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Thrombotic Thrombocytopenic Purpura or Disseminated Intravascular Coagulation? Diagnostic Dilemma in the ICU

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Background

DIC and TTP are two causes of thrombocytopenia that require timely diagnosis and different treatments. Both conditions can be difficult to recognize as clinical presentations vary and current diagnostic criteria lack specificity^{1,2,3,4}. DIC is a complex thrombo-hemorrhagic condition that is always secondary to an underlying disorder, the most common causes being sepsis or trauma. It is primarily a clinical diagnosis that must be confirmed by laboratory data (see figure 2). There is, however, no single laboratory test that can establish or exclude the diagnosis². TTP is a rare condition characterized by systemic microvascular thrombosis, with an incidence of 4 to 11 cases per million people. Like DIC, TTP has no specific diagnostic test and it shares many of the clinical and laboratory features of DIC that can make the two diagnoses difficult to differentiate. Prompt recognition of TTP is warranted as it responds well to plasmapheresis, and without treatment it is associated with a high mortality rate¹. Although clinical presentation and laboratory data often lead to the correct diagnosis, equivocal results can often preclude finding a clear etiology.

Hospital Course

This is the case of a 77 year old female with PMH of spinal degeneration s/p multiple spinal surgeries, hypertension, and hyperlipidemia, who presented to the surgical ICU s/p T9-T10 posterior fusion transverse osteotomy, L1-L2 transforaminal lumbar interbody fusion, and T11-T12 posterior laminectomy. Her operative course was prolonged due to an incidental durotomy. She required a phenylephrine infusion for the majority of the 11-hour case and fluid resuscitation of 3 units of PRBCs, 7700 ml of crystalloid, and 780 ml of cell saver. Blood Loss was estimated at 1500 ml and urine output was 1150 ml. Postoperatively she went to the SICU hemodynamically stable and intubated. By HD2, her renal function had worsened and she had developed thrombocytopenia (figure 1). A FENA done at the time was consistent with intrinsic renal damage. Despite being fully resuscitated and extubated on HD2, her renal function continued to worsen and her platelets continued to drop. HIT and sepsis were ruled out, but a peripheral blood smear obtained on HD3 showed microangiopathic hemolytic anemia, turning the differential diagnosis to TTP or DIC. By then, the patient was also noted to have oozing from an antecubital IV site. A DIC panel done on HD4 was inconclusive, having revealed an elevated FDP and D-dimer with a low ATIII but an elevated fibrinogen and marginally elevated PT and PTT. TTP was still being considered in the setting of renal failure which was likely acute tubular necrosis. On HD6 the patient developed uremic encephalopathy and she required dialysis. After the patient's platelets dropped to 21, plasma exchange was scheduled for HD7, but before initiating this treatment her platelets began to improve. The fact that her thrombocytopenia improved without intervention ruled out TTP as the etiology. She was transferred to the floor on HD9 with a diagnosis of DIC and AKI, likely due to an intra-operative event.

Figure 1. Hospital Course of Thrombocytopenia

	Baseline	HD1	HD2	HD3	HD4	HD5	HD6	HD7	HD8	HD9
platelets	310	111	53	48	24	25	21	41	76	153
Hb	13.5	14.5	12.2	13.1	10.4	8.5	7.2	8.4	8.4	7.1
BUN	13	13	19	35	48	71	103	124	99	86
creatinine	.73	1.12	1.82	3.94	5.16	6.35	7.27	8.16	6.92	5.72
LDH					1964	2576	2642	1704	1191	
PT					13.1	12.6	13.9	15.7		
PTT					36.1	26.4	34.6	33.3		
fibrinogen		173			549	404	455	521	446	

Figure 1. Abnormal values in red. Normal values for our lab: Platelets 140-440 x10⁹/mm³ Hb 10-16 g/dL BUN 7-23 mg/dL Cr 0.6-1.3 mg/dL LDH 110-240 IU/L PT 9.6-12.4 seconds PTT 22-34 seconds Fibrinogen 150-400 mg/dL

HD1: immediate post-operative values
HD2: HIT negative
HD3: HIT negative
HD4: FDP ↑, D-Dimer ↑, ATIII ↓, echymosis, PETC, ATN, blood smear = microangiopathic hemolytic anemia
HD5: ADAMT13 negative
HD6: repeat ADAMT13 negative
HD7: repeat ADAMT13 negative
HD7: encephalopathy, dialysis initiated, 2u PRBC, rising platelet count
HD8: rising platelet count

Figure 3. Weighing the Data

Figure 3. Summary of the lab values for the patient presented here. Note that because of the numerous supporting features for TTP and DIC, it was not until HD7 when the patient had spontaneous recovery of platelet count that TTP was ruled out and DIC was determined to be the final diagnosis.

FINDING	SUPPORTS TTP	SUPPORTS DIC
Thrombocytopenia	+	+
Fibrin Degradation Products ↑		+
D-Dimer ↑		+
ATIII ↓		+
Fibrinogen normal	+	
LDH ↑	+	
PT ↑, PTT ↑		+
Worsening Anemia	+	
Microangiopathic Hemolytic Anemia on blood smear	+	
ADAMT13 gene negative		+
Renal failure (ATN)	+	
Encephalopathy	+/-	
Spontaneous recovery of platelet count		+

Figure 2. TTP vs DIC

	Diagnostic Criteria	Differential	Pathophysiology	Laboratory Values	Treatment
TTP	(1) Unexplained microangiopathic hemolytic anemia and (2) thrombocytopenia (with or without neurologic involvement, renal failure, and fever) ⁵ .	ITP, autoimmune hemolytic anemia, HUS, DIC, PNH.	Severe deficiency of von Willebrand factor cleaving protease as a result of mutation in the ADAMT13 gene leading to systemic microvascular thrombosis ⁵ .	(1) ↓hct, (2) ↓Platelets (in absence of leukopenia), and (3) evidence of microangiopathic hemolytic anemia: schistocytes and reticulocytes on peripheral smear, ↑ LDH and indirect-reacting bilirubin, and negative direct Coomb's test ¹ .	Plasma exchange and glucocorticoids ¹ .
DIC	(1) An underlying disease known to be associated with DIC (eg. Sepsis, trauma, cancer, vascular disorders, toxins, or immunologic disorders. (2) thrombocytopenia, (3) prolongation of clotting times, (4) presence of fibrin-degradation products, and (5) low levels of coagulation inhibitors ² .	Liver failure, HIT, TTP, Vitamin K deficiency.	The systemic formation of fibrin resulting from increased generation of thrombin, the simultaneous suppression of physiologic anticoagulation mechanisms, and the delayed removal of fibrin as a consequence of impaired fibrinolysis ² .	(1) ↑PT, (2) ↑PTT, (3) ↓platelet count, (4) ↓fibrinogen, (5) ↑D-dimer, (6) ↑Fibrinogen degradation products, (7) ↑fibrin monomer, and (8) peripheral blood smear showing schistocytes ² .	Aggressive treatment of underlying disease ² .

Discussion

The clinical differentiation between DIC and TTP can be a diagnostic challenge. In our patient, the inconclusive DIC panel in addition to renal failure made TTP the most concerning alternative diagnosis. As mentioned previously, the literature shows that there is no conclusive diagnostic test for either condition, and diagnosis is based on clinical suspicion in conjunction with laboratory results.

Our patient had symptoms and laboratory values that were consistent with both TTP and DIC, and both diagnosis were considered for the majority of her hospital course (figure 3). It was ultimately the spontaneous recovery of her platelet count that ruled out TTP as the etiology. The initial DIC panel on HD 4 was considered "inconclusive" because of the elevated fibrinogen and marginally elevated clotting times, but the literature shows that in the acute phase response there is shortening of activated partial thromboplastin time and increased fibrinogen concentrations^{2,3}. Therefore a normal value for these measurements can not rule out DIC. As previously mentioned, the patient's acute renal failure was another reason TTP was strongly considered. Literature shows, however, that acute renal failure occurs infrequently in TTP. Our patient's renal failure was likely coincidental, secondary to an intraoperative insult. Critical care patients often have anemia and thrombocytopenia and the etiology is unlikely to be TTP even if MAHA is present¹.

Our case demonstrates the difficulties in confirming a diagnosis with sensitive but nonspecific criteria. TTP and DIC share similar characteristics, but missing a timely diagnosis of TTP can prove fatal for the patient without treatment.

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Abbreviations

- DIC= Disseminated Intravascular Coagulation
- TTP= Thrombotic Thrombocytopenic Purpura
- MAHA= Microangiopathic Hemolytic Anemia
- HD= Hospital day