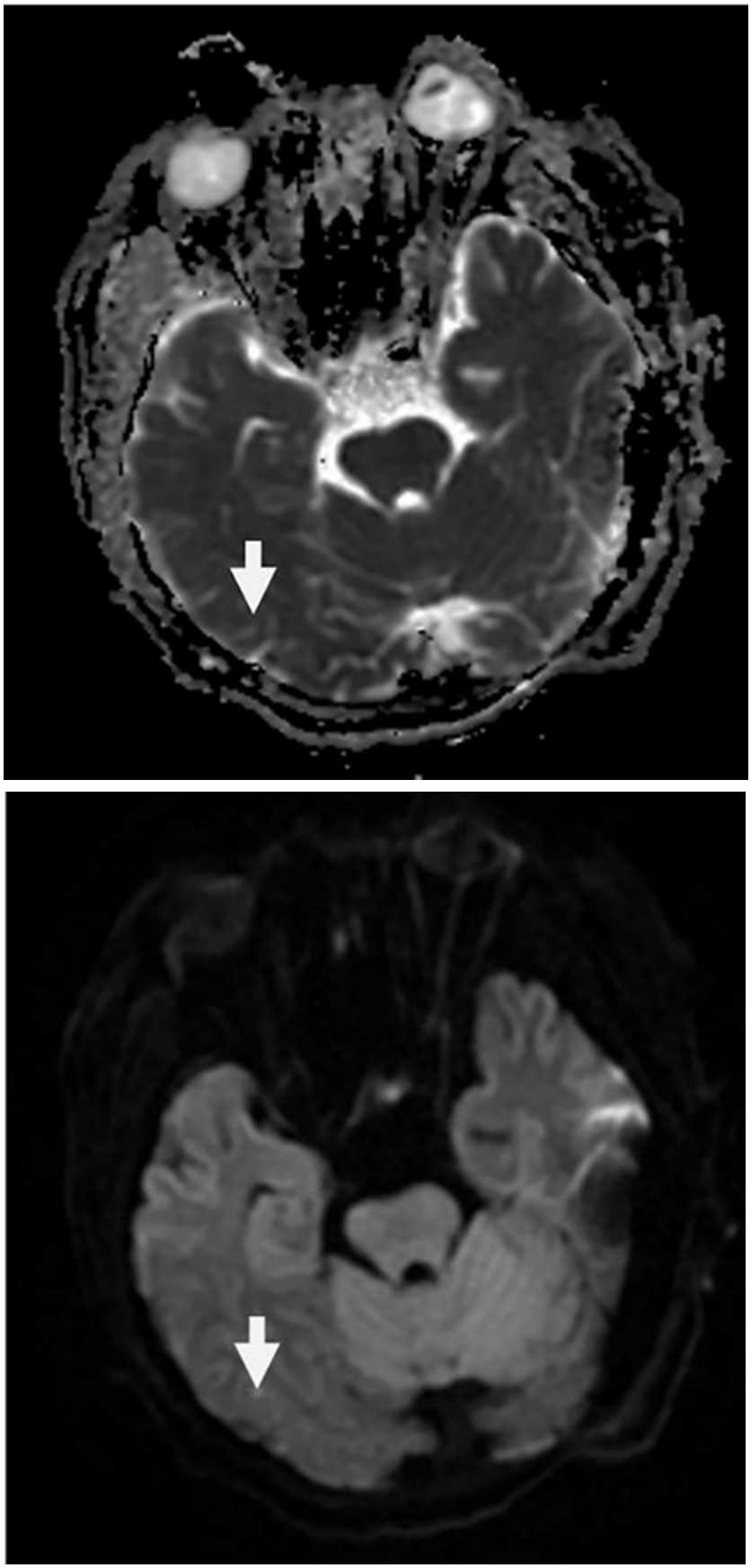
3.3. Laboratory, Imaging, and Other Examinations

Laboratory tests revealed significantly elevated lactate dehydrogenase (LDH) levels (median: 1223.5 IU/L), increased D-dimer levels (median: 2.84 ug/ml), and reduced ADAMTS13 activity (median: <1%). Total bilirubin (median: 59.84 umol/l), direct bilirubin (median: 15.04 umol/l), and indirect bilirubin (median: 42.305 umol/l) levels were also elevated in most patients. All 6 patients underwent peripheral blood smear examinations, with each smear counting 200 nucleated cells. The results revealed varying numbers of broken erythrocytes, indicating different degrees of heterogeneous erythrocytosis. This phenomenon is primarily attributed to the formation of broken erythrocytes and can be observed as tear drop-shaped cells, scattered lobes of erythrocytes, among other manifestations. Typical peripheral blood smears exhibited the presence of broken red blood cells, as highlighted by the arrows in Figure 1. All patients exhibited mild personality changes and neuropsychiatric symptoms. Among them, four cases presented imaging changes, with one case not undergoing head imaging. Among the patients who underwent head CT examination (n=3), multiple punctate, patchy, and blurred low-density shadows were observed. Two cases that underwent magnetic head examination showed new-onset speckled or patchy high signal, with the ADC map indicating low signal. These manifestations posed challenges in distinguishing them from lacunar cerebral infarction, and were considered to be associated with acute microvascular thrombosis, albeit lacking diagnostic specificity. Further details can be found in Table 2 and Figure 2.



Red arrow indicated the schistocytes.

Figure 1: Fragmented Erythrocytes in Peripheral Blood Smears of iTTP Patients (×100).



A：ADC; B: DWI; White arrow indicated the abnormal signal shadow.

Figure 2: MRI Imaging of Acute Microvascular Thrombosis in iTTP.

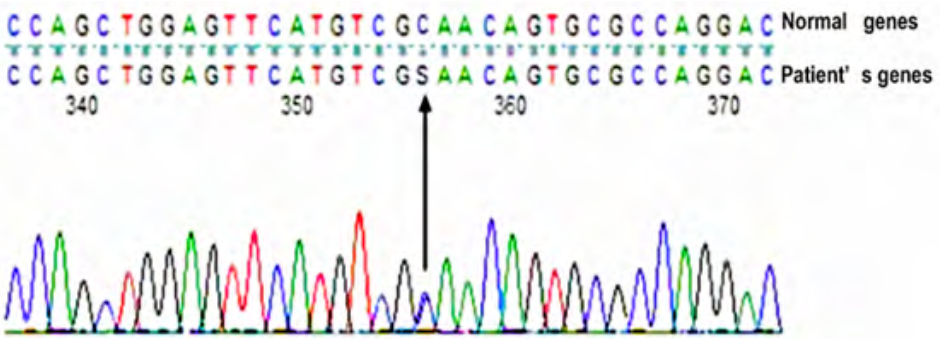
Table 2: Laboratory test information of TTP patients.

No.	PLT（×10^9/L）	D-Dimer(ug/ml)	ADAMTS13 activity (%)	ADATS13 inhibitor titer	TB (umol/l)	DB (umol/l)	IB (umol/l)	LDH（IU/L）
1	6	1.26	＜5	-	42.03	12.2	29.83	1305
2	17	2.16	＜1	＜1 2.62	54.68	14.77	39.91	2299
3	5	3.52	＜1	1.28	67.32	15.91	51.41	1142
4	5	0.69	＜1	1.25	65	20.3	44.7	886
5	13	17.23	＜1	1.43	73.16	15.31	57.85	982
6	7	5.42	0	＜0.6	49.35	12.19	37.16	1117
Med	6.5	2.84	＜1	1.28	59.84	15.04	42.31	1223.5

No, Number ; PLT, Platelet ; Med, Median; TB, Total bilirubin; DB, Direct bilirubin; IB, Indirect bilirubin; LDH, Lactate Dehydrogenase

3.4. Treatment and Outcomes

Given iTTP coupled with non-specific clinical, laboratory, and imaging manifestations, some patients experienced delays in ADAMTS13 activity and inhibitor testing. Consequently, the rate of misdiagnosis and underdiagnosis was notably high in this patient cohort. Out of the 6 cases, 2 patients (2/6) were misdiagnosed. One case (1/6) was misdiagnosed as acute infection, while the other case was misdiagnosed as acute coronary syndrome. The PLASMIC-S scoring system, known for its rapid and accurate prediction of ADAMTS13 activity, holds significant clinical value in the early diagnosis and treatment of iTTP [3]. In our cases, 5 out of 6 patients were classified in the high-risk group, with PLASMIC scores ranging from 6 to 7. This included 2 patients with a score of 7 and 3 patients with a score of 6. Notably, 1 patient initially classified in the intermediate-risk group with a score of 5 was later found to be in the high-risk group. Referring to the 2020 edition of the Guidelines for the Diagnosis and Treatment of Thrombotic Thrombocytopenic Purpura [4], all patients underwent ADAMTS13 activity testing, and all exhibited severe deficiency (<10%). Additionally, five patients underwent ADAMTS13 inhibitor tests, and the results were positive. One report of the ADAMTS13 gene testing revealed the presence of five variants, among which four were synonymous variants, while the c.1342C>G (p.Q448E) mutation on exon 12 was a missense mutation, as detailed in Figure 3. All patients underwent plasmapheresis, with a median of 7 sessions (range:5-11 sessions). The median start time of TPE was 8 days (range: 5-19 days) after the onset of symptoms. Corticosteroids were administered in combination with TPE in all but one patient. The median start time of steroid treatment was 7.5 days (range:3-14 days) after symptom onset. For patients under continuous hormone treatment, the hormone was gradually tapered and discontinued within one month following the recovery of platelet count and lactate dehydrogenase level. Rituximab was used in three patients, with a median start time of 9 days (range:9-18 days) after onset. IVIG was administered to two patients. Treatment efficacy was assessed following the recently revised definition of iTTP treatment outcomes by the International TTP Working Group [5]. Three patients achieved complete recovery, with normalization of platelet count and resolution of clinical symptoms. The median platelet recovery time was 24 days (range:23-40 days). Unfortunately, three patients died during the course of the disease, with death occurring at a median of 12 days (range:5-19 days) after the onset of symptoms. The causes of death included multi - organ failure (two patients) and refractory thrombocytopenia with severe bleeding (one patient), as detailed in Table 1.



Black arrow indicated the missense mutation of the patient's genes.

Figure 3: The missense mutation c.1342C>G (p.Q448E) on exon 12 of the patient's Exon12 exon.

4. Discussion

In clinical practice, the primary physician must demonstrate the ability to swiftly and accurately diagnose emergency situations, facilitating timely intervention and treatment guidance. Key clinical symptoms of iTTP often challenging to identify during initial diagnosis. Although moderate fever is infrequent at diagnosis, neurological signs, such as headache, convulsions, transient ischemic attacks (mild hemiparesis, aphasia, dysarthria, black haze), confusion, and coma, are crucial diagnostic indicators, present in 60% of patients. A thorough and systematic history is imperative [6]. Renal involvement is uncommon (approximately 18% of cases) and typically manifests with moderately elevated serum creatinine below 200 μmol/L [6]. Thrombocytopenia below 20×109/L is considered a poor prognostic factor [6]. Anemia commonly presents as normocytic normochromic hemolytic anemia with elevated indirect bilirubin, lactate dehydrogenase, decreased conjugated bead proteins, and a negative Coombs test. The diagnosis crucially relies on identifying finely fragmented erythrocytes on blood smear examination in the presence of reduced nucleated cells. However, fragmented red blood cells may vanish within the first 24 to 48 hours of the disease course, emphasizing the importance of early bone marrow aspiration and peripheral blood smears [7]. For the challenging differentiation of iTTP and cTTP with atypical clinical symptoms in the early stages, commonly utilized methods involve assessing ADAMTS13 activity and autoantibodies. iTTP is diagnosed in the presence of anti-ADAMTS13 autoantibodies, while cTTP is suspected when ADAMTS13 activity is significantly reduced to <10%, and anti-ADAMTS13 autoantibodies are negative. In cases of suspected cTTP, evaluating ADAMTS13 activity in both parents and children and performing ADAMTS13 genetic analysis is essential for accurate diagnosis [8]. In our research, an intriguing case came to our attention. A patient experienced a rash and fever a month after receiving the COVID-19 vaccine, preceding the initial signs of iTTP by one week. There is evidence suggesting that the vaccine or its adjuvant components can generate autoantibodies, leading to cross-reactivity, potentially accelerating the development of autoimmune diseases [9]. Consequently, the COVID-19 vaccine's role in expediting iTTP development cannot be ruled out in this patient. The patient was found to harbor four synonymous variants and one missense variant. Notably, the c.1342C>G (p.Q448E) mutation on exon 12 causes the amino acid at the 448th position to change from glutamine (Q), a polar uncharged amino acid, to glutamate (E), which is acidic. Interestingly, in a 2002 study published in PNAS by Kokame et al [10], the c.1342C>G (p.Q448E) mutation was identified as a single nucleotide polymorphism (SNP). Notably, although this variant does not substantially change the activity of ADAMTS13 on its own, it has the potential to modulate the activity of other pathologic variants within the context of the overall biological system. This modulation might occur through various molecular mechanisms, such as influencing protein-protein interactions or altering the conformational dynamics of ADAMTS13 and related molecules. The finding that this SNP can affect the activity of other pathologic variants, despite having a relatively minor direct impact on ADAMTS13 activity, highlights the complexity of genetic regulation in the context of iTTP and related disorders. Understanding these interactions could provide valuable insights into the pathophysiology of iTTP and potentially lead to the development of more targeted therapeutic strategies. Adding to the complexity, a missense mutation c.2708C>T (p.S903L) on exon 21 was detected in the patient's daughter. Although the daughter did not succumb to the disease after the initial injection of the COVID-19 vaccine, the possibility cannot be discounted that the patient's augmented genetic susceptibility to iTTP might have been triggered by the re - inoculation of the inactivated virus vaccine, thereby leading to the manifestation of the disease. Consequently, a thorough medical history before vaccination is crucial, and careful clinical monitoring post-vaccination is advisable for patients with autoimmune diseases or suspected autoimmune predispositions in clinical or family histories. The mortality rate for TTP is reaching up to 90%, yet it has been significantly reduced to less than 10% through TPE [11]. The mechanism involves TPE not only replenishing plasma ADAMTS13 activity and eliminating anti-ADAMTS13 autoantibodies but also removing abnormal oversized relative molecular mass von Willebrand factor (vWF) multimers [12].Some studies indicate that the timing of plasma exchange within 8 hours or 24 hours after disease diagnosis does not significantly affect the risk of patient death, whereas a delay of more than 24 hours in plasma exchange is linked to a notable increase in mortality and major thrombotic events [13]. Matsumoto et al [8] have concluded that delayed plasma exchange independently contributes to therapeutic failure. Therefore, in the clinical practice for all patients with iTTP after diagnosis, TPE should be initiated as early as possible. Protocols vary, encompassing decisions on whether to taper or discontinue plasma therapy upon the return of platelet counts to normal, the volume of plasma replaced (1, 1.5, or 2 plasma volumes), and the frequency of plasma replacement (once or twice daily). Some scholars suggest that the number of TPE treatments may not significantly impact patient prognosis, and the selection can be based on the clinical manifestations and laboratory results of patients. Patients with persistent unremitting symptoms and abnormal laboratory tests may benefit from more frequent plasma exchange to achieve early remission. The recommended daily TPE plasma volume is 60 mL/kg (1.5 plasma volumes), administered 1-2 times/day, initiated within 6 hours after diagnosis, until the platelet count surpasses 150×109/L for 48 hours, and the lactate dehydrogenase (LDH) is less than 1.5 times the upper limit of normal [14,15]. Unfortunately, regional and technological limitations, as well as economic conditions, often lead to delayed application of TPE. Our findings reveal that, among all patients, a plasma volume

within the range of 1.0 to 2.0 was implemented as the first-line treatment strategy, accompanied by a plasma replacement frequency of either once or twice per day. The frequency and volume of plasmapheresis were individualized based on the patient's clinical condition and response to treatment. In clinical practice, apart from TPE, patients with TTP may receive treatment with corticosteroids, immunosuppressive agents, and drugs inhibiting the collagen-von Willebrand factor (vWF)-platelet response axis. Current strategies frequently include escalating to twice-daily plasma exchange and utilizing rituximab or other immunosuppressive therapies. Rituximab, a monoclonal antibody targeting the CD20 antigen on B lymphocytes, is presently employed in treating B-cell tumor formation and autoimmune diseases. Literature reports [16] suggest that rituximab can work by eliminating circulating B lymphocytes, reducing the production of anti-ADAMTS13 autoantibodies. The use of rituximab alone in treating refractory/relapsed TTP has resulted in remission in 87%-100% of patients, according to Cuker [17]. He also suggests that integrating rituximab with plasma exchange and hormonal therapy reduces the risk of TTP recurrence. It should be emphasized that within the group of 6 patients, economic constraints led 3 patients to forgo rituximab treatment. Among the three iTTP patients who did receive rituximab treatment, one patient succumbed as the treatment proved ineffective, while the other two patients achieved remission and have remained relapse-free to date. Clinically Ofatumumab and Otolizumab are fully humanized second-generation anti-CD20 antibodies, have proven effective and safe in iTTP patients intolerant to rituximab. Recently, a novel immunosuppressive drug, Caplacizumab, was introduced. It is a humanized single-variable domain immunoglobulin fragment specifically targeting the A1 structural domain of VWF, blocking its interaction with the platelet GP1b-IX-V receptor, preventing micro thrombosis [18]. Caplacizumab has demonstrated improved outcomes in iTTP when used in combination with standard therapy, offering an attractive new therapeutic option for acquired TTP in clinical settings [18]. However, this drug is expensive and has a relatively low availability rate [19]. According to our experience, due to the lower economic level and relatively small population, availability is even lower in the northeastern region of the country. Multiple trials have confirmed the integration of quadruple therapy-comprising TPE, glucocorticoids, rituximab, and Caplacizumab-into the standard of care for immune TTP across several Western countries [20]. Targeted therapy with ADAMTS-13 offers an avenue to address the root cause of TTP, eliminating dependence on plasma therapy conditions [21]. This holds significant promise for the future treatment of iTTP, expanding decision-making options for patients in China facing refractory relapses. To summarize the cases, the potential reasons for the misdiagnosis of these patients include several factors. Patients presenting with thrombocytopenia or primary diseases as their initial manifestation in non-hematological departments often do not exhibit the typical "triad" or "pentad" symptoms at the time of diagnosis. This failure to recognize the disease early on leads to delayed TPE. In the context of the PLASMIC scoring system, it holds clinical significance in the early management of iTTP [3]. Furthermore, iTTP demands chronic and comprehensive management throughout the course. Patients diagnosed with iTTP may encounter lasting effects. The Oklahoma Health Sciences Center has revealed a notably higher incidence of cognitive abnormalities and depression among TTP patients when compared to the general population [22]. Additional research into cognitive dysfunction and depressive status in TTP patients is warranted, with routine assessments of cognitive difficulties recommended post-recovery from acute episodes. This complex nature of iTTP, from its diagnostic hurdles to the need for long-term care and vigilant comorbidity management, highlights the urgency for more refined diagnostic tools, accessible treatment options, and comprehensive follow-up protocols. Medical teams need to be acutely aware of not only the acute symptoms but also the potential long-term consequences and associated conditions to ensure the best possible quality of life and survival rates for iTTP patients. Future research efforts should focus on bridging these gaps in knowledge and whole-process management, aiming to reduce the morbidity and mortality associated with this rare yet debilitating disease. In the pursuit of enhancing patient prognosis and outcomes, numerous challenges and complications associated with iTTP treatments demand attention. As new drugs are continually introduced, and clinical data is updated, TPE and hormone-based diagnostic and treatment programs are refined. This ongoing improvement is anticipated to offer a broader array of choices and options, fostering multidisciplinary and comprehensive diagnostic and treatment strategies for iTTP in the future.

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7. Conflict of Interest

The authors declare no competing interests.

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